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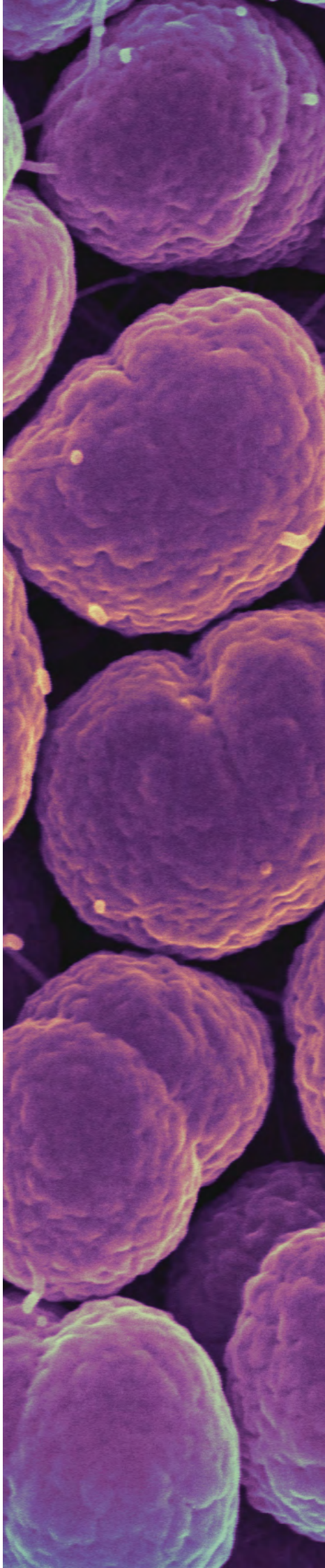
Kotahitanga

Uniting Aotearoa against infectious disease and antimicrobial resistance

A report from the Prime Minister's Chief Science Advisor, Kaitohutohu Mātanga Pūtaiao Matua ki te Pirimia.

Full report



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Front cover: Colourised scanning electron micrograph of Neisseria gonorrhoeae bacteria, which causes gonorrhoea. Image credit: National Institute of Allergy and Infectious Diseases, National Institutes of Health/Flickr (CC BY-NC 2.0).
Back cover: Muka face mask. Matthew McIntyre-Wilson; artist; 2020; Wellington. Te Papa Tongarewa Museum of New Zealand (ME024617).

Kotahi te aho ka whati, ki te kāpuia e kore e whati.

- Tāwhiao

Foreword

Kia ora koutou,

The threat posed by infectious diseases is well understood. COVID-19 has provided a salient reminder that pathogens continue to threaten the wellbeing of New Zealanders and that health in Aotearoa New Zealand is intimately linked to the international environment. There are many infectious disease threats facing Aotearoa New Zealand besides COVID-19. A range of established, emerging, and re-emerging viruses, bacteria, fungi, and parasites can harm our people, animals, and plants. We need to be prepared.

Increasingly, these pathogens are evolving to resist the effects of the antimicrobials that were developed to kill or control them. The growing threat of antimicrobial resistance, largely driven by overuse and misuse of antimicrobial drugs, is well understood by scientists and healthcare practitioners. We understand how microbes acquire and transmit resistance, the challenges of the drug discovery pipeline, and the deadly future that awaits us if we lose our ability to fight even the most common infections with safe and affordable drugs. In contrast to some of our previous projects in the Office, much of the science around antimicrobial resistance is settled, and the evidence needed to inform government action is abundant.

Not only is the science underlying antimicrobial resistance clear – so too are the solutions. The greatest challenge is to focus on infection prevention – rather than waiting for people to get sick and then being forced to focus on treatment – as well as curbing inappropriate use of antimicrobials through more judicious use when infection inevitably occurs.

There is an international consensus on these points, with the World Health Organization, the World Organisation for Animal Health, and the Food and Agricultural Organization publishing a global action plan on antimicrobial resistance in 2015, which was endorsed by the United Nations General Assembly in 2016. The World Health Organization considers antimicrobial resistance to be among the top ten health threats facing the globe. Meanwhile, the World Bank has described the global response to antimicrobial resistance as “dangerously inadequate.”

Flowing from this international consensus came our own domestic action plan in 2017, which outlined a series of objectives and actions to help Aotearoa New Zealand combat antimicrobial resistance. But despite the science and solutions being clear, and despite these international and domestic action plans, we fell short at implementation – almost none of the recommendations made in our 2017 action plan have been put into place (see scorecard below).

This report is intended to serve as a reminder of the mounting threat posed by infectious diseases and antimicrobial resistance in Aotearoa New Zealand. It brings together international and domestic science and case studies, detailing the infectious disease and antimicrobial resistance landscape globally and at home, where we are in tackling these threats, and how we could do better. There is plenty of room for improvement, as well as many examples of inspiring solutions at home and abroad that could be drawn on or scaled up to help Aotearoa New Zealand unite against these threats.

The panel that guided this project made a number of recommendations, none of which are unexpected or new. The panel’s recommendations have their roots in our 2017 national action plan as well as in international action plans, plans made in other jurisdictions, and solutions advocated for by scientists, practitioners, and industries.

It became clear during this project that tackling infectious diseases and antimicrobial resistance in Aotearoa New Zealand is a matter of rolling up our collective sleeves and getting it done. To achieve this we need leadership, unity, resolve, and resources. The time for action is now: the longer we wait to unite against these threats, the more suffering New Zealanders will face. This is a matter of urgency.

Harms resulting from inaction in the face of these threats will disproportionately affect Māori and Pacific peoples, whose health outcomes are significantly worse compared with other peoples in Aotearoa New Zealand, an inequity that has long been noted but never resolved. We have an obligation to address these inequities. For Māori, we must honour Te Tiriti o Waitangi, working in partnership to achieve equity in health outcomes. For Pacific peoples here, in the Realm and beyond, we have a duty too, with physical, social, historical, political, and cultural ties that run deep.

A huge thank you to our hard-working panel who came together during a tough year to produce this report, despite the challenges (and the irony) of working on this project during a global pandemic. Ka pai. To the very many members of our wider reference group – thank you too for the detailed reading, the participation in workshops, and the answers to our many questions. This project has been a joy in that, despite the dark material, there is a remarkable consensus on what we need to do tackle this global challenge as it reaches our shores. Finally, to the small but perfectly formed OPMCSA team, and especially Ellen Rykers, who stepped up to lead the work mid-year. Thank you for beavering away to produce this report, dispersed across the country and camped in spare rooms, while many of the panel were distracted by the day-to-day pressures of responding to COVID-19.

Ngā mihi nui,

Professor Dame Juliet Gerrard DNZM HonFRSC FRSNZ
Prime Minister's Chief Science Advisor
Kaitohutohu Mātanga Pūtaiao Matua ki te Pirimia

Dr Matire Harwood MBChB
Kotahitanga panel co-chair
University of Auckland and Papakura Marae Health Clinic

Mō tatou, ā, mō kā uri ā muri ake

New Zealand's Antimicrobial Resistance Action Plan scorecard

Below the panel and Office of the Prime Minister's Chief Science Advisor have scored national progress against the priority action areas in the 2017 New Zealand Antimicrobial Resistance Action Plan. These scores do not reflect grassroots/regional action led by individuals.

Objectives	Priority action areas	Our assessment	Equity focus in action?
Objective 1: Awareness and understanding – Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.	**Priority action area 1**: Strengthen consumer awareness to improve understanding of antimicrobial resistance and the importance of using antibiotics appropriately.	💬 Some action	✗ No
	Priority action area 2: Strengthen communication and education initiatives on antimicrobial resistance and stewardship for all prescribers, and those working in the human health, animal health and agricultural sectors.	💬 Some action (animal and agricultural health only) 💬 A little action (human health)	✗ No
Objective 2: Surveillance and research – Strengthen the knowledge and evidence base about antimicrobial resistance through surveillance and research.	**Priority action area 3**: Establish a coordinated national surveillance programme of antimicrobial resistance and antimicrobial use in humans, animals and agriculture.	✗ No action	
	Priority action area 4: Develop lists of priority organisms, key resistance genes and antimicrobials for national reporting.	💬 A little action	
	Priority action area 5: Implement national minimum standard for laboratory testing and reporting of antimicrobial susceptibility.	💬 Some action	
	Priority action area 6: Support national priorities for research on antimicrobial resistance, antimicrobial consumption and stewardship in human health, animal health and agriculture.	✗ No action	

Objectives	Priority action areas	Our assessment	Equity focus in action?
Objective 3: Infection prevention and control – Improve infection prevention and control measures across human health and animal care settings to prevent infection and transmission of micro-organisms.	**Priority action area 7**: Develop and update national guidelines and standards for infection prevention and control to achieve a nationally consistent approach, and enhance accreditation and quality assurance programmes so that more practitioners follow best-practice infection prevention and control measures across human health, animal health and agriculture.	💬 Some action	✗ No
	Priority action area 8: Promote a cohesive and sustainable 'one team' approach to infection prevention and control functions in all human healthcare facilities.	✗ No action	
	Priority action area 9: Encourage continued immunisation to prevent infections.	💬 Some action	✗ No
	Priority action area 10: Promote prevention and control of zoonotic infections.	✗ No action	
	Priority action area 11: Encourage alternative approaches to reduce infection and the need for antimicrobial use in animals.	✔ Action	✗ No
Objective 4: Antimicrobial stewardship – Optimise the use of antimicrobial medicines for human health, animal health and agriculture, including by maintaining and enhancing the regulation of animal and agriculture antimicrobials.	**Priority action area 12**: Develop a national programme or standard for antimicrobial stewardship in all sectors of human health, including resources and/or targets for use in all sectors.	💬 A little action	✗ No
	Priority action area 13: Develop a national programme or standard for antimicrobial steawrdship in animal health.	💬 Some action	
	Priority action area 14: Establish a programme of regularly monitoring the controls on antimicrobial veterinary medicines.	✗ No action	
	Priority action area 15: Review the controls (conditions of registration), labelling and advertising of antimicrobial-	💬 Some action	✗ No

Objectives	Priority action areas	Our assessment	Equity focus in action?
	based trade name products to ensure they are fit for purpose.		
Objective 5: Governance, collaboration and investment – Establish and support clear governance, collaboration and investment arrangements to for a sustainable approach to countering antimicrobial resistance.	**Priority action area 16**: Establish a sustainable national governance structure to coordinate all efforts to minimise antimicrobial resistance.	💬 A little action	✗ No
	Priority action area 17: Ensure that there is sustainable investment in initiatives to minimise the impacts of antimicrobial resistance. This includes ongoing investment in surveillance, communication, stewardship and infection prevention and control.	✗ No action	
	Priority action area 18: Establish the necessary national and international links and collaborations to implement the Antimicrobial Resistance Action Plan effectively.	💬 A little action	

Contents

1 Part one: Introduction to this report

1.1 Motivation for this project

In 2020, much of the world came to a standstill. The COVID-19 pandemic has demonstrated the health, social, and economic costs associated with the spread of a pathogen that can't be easily treated.

While Aotearoa New Zealand's pandemic response has generally proved successful when compared with many other countries and territories,[1] the pandemic is still playing out. Meanwhile, many other health threats fell onto the backburner as we turned our focus to COVID-19. By amplifying awareness of the costs of infectious disease, COVID-19 has the potential to catalyse evidence-based action to tackle threats across the infectious diseases landscape – including infections caused by bacteria, fungi, and parasites, as well as other viruses.

Chief among these threats is antimicrobial resistance (AMR), where microbes develop the ability to resist the effects of the antimicrobials designed to kill them or suppress their growth. AMR is on the rise globally.[2] The World Health Organization (WHO) lists AMR among the top ten global healthcare challenges of the decade.[3] AMR threatens to make many infections untreatable, dramatically increasing the risk of death and disability and jeopardising the safety of both elective and essential medical procedures. It is already becoming increasingly difficult to treat some diseases due to drug resistance. Worldwide, an estimated 700,000 people are killed by drug-resistant microbes every year.[4] AMR-related deaths have already occurred in Aotearoa New Zealand.[5]

If we don't act, it is estimated that by 2050, **10 million people will perish worldwide every year** due to untreatable infections – more than will die from cancer.

Antimicrobials should be used as needed to protect human, animal, and plant health. However, antimicrobials are often used inappropriately – for example, in situations where non-antimicrobial alternatives exist or where antimicrobials wouldn't be expected to provide any health benefits. Continuing inappropriate use of antimicrobials will leave future generations with fewer options to prevent and treat infectious diseases. If we don't act, it is estimated that by 2050, 10 million people will die worldwide every year due to untreatable infections – more than will die from cancer.[6] Routine surgeries such as hip replacements, root canals, and caesareans will become riskier, as will disease treatments that compromise immunity, such as chemotherapy. Some have called the shift to a post-antibiotic era 'the end of modern medicine'.[7]

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[1] Chang, R., Varley, K., Munoz, M., *et al.* (2021). The COVID resilience ranking. *Bloomberg*. Retrieved from https://www.bloomberg.com/graphics/covid-resilience-ranking/

[2] O'Neill, J. (2016). *Tackling drug-resistant infections globally: Final report and recommendations*. UK: HM Government and Wellcome Trust. Retrieved from https://amr-review.org/

[3] World Health Organization. (2020, 13 January). *Urgent health challenges for the next decade* [Press release]. Retrieved from https://www.who.int/news-room/photo-story/photo-story-detail/urgent-health-challenges-for-the-next-decade

[4] O'Neill, J. (2016). *Tackling drug-resistant infections globally: Final report and recommendations*. UK: HM Government and Wellcome Trust. Retrieved from https://amr-review.org/

[5] Stuff reporters. (2019, 17 October). Person dies after contracting superbug in overseas hospital, *Stuff*. Retrieved from https://www.stuff.co.nz/national/health/116654389/person-dies-after-contracting-superbug-in-overseas-hospital; Biddle, D.-L. (2016, 11 November). Patient dies after being misdiagnosed at a Waikato hopsital, *Stuff*. Retrieved from https://www.stuff.co.nz/national/health/86350367/patient-dies-after-being-misdiagnosed-at-a-waikato-hopsital

[6] O'Neill, J. (2016). *Tackling drug-resistant infections globally: Final report and recommendations*. UK: HM Government and Wellcome Trust. Retrieved from https://amr-review.org/

[7] Wiles, S. (2017). *Antibiotic resistance: The end of modern medicine*. Wellington, New Zealand: Bridget Williams Books Ltd.

In Aotearoa New Zealand, the proportion of infections that are caused by drug-resistant microbes is lower than in many other countries – but rising. For example, common infections such as urinary tract infections (UTIs) and sexually transmitted infections (STIs) are becoming increasingly difficult to treat (for details, see part four of this report). We have a window of opportunity to take decisive, concrete actions to keep our rates of AMR as low as possible, prolonging the effectiveness of antimicrobials for future generations.

A recent government self-assessment evaluated Aotearoa New Zealand's progress on tackling AMR and found significant room for improvement.[8] Despite having a national AMR action plan since 2017, very little progress has been made on addressing this threat (for details, see section 4.9.1, appendix 7.5, and the scorecard accompanying this foreword).

The problem of AMR occurs in the wider context of infectious diseases. There are a range of infectious diseases that threaten the health of Aotearoa New Zealand's people, animals, and plants. Some are prevalent on our shores and cause significant health and wellbeing losses, often disproportionately impacting Māori and Pacific peoples.[9] Other infectious diseases threaten our livestock, agricultural industries, and the wider environment – *Mycoplasma bovis* in cows[10] is a current example.

The growing threat of AMR is well understood by scientists and healthcare practitioners … this report represents a **solid evidence foundation to support action**.

The growing threat of AMR is well understood by scientists and healthcare practitioners. We understand how microbes acquire and transmit resistance, the challenges of the drug discovery pipeline, and the deadly future that awaits us if we lose our ability to fight even the most common infections with safe and affordable drugs. By pulling together international and local evidence and reflecting on existing policies, actions, and plans from various workstreams across government, academia, industry, and healthcare, this report represents a solid evidence foundation to support action.

[8] World Health Organization. (2020). Global database for the tripartite antimicrobial resistance (AMR) country self-assessment survey (TrACSS). Retrieved 4 August 2021 https://amrcountryprogress.org/

[9] Baker, M.G., Barnard, L.T., Kvalsvig, A., *et al.* (2012). Increasing incidence of serious infectious diseases and inequalities in New Zealand: A national epidemiological study. *The Lancet, 379*(9821), 1112-1119. https://doi.org/10.1016/S0140-6736(11)61780-7

[10] Ministry for Primary Industries. (n.d., 15 July 2021). *Mycoplasma bovis* disease eradication programme. Retrieved 4 August, 2021, from https://www.mpi.govt.nz/biosecurity/mycoplasma-bovis/

1.2 Our panel

We gratefully acknowledge the efforts of our panel whose expertise, guidance and mahi have led the *Kotahitanga: Uniting Aotearoa against infectious diseases and antimicrobial resistance* project for the Office of the Prime Minister's Chief Science Advisor (OPMCSA), Kaitohutohu Mātanga Pūtaiao Matua ki te Pirimia. Ngā mihi nui.

- Dr Matire Harwood (Ngāpuhi) (co-chair), University of Auckland and Papakura Marae Health Clinic
- Dr Anneka Anderson (Kāi Tahu, Kāti Māmore), University of Auckland
- Professor David Murdoch, University of Otago
- Dr Dianne Sika-Paotonu, University of Otago
- Professor Jack Heinemann, University of Canterbury
- Dr Kristin Dyet, Institute of Environmental Science and Research Limited (ESR)
- Associate Professor Mark Thomas, University of Auckland and Auckland District Health Board (DHB)
- Distinguished Professor Nigel French, Massey University
- Dr Sharon Gardiner, Canterbury DHB
- Associate Professor Siouxsie Wiles, University of Auckland

Figure 1: The Kotahitanga panel and OPMCSA staff. From left to right: Kristin Dyet, Ellen Rykers, Siouxsie Wiles, Rachel Chiaroni-Clarke, Mark Thomas, Dianne Sika-Paotonu, Nigel French, Juliet Gerrard, Jack Heinemann, Matire Harwood, Sharon Gardiner, George Slim, Anneka Anderson, David Murdoch.

See appendix 7.1 for the terms of reference for this project, as agreed with the Prime Minister in early 2021.

1.3 Acknowledgements

We thank the many researchers, health practitioners, stakeholders and interested parties who agreed to be on our reference group, met with the team, provided introductions and generously contributed time, energy and suggestions to this project through conversation, attending a workshop, peer review or high-level comments on the report. We are particularly grateful to those who hosted the team to give us the necessary insights into the challenges of tackling infectious disease and antimicrobial resistance on the ground. We would also like to acknowledge those who chose not to be included on this list.

Though we have incorporated as much feedback as possible, we acknowledge that not all suggestions were consistent and not all could be incorporated. Our acknowledgement of people who helped us with this project in no way indicates their endorsement of the project itself. We have done our utmost to keep track of everyone who has contributed to both this report and our work on rheumatic fever and they are recorded below. Please accept our sincere apologies for any inadvertent errors.

Aaron Randall, Hutt Valley DHB
Adam Wardle, Waikato DHB
Adrian Cookson, AgResearch
Aimee Daum, University of Auckland
Alastair McLean, Western Heights Health Centre
Alesha Smith, Otago
Alex de Roo, Canterbury DHB
Alicia Gataua, Mana Kidz
Alison Leversha, Auckland DHB
Allan Kinsella, MPI
Amanda Kvalsvig, University of Otago
Amy Chan, University of Auckland
Andrea McNeill, ESR
Andrew Munkacsi, Victoria University of Wellington
Andrew Thompson, University of Auckland
Angela Cornelius, ESR
Anja Werno, Capital & Coast DHB
Ann Whitfield, IPCNC and Auckland DHB
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Arindam Basu, University of Canterbury
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Brendan Arnold, Southern DHB
Brent Gilpin, ESR
Brent Kleiss, NZ Pork
Bronwyn Petrie, Ministry of Health
Bruce Arroll, University of Auckland
Bruce Welch, vet consultant to pig farmers
Bryan Betty, RNZCGP
Carla White, Health Literacy NZ Ltd
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Caroline Murray, Fonterra
Carolyn Clissold, IPCNC and Capital & Coast DHB
Carolyn Gates, Massey University
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Cat Li, Capital & Coast DHB
Cath McLeod, New Zealand Food Safety & Science Research Centre
Catherine Jackson, Northland DHB
Cheryl Brunton, Canterbury DHB
Chey Dearing, Eastern Institute of Technology
Chloe Campbell, Pharmaceutical Society of New Zealand
Chloe Innes, Aorere College (and the students at Aorere College)
Christine Couldrey, LIC
Chris Houston, Beef+Lamb NZ
Clare Possenniskie, Ministry of Health
Clive Hackett, Canterbury Linen Services
Colin Simpson, Victoria University of Wellington
Collette Bromhead, Massey University
Collin Tukuitonga, University of Auckland
Daniel Pletzer, University of Otago
Danielle Middleton, Manaaki Whenua
Darren Day, Victoria University of Wellington
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David Grolman, Pfizer
David Hayman, Massey University
David Lawton, NZ Pork and vet consultant
David Roberts, Mid-Central DHB

David Saul, MicroGEM NZ
Delma Augustine, ACC
Delwynne Sheppard, Northland DHB
Dianne Schumacher, DCANZ
Donna Kielar, National Hauora Coalition
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Ed Catherwood, AgriHealth and ARPPA
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Justine Lancaster, HealthPathways
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Kiki Maoate, University of Otago
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Kimberley Sanerivi, Ministry of Health

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Rachel Webb, KidzFirst/Starship and Counties Manukau DHB
Ramesh Ganesan, ESR
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Ruth Bijl, Auckland DHB
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Steve Ritchie, University of Auckland and Auckland DHB
Susan Jack, Southern DHB
Susan Morpeth, Middlemore Hospital
Susan Taylor, Middlemore Hospital
Susan Wood, Canterbury DHB
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Tracy Ashworth, Hawke's Bay DHB
Una Ren, ESR
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Vince Arbuckle, MPI
Virginia Hope, ESR
Warren Hughes, MPI
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William Leung, University of Otago
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1.4 Recommendations

AMR is a wicked problem. Addressing it will require interventions across the whole health system: from preventing infections, to ensuring access to appropriate antimicrobial therapy for current and future generations, to optimising the use of antimicrobials – including by not using antimicrobials when we are confident that they will provide nil or trivial benefit.

We have grouped specific, tangible recommendations into six themes. Indicative timeframes are provided for each recommendation, with three options: those that can be actioned immediately (within two years), those that can be achieved within 2-3 years, and longer-term actions to be implemented within five years.

The implications of AMR and approaches to mitigate its risks have been well traversed. This means that many of these recommendations are not new ideas and build on the work of others, including the *2017 New Zealand AMR Action Plan*.

The recommendations are designed to uphold equity and champion the importance of a holistic approach – which we refer to as kotahitanga – that interweaves human, animal, plant, and environmental health.

The panel acknowledges that in addition to the detailed recommendations below, action needs to be taken to address inequities in the wider determinants of human health. However, these are largely outside of the scope of this report.

The panel recognises the role of Te Tiriti o Waitangi in both the need to achieve equitable health outcomes and the partnership approach required to achieve these outcomes. All recommendations are consistent with Te Tiriti.

Recommendations relating to Pacific peoples refer to people living in Aotearoa New Zealand. The panel recognises that recommendations in the Aotearoa New Zealand context may not be relevant to the different contexts throughout the Pacific, while acknowledging the importance of working alongside our Pacific partners to address these challenges.

We also note that current health reforms present an opportunity to introduce structural and significant changes, made in partnership with communities affected – especially Māori and Pacific peoples, the elderly, disabled people, and regional and remote communities.

Theme 1: Elevate and expand antimicrobial stewardship

Preserving our antimicrobials for future generations requires careful antimicrobial stewardship (AMS) now. Effective AMS requires useful and accessible data, guidance, standards, and initiatives, as well as overarching national leadership.

Recommendations			Timeframe
(a) Develop a coordinated national approach to AMS to provide overarching governance and leadership. The approach should adopt a strong equity focus and engage Māori and Pacific peoples. *This recommendation builds on the themes in the following priority action areas from the 2017 New Zealand AMR Action Plan:* • *Priority action area 12: Develop a national programme or standard for AMS in all sectors of human health, including resources and/or targets for use in all sectors.* • *Priority action area 13: Develop a national programme or standard for AMS in animal health.* • *Priority action area 16: Establish a sustainable national governance structure to coordinate all efforts to minimise AMR.*	**(i)**	Establish an infectious diseases and AMR ministerial portfolio. The Minister with responsibility for Infectious Diseases and AMR Action should work with officials across the Ministry of Health (MoH), Ministry for Primary Industries (MPI), and Ministry for the Environment (MfE), to advance Aotearoa New Zealand's response to AMR.	⏫ Immediate
	(ii)	Create stronger linkages between the human, animal, plant, and environmental health sectors involved with antimicrobial use with relevant government agencies to enable multi-way knowledge sharing on AMS. This may involve stronger links between the restructured health localities (currently DHBs) and the veterinary profession.	⏫ Immediate
	(iii)	Establish a national AMS expert group (equivalent to the current National Infection Prevention and Control Expert Group, NIPCEG) to embed expert advice in policy making. The expert group will develop a national strategy for AMS. The AMS expert group should include dedicated but closely cooperating sub-groups from the human, animal, and plant health sectors, with clear reporting lines to relevant Ministries.	⏫ Immediate
	(iv)	Establish a national centre for AMS in human health that takes responsibility for leading the human health components of the AMS strategy.	⏫ Immediate
	(v)	Establish regional AMS groups that engage with the national centre and facilitate regional AMS activities. These groups should have cross-sector representation and a focus on equity.	⏫ Immediate
	(vi)	Set ambitious targets for equitably reducing the quantity and improving the quality of antimicrobial prescribing for human health as part of the AMS strategy.	⏫ Immediate
	(vii)	Develop and maintain national antimicrobial prescribing guidance for human health. Considerations: • Development of the guidance should build on the ACC scoping work, aiming to align existing regional guidance and use a clinician-led collaborative model to facilitate uptake.	⏫ Immediate

Recommendations			Timeframe
		• The guidance should include treatment of infections due to multidrug-resistant organisms and include a strong AMS and equity lens. • Development of paediatric guidance may offer a first step to this initiative, using Starship's existing guidance.	
	(viii)	Develop new clinical care standards for AMS to address gaps in the current health and disability standards with extension to cover all health professionals involved with antimicrobial use including doctors, nurses, pharmacists, midwives, and dentists in the community. Ensure these standards have a strong equity focus.	⏫ Immediate
(b) Build AMS capacity and expertise at all levels. Support implementation of AMS across the human and animal health systems and plants and the environment, including but not limited to: primary care, aged residential care, public and private hospitals, dentistry, optometry, midwifery, pharmacy, veterinary care, agriculture, and biosecurity. *This recommendation builds on the themes in the following priority action area from the 2017 New Zealand AMR Action Plan:* • *Priority action area 17: Ensure that there is sustainable investment in initiatives to minimise the impacts of AMR. This includes ongoing investment in surveillance, communication, stewardship and infection prevention and control.*	**(i)**	Establish clinical leadership roles focused on AMS (and alongside infection prevention and control) at the director level of all DHBs (or equivalent) and link these through the national centre for AMS.	⏫ Immediate
	(ii)	Require all DHBs (or equivalent), private hospitals and primary health organisations (PHOs) to report annually and transparently on their goals, activities, and outcomes with respect to AMS.	⏫ Immediate
	(iii)	Set minimum full-time equivalent (FTE) requirements (considering roles for pharmacists, doctors and nurses as appropriate) for AMS at all hospitals (both public and private) and PHOs.	⏫ Immediate
	(iv)	Provide support for dedicated AMS pharmacists embedded within PHOs and/or general practice (GP) clinics.	⏫ Immediate
	(v)	Formalise a system for connecting aged residential care and community healthcare workers with antimicrobial stewardship expertise at regional and national levels.	⏫ Immediate
	(vi)	Set targets for equitably increasing the AMS workforce. Ensure this is resourced appropriately.	⏫ Immediate
	(vii)	Enhance AMS education for all health professionals involved with antimicrobial use through the tertiary curriculum and continuing professional development and support health professionals to upskill in this area.	⏫ Immediate
	(viii)	Focus on sustainable susceptibility by developing a more holistic view of AMS. This may include investigating the chemical microbial exposome and testing products (e.g. pesticides) for their antimicrobial activity.	➖ 5 years

Recommendations			Timeframe
(c) Improve antimicrobial data governance: collection, quality, and reporting. *This recommendation builds on the themes in the following priority action area from the 2017 New Zealand AMR Action Plan:* • *Priority action area 3: Establish a coordinated national surveillance programme of AMR and antimicrobial use in humans, animals and agriculture.*	**(i)**	Monitor and report transparently the quantity of antimicrobials used throughout the human health sector, and ensure this data includes ethnicity to monitor equity-based outcomes. This may require various health services including hospitals, clinics, and pharmacies to provide data in a standardised way and will require some data gaps to be resolved (e.g. practitioner supply orders, community pharmacy trimethoprim sales).	⏫ Immediate
	(ii)	Develop and implement a platform to display human health antimicrobial usage data in both community and hospital settings (from individual prescriber to national level), and an equivalent for antimicrobial usage in animal and plant health. Make these platforms publicly accessible and ensure they are presented in a useful way.	⏫ Immediate
	(iii)	Implement the hospital National Antimicrobial Prescribing Survey (NAPS) in both public and private hospitals, with modification for local context. Require all hospitals to participate, and for the results to be published publicly by the national centre for AMS on the new platform described under **1(c)(ii)**.	⏫ Immediate
	(iv)	Evaluate other existing (and future) NAPS modules for applicability in other settings including aged residential care, veterinary care, and primary care. Aim to implement applicable modules with modification for the local context or make an alternative auditing system available if the NAPS modules are unsuitable.	🔼 2-3 years
	(v)	Introduce a requirement for inclusion of a meaningful indication within all antimicrobial prescriptions, as well as treatment durations or review or stop dates. This could be implemented through updated clinical care standards (see recommendation **1(a)(vii)**).	🔼 2-3 years
	(vi)	Implement mechanisms to provide prescriber benchmarking and feedback on both quality and quantity of antimicrobial prescribing, delivered through the national centre for AMS.	⏫ Immediate
	(vii)	Develop a system to enable collection of antimicrobial use data in animals and plants. This could be first implemented as sentinel surveillance at selected veterinary practices before being rolled out more widely.	⏫ Immediate
	(viii)	Develop a national centralised platform to collate data on antimicrobial use in animals and plants.	🔼 2-3 years

Recommendations			Timeframe
(d) Review funding, registration, and access to antimicrobials. *This recommendation builds on the themes in the following priority action area from the 2017 New Zealand AMR Action Plan:* • *Priority action area 14: Establish a programme of regularly monitoring the controls on antimicrobial veterinary medicines.* • *Priority action area 15: Review the controls (conditions of registration), labelling and advertising of antimicrobial-based trade name products to ensure they are fit for purpose.*	**(i)**	Review Pharmac antimicrobial restrictions in the community and ensure they align with DHB hospital restrictions and AMS principles.	⏫ Immediate
	(ii)	Review antimicrobial products and registered uses across both human health and veterinary sectors to ensure they align with AMS principles.	⏫ Immediate
	(iii)	Prioritise AMS under Pharmac's factors for consideration, including by actively seeking to fund drugs that align with AMS principles. This may involve subsidising antimicrobials that facilitate oral management of infections in the community in line with AMS principles.	⏫ Immediate
	(iv)	Establish a transparent national supply of rarely used antimicrobials for treating infections due to multidrug-resistant organisms in a timely manner, accessible to all DHBs (or equivalent).	⏫ Immediate
	(v)	Ban direct-to-consumer advertising of antimicrobial medicines.	⏫ Immediate
	(vi)	Investigate innovative approaches to promote AMS among those who prescribe, dispense and use antimicrobials, with a view to making the national approach to tackling AMR proactively AMS focused.	➖ 5 years

Theme 2: Develop an integrated surveillance and outbreak response system

Good surveillance will help us detect outbreaks early and respond quickly. Surveillance may be of specific microbes (including those that are drug-resistant), infections, or genes that encode resistance. Surveillance of antimicrobial medicines, which informs AMS, is addressed in theme 1.

Recommendations			Timeframe
(a) Establish an integrated surveillance system for microbes (including those that are drug-resistant), antimicrobial drugs, infections, and genes that encode resistance across human health, food production, animal health, and the environment. Surveillance of antimicrobial use is primarily addressed in theme 1. *This recommendation builds on the themes in the following priority action areas from the 2017 New Zealand AMR Action Plan:* • *Priority action area 3: Establish a coordinated national surveillance programme of AMR and antimicrobial use in humans, animals and agriculture.* • *Priority action area 4: Develop lists of priority organisms, key resistance genes and antimicrobials for national reporting.* • *Priority action 5: Implement national minimum standard for laboratory testing and reporting of antimicrobial susceptibility.* • *Priority action area 17: Ensure that there is sustainable investment in initiatives to minimise the impacts of AMR. This includes ongoing investment in surveillance, communication, stewardship and infection prevention and control.*	**(i)**	Ensure ESR is resourced to coordinate an integrated surveillance system and diagnostic laboratories are supported to contribute, including retaining culturing capability and boosting whole genome sequencing capability.	⏫ Immediate
	(ii)	Identify and track priority microbes, antimicrobial drugs, infections, and genes that encode resistance. Develop guidelines for adding and removing from these priority lists.	🔼 2-3 years
	(iii)	Standardise data systems across public and private human health diagnostic labs and veterinary diagnostic labs to facilitate efficient data sharing and the ability to compare data.	🔼 2-3 years
	(iv)	Implement simplified permission mechanisms for timelier data and isolate sharing between human health, animal health, and food production.	⏫ Immediate
	(v)	Publish regular reports on AMR threats in a timely manner. This should include reports on nationally standardised antimicrobial susceptibility testing to support AMS efforts such as the development of national guidance.	⏫ Immediate
	(vi)	Implement regular environmental reporting that includes surveying for priority and emerging microbes, drugs, and genes. This may begin with a comprehensive baseline survey, followed by regular wastewater testing at sentinel sites such as aged residential care, hospitals, ports, farms with animals and/or irrigation, water bodies used for recreation, and mahinga kai sites.	⏫ Immediate
	(vii)	Build on and expand existing patient screening systems for priority microbes, genes, infections, and diseases. Develop mechanisms to update screening requirements in a systematic way, based on new evidence.	⏫ Immediate
	(viii)	Connect the national surveillance system to global surveillance efforts such as the World Health Organization's (WHO's) Global AMR and Use and Surveillance System (GLASS).	⏫ Immediate

Recommendations			Timeframe
(b) Enhance outbreak responses.	**(i)**	Enhance existing protocols for responding to an outbreak of a disease or multidrug-resistant organism at both regional and national levels, including enhancing lab capability across the country. Ensure that responses incorporate infectious diseases, microbiology, predictive/risk-based modelling, public health, and infection prevention and control (IPC) expertise including, where relevant, animal health expertise. Boost field epidemiology expertise in public health units to support this.	⏫ Immediate
	(ii)	Develop and implement national guidelines for managing carbapenemase-producing Enterobacterales (CPE) in the community, including in aged-care facilities.	⏫ Immediate
	(iii)	Develop a decision tree or threshold at which MPI is required to implement a public health response in collaboration with the public health agency. This may be based on the Food and Agriculture Organization (FAO) risk communication guidelines and may also be supported by enhanced connections and agreed protocols with media.	⏫ Immediate
	(iv)	Investigate ways to improve and expand collection of data and risk factor information from patients presenting with food- and water-borne illnesses (and the wider public) to better support timely outbreak tracing. This may involve creating a FluTracking equivalent for food- and water-borne illnesses.	⏫ Immediate

Theme 3: Strengthen infection prevention and control

Preventing infections before they occur is the best way to tackle drug-resistant infections – and infectious diseases more broadly. With COVID-19 amplifying awareness of basic infection prevention and control (IPC) such as hand hygiene and ventilation, there is a significant opportunity to capitalise on this and to elevate IPC and embed it into our overall approach to health.

Recommendations			Timeframe
(a) Develop a coordinated national approach to IPC to provide overarching governance and leadership. *This recommendation builds on the themes in the following priority action area from the 2017 New Zealand AMR Action Plan:* • *Priority action area 16: Establish a sustainable national governance structure to coordinate all efforts to minimise antimicrobial resistance.*	**(i)**	Create stronger linkages between the human, animal, plant, and environmental health sectors, with relevant government agencies to enable multi-way knowledge sharing on IPC. This may involve stronger links between the restructured health localities (currently DHBs), the veterinary profession, and biosecurity.	⏫ Immediate
	(ii)	Formalise and provide ongoing support for NIPCEG to embed expert advice into policy making.	⏫ Immediate
	(iii)	Establish a national centre dedicated to IPC with responsibility for implementing the national IPC strategy.	⏫ Immediate
(b) Strengthen and expand standards related to IPC. *This recommendation builds on the themes in the following priority action area from the 2017 New Zealand AMR Action Plan:* • *Priority action area 7: Develop and update national guidelines and standards for IPC to achieve a nationally consistent approach, and enhance accreditation and quality assurance programmes so that more practitioners follow best-practice IPC measures across human health, animal health and agriculture.*	**(i)**	Strengthen and adapt existing facility design standards for hospitals, GP clinics, aged residential care, sheltered living, prisons, schools and early childhood education centres, tattoo parlours, beauty parlours, and other community settings to improve IPC.	⏫ 2-3 years
	(ii)	Maintain and develop (where appropriate) evidence-based standards related to cleaning and disinfection procedures for hospitals, GP clinics, aged residential care, sheltered living, prisons, schools and early childhood education centres, tattoo parlours, beauty parlours, and other community settings. Require regular audits to be undertaken by IPC experts to ensure standards are being met.	⏫ 2-3 years

Recommendations			Timeframe
(c) Build IPC capacity and expertise at all levels. Support implementation of IPC across the human, animal, plant, and environmental health systems, including but not limited to: primary care, aged residential care, public and private hospitals, dentistry, optometry, midwifery, biosecurity, pharmacy, and veterinary care. *This recommendation builds on the themes in the following priority action areas from the 2017 New Zealand AMR Action Plan:* • *Priority action area 8: Promote a cohesive and sustainable 'one team' approach to IPC functions in all human healthcare facilities.* • *Priority action area 10: Promote prevention and control of zoonotic infections.* • *Priority action area 11: Encourage alternative approaches to reduce infection and the need for antimicrobial use in animals.*	**(i)**	Establish leadership roles focused on infection prevention and control (and alongside AMS) at the director level of all DHBs (or equivalent).	⌃⌃ Immediate
	(ii)	Require all DHBs, private hospitals, and PHOs to report annually on their IPC goals, activities, and outcomes.	⌃ 2-3 years
	(iii)	Implement minimum FTE requirements for IPC at all hospitals (both public and private).	⌃ 2-3 years
	(iv)	Establish IPC nurse practitioner roles and develop associated training pathways.	⌃ 2-3 years
	(v)	Require each DHB (or equivalent) to establish a community IPC workforce to support IPC in a range of community settings and undertake audits as per recommendation **3(b)(ii)**.	⌃ 2-3 years
	(vi)	Set targets for equitably increasing the IPC workforce. Ensure this is resourced appropriately.	⌃⌃ Immediate
	(vii)	Develop an initiative to upskill primary care providers on IPC.	⌃⌃ Immediate
	(viii)	Support farmers to implement alternatives to antimicrobials, such as for dry cow therapy and treatment of necrotic enteritis in poultry.	⌃⌃ Immediate
	(ix)	Review the agricultural compounds and veterinary medicines registration system to allow expediting of antimicrobial alternatives that don't have food safety or residue issues, such as vaccines and probiotics, where international data supporting use of these alternatives exists.	⌃⌃ Immediate
	(x)	Review current animal husbandry practices and investigate ways these could be improved to reduce infection.	⌃⌃ Immediate
(d) Improve data governance: collection, quality and reporting.	**(i)**	Standardise national reporting for surgical site infections (SSIs).	⌃⌃ Immediate
	(ii)	Build on and expand existing point prevalence surveys and ensure these are carried out regularly.	⌃⌃ Immediate
	(iii)	Investigate options for rolling out a national standardised IPC surveillance and alert system, potentially using the ICNet system already employed by Canterbury DHB.	⌃ 2-3 years
	(iv)	Investigate new ways of collecting IPC data, such as phone apps for on-ward surveys.	⌃ 2-3 years

Recommendations			Timeframe
(e) Enhance vaccine use. *This recommendation builds on the themes in the following priority action areas from the 2017 New Zealand AMR Action Plan:* • *Priority action area 9: Encourage continued immunisation to prevent infections.* • *Priority action area 10: Promote prevention and control of zoonotic infections.* • *Priority action area 11: Encourage alternative approaches to reduce infection and the need for antimicrobial use in animals.*	**(i)**	Continue to develop and improve an ongoing, accessible, and culturally safe communication campaign to encourage vaccine uptake in human health, with a strong focus on equity and underserved people. The campaign should: • be evidence-based; • be based on behavioural science; • include evaluation (including through Indigenous frameworks); • be multi-pronged with a range of different media, including face-to-face communications; • be co-designed with Māori and Pacific peoples; • be available in multiple languages; and • build on and align with existing initiatives.	» Immediate
	(ii)	Support equity in immunisation and evaluate how equitable immunisation can be championed within the health reforms, including by identifying and removing barriers to access.	» Immediate
	(iii)	Make vaccines available for seasonal workers entering Aotearoa New Zealand in order to protect the incoming workers and people in Aotearoa New Zealand against infectious disease outbreaks.	» Immediate
	(iv)	Review the immunisation schedule as part of a wider infectious diseases strategy, in collaboration with existing initiatives.	» Immediate
	(v)	Prioritise the development/acquisition of a group A *Streptococcus* vaccine.	» Immediate
	(vi)	Develop an ongoing, accessible communications campaign to encourage wider use of vaccination in animals and develop best immunisation practice guidelines for vets. The communication campaign should: • be evidence-based; • be based on behavioural science; • include evaluation; and • be multi-pronged with a range of different media, including face-to-face communications.	» Immediate
	(vii)	Investigate barriers to vaccine use in animal husbandry and implement strategies to increase vaccine coverage. This may involve subsidising animal vaccines for zoonotic diseases.	» Immediate

Theme 4: Grow Aotearoa New Zealand's infectious diseases capability and engage internationally

Aotearoa New Zealand's ability to manage infectious disease and AMR threats relies heavily on the strength of our workforce of researchers and practitioners. Our research efforts can be optimised if they are joined up, including across the human, animal, plant, and environment interface, and with valuable inclusion of mātauranga Māori and international insights.

Recommendations			Timeframe
(a) Build on the newly announced Strategic Science Investment Fund to establish an inclusive infectious diseases network with diverse representation from academia and frontline practitioners, focused on both capacity building and research.	**(i)**	The Fund should harness both research excellence and operational aspects (e.g. outbreak response capacity). Clear links to policy and a focus on capability development should be embedded in its design.	^ 2-3 years
	(ii)	The network should adopt a holistic approach to infectious diseases with representation across human, animal, plant, and environmental health.	^ 2-3 years
	(iii)	Engage with iwi and Indigenous knowledge including mātauranga Māori.	^ 2-3 years
	(iv)	Ensure the network has strong connections and integration with policy makers.	^ 2-3 years
	(v)	Create a searchable database of people and their expertise to encourage collaboration.	^ 2-3 years
(b) Develop a national strategy for infectious diseases. This strategy may be led by the infectious diseases network. *This recommendation builds on the themes in the following priority action area from the 2017 New Zealand AMR Action Plan:* • *Priority action area 6: Support national priorities for research on AMR, antimicrobial consumption and stewardship in human health, animal health and agriculture.*	**(i)**	Ensure this strategy has a focus on equity.	^ 2-3 years
	(ii)	Ensure this strategy integrates with the *New Zealand AMR Action Plan*, as well as the associated workstreams in AMS and IPC.	^ 2-3 years
	(iii)	As part of the strategy, develop national research priorities for infectious diseases and AMR, and identify gaps in Aotearoa New Zealand's expertise.	^ 2-3 years
	(iv)	Include communications as part of the strategy.	^ 2-3 years
	(v)	Review the immunisation schedule as part of this strategy (see recommendation **3(e)(iv)**).	^ 2-3 years

Recommendations			Timeframe
(c) Build Aotearoa New Zealand's infectious diseases workforce.	**(i)**	Set targets and allocate resources for equitably increasing the infectious diseases workforce (including AMS, IPC, and medical laboratory scientists) across frontline health practitioners, academia, and government agencies. See also recommendations **1(b)(vi)** and **3(c)(vi)**.	^ 2-3 years
	(ii)	Investigate approaches to improving the availability of infectious diseases expertise to clinicians working in both hospitals and community settings in regional areas (outside main centres). This might include: • providing opportunities for physicians to undertake infectious diseases training in regions rather than only large centres; • requiring minimum FTE in infectious diseases across hospitals (considering roles for doctors, pharmacists, and nurses as appropriate); and/or • a formal advice system to ensure hospital and community clinicians in the regions can access infectious disease and microbiology expertise in a timely manner.	^^ Immediate
	(iii)	Enhance infectious diseases topics including AMS, AMR, and IPC into tertiary curricula for all health professions and ongoing professional development.	^^ Immediate
	(iv)	Establish scholarships and fellowship positions for tertiary education in the infectious diseases field, including both clinical and lab-based.	^^ Immediate
	(v)	Investigate ways of engaging rangatahi and tamariki in AMR and infectious disease conversations through hui and workshops, resources, and curricula at primary, intermediate, and secondary level.	^ 2-3 years
(d) Understand and remove barriers to quality improvement work and data sharing.	**(i)**	Streamline and standardise ethics requirements and processes for quality improvement work and enhance access to routinely collected data as a tool for quality improvement.	^^ Immediate
	(ii)	Ensure isolates and metadata can be shared in an ethical and efficient way.	^^ Immediate
	(iii)	Enable the Food Safety Science and Research Centre to conduct research for public health, including mātauranga Māori, that is not dependent on industry funding.	^^ Immediate

Recommendations			Timeframe
(e) Strengthen international connections. *This recommendation builds on the themes in the following priority action area from the 2017 New Zealand AMR Action Plan:* • *Priority action area 18: Establish the necessary national and international links and collaborations to implement the AMR Action Plan effectively.*	**(i)**	Support two-way knowledge sharing between Aotearoa New Zealand and the Pacific to lift capability across the region.	⏫ Immediate
	(ii)	Support researchers, practitioners and policy makers to connect and engage internationally to inform best practice.	⏫ Immediate
(f) Evaluate Aotearoa New Zealand's biomedical manufacturing infrastructure needs.	**(i)**	Investigate the costs and benefits of developing onshore capability to manufacture biomedical products under an emerging scenario of a globally distributed model (e.g. to manufacture mRNA vaccines under license for local use).	^ 2-3 years

Theme 5: Enhance health literacy

Health literacy, defined by New Zealand's MoH as "the capacity to obtain, process and understand basic health information and services in order to make informed and appropriate health decisions", is everyone's responsibility, including human and animal healthcare providers and practitioners.

Recommendations		Timeframe
(a) Strengthen communications: human health. *This recommendation builds on the themes in the following priority action areas from the 2017 New Zealand Antimicrobial Resistance Action Plan:* • *Priority action area 1: Strengthen consumer awareness to improve understanding of antimicrobial resistance and the importance of using antibiotics appropriately.* • *Priority action area 2: Strengthen communication and education initiatives on antimicrobial resistance and stewardship for all prescribers, and those working in the human health, animal health and agricultural sectors.*	**(i)** Enhance and expand ongoing, accessible, and culturally safe communications campaigns aimed at: • healthcare workers including prescribers, pharmacists, and nurses; • patients and the public; and • aged residential carers. Among other things, these campaigns should consider focussing on: • AMR; • antimicrobial use including topical antimicrobials and managing patient expectations around antibiotic use; • important infections such as sepsis, STIs, and rheumatic fever; and • IPC measures such as vaccines (see also **3(e)(ii)**) and safe food handling. The communications plans should be: • equity-focused; • evidence-based; • based on behavioural science; • evaluated (including through Indigenous frameworks); • multi-pronged with a range of different media, including face-to-face communications; • co-designed with Māori and Pacific peoples; • available in multiple languages; and • coordinated and aligned to animal health and agriculture initiatives (where relevant) to ensure consistent messaging.	⏫ Immediate

Recommendations			Timeframe
	(ii)	Develop accessible and culturally safe tools to help health professionals discuss prescribing decisions with patients in a shared decision-making model. These tools could be developed and embedded as part of national antimicrobial prescribing guidelines so that messaging aligns.	^ 2-3 years
	(iii)	Increase support for primary, intermediate, and secondary school teachers to access resources on AMR and infectious diseases for teaching science, and to utilise them in integrated, student-centred pedagogies. This may involve developing curriculum components for primary, intermediate, and secondary school. See also recommendation **3(c)(iv)**.	^ 2-3 years
	(iv)	Trial a public-facing, timely risk communication tool for infection risk associated with food and water. This may build on the industry Environmental Risk Information Services (ERIS) platform.	^^ Immediate
(b) Strengthen communications: Animal health and agriculture. *This recommendation builds on the themes in the following priority action areas from the 2017 New Zealand AMR Action Plan:* • *Priority action area 1: Strengthen consumer awareness to improve understanding of AMR and the importance of using antibiotics appropriately.* • *Priority action area 2: Strengthen communication and education initiatives on AMR and stewardship for all prescribers, and those working in the human health, animal health and agricultural sectors.*	**(v)**	Strengthen existing communications campaigns aimed at vets on AMR, antimicrobial use, vaccines, and IPC, and expand to new audiences including farmers and pet owners. Ensure there is coordination and alignment with human health initiatives for consistent messaging.	^^ Immediate

Theme 6: Reimagine primary care

The health reforms offer an opportunity to reimagine how we deliver primary care in Aotearoa New Zealand through an AMS lens, aiming to achieve better outcomes for our people when it comes to infectious diseases. This may involve incorporating some primary healthcare into a national service. Some of the recommendations in this theme are also relevant to hospital and specialist services, but here we focus on primary care, as that is where the majority of health interactions occur, and where most of our antimicrobial use sits.

Recommendations			Timeframe
(a) Enhance equity and remove barriers to accessing healthcare and appropriate antimicrobial therapies.	**(i)**	Investigate and implement mechanisms to make transport to healthcare more accessible.	⌃⌃ Immediate
	(ii)	Encourage and facilitate more virtual consultations to make healthcare more accessible, building on experience gained through the COVID-19 pandemic.	⌃⌃ Immediate
	(iii)	Increase mobile clinics and school-based clinics, with a focus on equity and reaching underserved communities.	⌃⌃ Immediate
	(iv)	Investigate mechanisms for removing financial barriers to prescription antimicrobials. These may include: • removing the $5 co-payment for people with a community services card; • lowering the threshold for the prescription subsidy scheme; • implementing a programme for Māori and Pacific peoples similar to the Closing the Gap programme under Australia's Pharmaceutical Benefits Scheme; and/or • extending the age limit for free prescriptions to people 25 and under.	⌃ 2-3 years
(b) Rethink prescriptions.	**(i)**	Investigate making delayed antimicrobial prescriptions with clear criteria standard practice and integrate advice on this into antimicrobial prescribing guidance (see recommendation **1(a)(vi)**). Evaluate the best approach for doing this including providing specific dates within the prescription between which the antimicrobial can be collected.	⌃ 2-3 years

Recommendations			Timeframe
	(ii)	Require the prescriber to include a meaningful indication for antimicrobial use within the prescription. Evaluate approaches to standardising this using a set of indication codes.	^ 2-3 years
	(iii)	Support embedding AMS pharmacists within hospitals and the community (e.g. PHOs, GP clinics) to improve prescribing practices.	^ 2-3 years
	(iv)	Make prescriber benchmarking or feedback standard practice in hospitals and in the community and investigate how this can be displayed on dashboards or through the patient management software. See also recommendation **1(c)**.	^ 2-3 years

1.5 Project outputs

This project has culminated in three major outputs: a full report targeted at policy officials (this document), a short report designed for senior decision makers and officials, and a report on rheumatic fever designed for policy officials. These are all available on the OPMCSA website.

1.5.1 Structure of this report

Part one: Introduction

This section introduces the motivation for this project and the expert panel who have guided *Kotahitanga: Uniting Aotearoa against infectious disease and antimicrobial resistance*. This part also lays out the recommendations of the panel.

Part two: Background and global context

Part two describes what AMR is, how it arises, the global scale of the problem, and existing initiatives and reports. It places AMR in the broader context of the infectious diseases landscape. It also introduces the concept of kotahitanga – unity or togetherness – as a way to approach the challenge of AMR and infectious disease in Aotearoa New Zealand. Like One Health, an appeal to kotahitanga calls for unity against the growing threat of AMR and infectious disease across human, animal, plant, and environmental health, and also emphasises the importance of striving for equity in health outcomes across our diverse communities.

Part three: Infectious diseases in Aotearoa New Zealand

Part three explores the infectious diseases landscape in Aotearoa New Zealand. It is included because the problem of AMR doesn't exist in isolation: AMR, and action taken to address it, occurs in the wider context of infectious diseases. This section begins by describing how the country's context – particularly its physical isolation, agriculture-based economy, strict biosecurity practices, and connections with the Pacific – contribute to a unique infectious diseases riskscape. It looks at how infectious diseases can impact humans as well as animals and plants with economic and cultural importance. This section shines a light on the inequity in the impacts of infectious diseases, with Māori and Pacific peoples disproportionately affected, as well as remote, rural, and materially deprived communities and individuals.

Part four: Drug-resistant infections in Aotearoa New Zealand

Part four looks at the types of resistant organisms present in Aotearoa New Zealand, as well as their prevalence and trajectory. It covers AMR organisms in humans, animals, plants, and the environment. Evidence affirms that AMR organisms are present in the country, but surveillance is patchy and opportunistic, especially for plants and the environment but also for animals and humans. Case studies are included to highlight the human health challenges posed by AMR organisms. This section also looks at antimicrobial use across humans, animals, and plants, and environmental contamination from these uses. Again, data is patchy, a situation largely resulting from lack of oversight of antimicrobial prescription and use.

Part five: Prevention and solutions

Part five explores solutions that could be deployed to reduce the burden posed by AMR and infectious disease in Aotearoa New Zealand. Solutions are grouped by theme, focusing on prevention, detection, treatment, and people and capability. Some of the solutions described are being used overseas: we could draw inspiration from other countries' approaches to the global challenge of AMR. Some solutions are already being used in Aotearoa New Zealand, often in isolated situations or as pilot programmes: these could be resourced and rolled out more widely to achieve heightened impact.

2 Part two: Background and global context

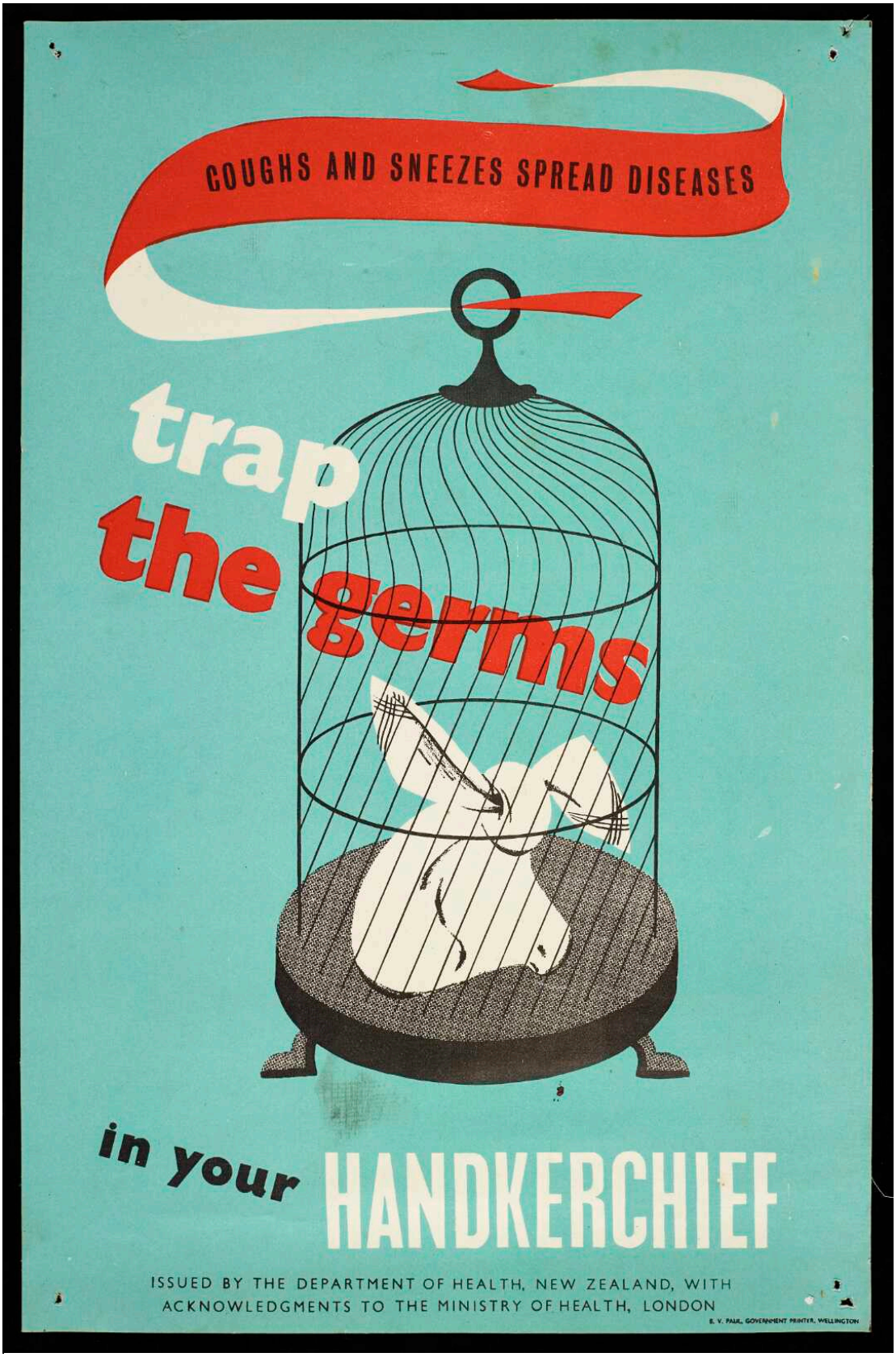

Figure 2: A New Zealand government Department of Health poster from the 1940s. Image credit: New Zealand Department of Health / Alexander Turnbull Library Ref: Eph-C-HEALTH-NZDH-1940s-01.

2.1 Key messages

- The age of infectious disease is far from behind us, even as the health burden posed by non-communicable diseases like diabetes and heart disease grows. The 17 million people estimated to have been killed by COVID-19 as of October 2021 join the roughly eight million people who are killed by other infectious diseases around the world each year.

- In addition, microbes are evolving to resist the effects of the antimicrobial drugs designed to kill or control them, making it harder to treat and prevent infections – a phenomenon known as AMR. Each year, approximately 700,000 people around the world die as the result of an infection caused by a drug-resistant pathogen, a toll that is predicted to reach 10 million by 2050.

- AMR primarily results from the use – especially overuse and inappropriate use – of antimicrobial drugs. Every time microbes are exposed to antimicrobials, only those that survive go on to reproduce, leading to the proliferation of resistant microbes. Resistance genes can also spread horizontally between bacteria.

- AMR has been observed in humans, plants, and animals, having impacts on human health, animal welfare, and agricultural productivity. Antimicrobial drugs, microbes, and genes can move between the human, animal, and plant worlds, and the wider environment. Tackling AMR requires kotahitanga – unity, togetherness – across these sectors.

- AMR has received increasing international attention in the last decade, including with the creation of an international action plan which prompted Aotearoa New Zealand to develop an AMR action plan of our own in 2017. Very little progress has been made on implementing our domestic AMR action plan.

- The challenge of combatting infectious diseases and AMR intersects with other global issues including demographic change, COVID-19, and climate change. Tackling infectious disease and AMR in Aotearoa New Zealand requires a multidisciplinary approach that is connected to international efforts.

2.2 A brief history of infectious disease and antimicrobial resistance

2.2.1 Infectious disease shaped our past and influences our present

Infectious diseases have been a feature of life and death throughout history. In 1800, the global life expectancy was around 30 years.[11] The first vaccine, for smallpox, had just been introduced in 1796.[12] Plague epidemics (caused by the bacterium *Yersinia pestis*) that had ravaged the Eurasian continent over the previous centuries were largely under control, thanks to public health measures such as quarantine, cordons sanitaire and contact tracing (first developed during the Renaissance).[13]

However, people were still at major risk of perishing from an infection, or for some survivors, suffering lingering and debilitating effects. Up to half of all deaths in England in the 1800s were attributable to infectious diseases, with people dying from conditions including tuberculosis (TB), bronchitis, scarlet fever, and diarrhoea.[14]

Increasing urbanisation in Europe led to large numbers of people living in cramped and unsanitary conditions, ripe for the spread of infectious diseases. Meanwhile growing inter-regional and international travel transitioned periodic epidemic waves to persistent outbreaks of infectious disease.[15]

Globalisation and colonial military campaigns introduced new pathogens to susceptible populations of Indigenous peoples, including Māori. Very few infectious diseases were present in Aotearoa New Zealand before European contact in 1769 – with the possible exception of TB (although if present, this was likely to be a less pathogenic strain) and leprosy (or a similar affliction, known to Māori as 'ngerengere' or 'tūhawaiki').[16]

From 1769, colonisers brought smallpox, measles, whooping cough, influenza, dysentery, STIs, and TB to the shores of Aotearoa New Zealand. Epidemics of flu-like illnesses swept through the Tāmaki isthmus (present-day Tāmaki Makaurau Auckland) in 1790 and 1810, while on Rēkohu Wharekauri (the Chatham Islands), Moriori suffered a severe measles outbreak in 1791. There were isolated occurrences of smallpox but no major outbreaks.

Infectious diseases, combined with land loss, social and cultural upheaval, and warfare devastated Māori. The total population contracted by two-thirds between 1840 and 1900. In 1881, the average Māori life expectancy was estimated to be just 18 years, compared to 53 years for non-Māori males and 56 years for non-Māori females.[17] In fact, between 1870 and 1940, non-Māori New Zealanders had the highest life expectancy in the world,[18] attributed to a lack of crowding, mild climate, lower infant and child mortality, and the 'healthy migrant' theory – only the fittest embarked on and survived the arduous journey to the opposite side of the world.

From 1918 to 1919, the world experienced the most severe pandemic in recent history, caused by an influenza virus that jumped from birds to humans. The pandemic resulted in an estimated 500

[11] Riley, J.C. (2005). Estimates of regional and global life expectancy, 1800-2001. *Population and Development Review, 31*(3), 537-543.
[12] Stewart, A.J., & Devlin, P.M. (2006). The history of the smallpox vaccine. *Journal of Infection, 52*(5), 329-334. https://doi.org/10.1016/j.jinf.2005.07.021
[13] Shaw-Taylor, L. (2020). An introduction to the history of infectious diseases, epidemics and the early phases of the long-run decline in mortality. *The Economic history review, 73*(3), E1-E19. https://doi.org/10.1111/ehr.13019
[14] Ibid.
[15] Ibid.
[16] Woodward, A., & Blakely, T. (2015). *The healthy country? A history of life and death in New Zealand*. Auckland, New Zealand: Auckland University Press.
[17] Ibid.
[18] Oeppen, J., & Vaupel, J.W. (2002). Broken limits to life expectancy. *Science, 296*(5570), 1029. https://doi.org/10.1126/science.1069675

million infections and 50 million deaths worldwide,[19] a death toll exceeding that of World War I. In Aotearoa New Zealand, the pandemic influenza virus caused an outbreak that lasted two months at the end of 1918, killing 9,000 people (compared to 18,000 New Zealand soldiers killed in the four years of World War I). The death toll for Māori was roughly eight times higher than that of Europeans.[20] The *Tulane* steamship travelled from Aotearoa New Zealand to Samoa in 1918, which at the time was under New Zealand administration. Sick passengers disembarked at the port in Apia, seeding pandemic influenza in Samoa, which killed one-fifth of the Samoan population.[21]

Since the 1918 influenza pandemic, new infectious diseases have continued to emerge – predominantly from the animal world – and evidence suggests the frequency of emergence is increasing.[22] For example, human immunodeficiency virus (HIV), various influenza strains, Ebola virus, West Nile virus, and Zika virus all jumped from animal hosts to humans in the 1900s. This century, three novel coronavirus diseases – SARS, MERS, and COVID-19 – have sparked outbreaks around the world.[23] While novel infectious diseases haven't always reached Aotearoa New Zealand's shores, COVID-19 reminds us that the next one has scope to impact us regardless of where it emerges.

In Aotearoa New Zealand's recent history of infectious diseases (besides the ongoing COVID-19 pandemic) we have faced outbreaks of measles[24] and meningococcal disease.[25] As with the 1918 flu, travellers from Aotearoa New Zealand seeded measles cases in the Pacific in 2019, both in Samoa[26] and Tonga (for more details see section 3.3.3).[27]

2.2.2 The era of antimicrobial discovery

Humans have been treating infections since prehistory, including use of materials with antimicrobial properties such as herbs, honey, and even topical applications of mouldy bread.[28] In Aotearoa New Zealand, rongoā Māori (the traditional Māori healing system) involves a variety of plants (e.g. kawakawa, mānuka) and other natural resources as medicine, including to treat infectious diseases.[29]

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[19] Piret, J., & Boivin, G. (2021). Pandemics Throughout History. *Frontiers in Microbiology, 11*(3594). https://doi.org/10.3389/fmicb.2020.631736

[20] Ministry for Culture and Heritage. (2020, 22 April). The 1918 influenza pandemic. Retrieved 24 November, 2021, from https://nzhistory.govt.nz/culture/influenza-pandemic-1918

[21] Ministry for Culture and Heritage. (2020, 22 April). Influenza hits Samoa. Retrieved 24 November, 2021, from https://nzhistory.govt.nz/media/photo/influenza-pandemic-hits-samoa

[22] Jones, K.E., Patel, N.G., Levy, M.A., *et al.* (2008). Global trends in emerging infectious diseases. *Nature, 451*(7181), 990-993. https://doi.org/10.1038/nature06536

[23] United Nations Environment Programme, & International Livestock Research Institute. (2020). *Preventing the next pandemic: Zoonotic diseases and how to break the chain of transmission.* Nairobi, Kenya: Retrieved from https://www.cbd.int/doc/c/084c/e8fd/84ca7fe0e19e69967bb9fb73/unep-sa-sbstta-sbi-02-en.pdf

[24] Turner, N. (2019). A measles epidemic in New Zealand: Why did this occur and how can we prevent it occurring again? *The New Zealand Medical Journal, 132*(1504), 8-12.

[25] Wong, S., & Reid, S. (2019). *Group B meningococcal disease in New Zealand: Epidemiology and prevention*. Retrieved from https://www.researchreview.co.nz/getmedia/6c247559-19f8-45ca-bf0e-4ac3fed38cdb/Educational-Series-Group-B-Meningococcal-Disease-in-NZ.pdf.aspx?ext=.pdf

[26] Government of Samoa. (2020, 20 January). *Health Emergency Operation Centre: Update on the measles outbreak, January 20, 2020* [Press release]. Retrieved from https://reliefweb.int/report/samoa/health-emergency-operation-centre-update-measles-outbreak-january-20-2020

[27] Government of Tonga. (2020). *Tonga measles outbreak 2019-20 - Situation report #18*. Retrieved from https://reliefweb.int/report/tonga/tonga-measles-outbreak-2019-20-situation-report-18

[28] Gould, K. (2016). Antibiotics: from prehistory to the present day. *Journal of Antimicrobial Chemotherapy, 71*(3), 572-575. https://doi.org/10.1093/jac/dkv484

[29] Science Learning Hub – Pokapū Akoranga Pūtaiao. (2018, 21 November). Rongoā Māori. Retrieved 4 August, 2021, from https://www.sciencelearn.org.nz/resources/185-rongoa-maori; Te Papa Tongarewa – Museum of New Zealand. (n.d.). Māori medicine: Rongoā Māori. Retrieved 4 August, 2021, from https://www.tepapa.govt.nz/discover-collections/read-watch-play/maori/maori-medicine; bpac nz. (2008). Demystifying Rongoā Māori: Traditional Māori healing. *Best Practice Journal, 13*, 32-36.

Antimicrobials: Key terms

Biocides are substances that destroy living things. Types of biocides include pesticides (to kill or control animal pests), herbicides (to kill or control weeds), and antimicrobials (to kill or control microbes).

Antimicrobials kill or suppress the growth of microbes and are often used to prevent and treat infections in humans, animals, and plants. There are four main types of antimicrobials: antibiotics (for bacteria), antivirals (for viruses), antifungals (for fungi), and antiparasitics (for parasites).

Antibiotics, being specific for bacteria, are not effective against viruses such as those that cause the common cold, nor do they work against fungi or parasites. Antibiotics work by either killing bacteria (**bactericidal**) or suppressing bacterial growth (**bacteriostatic**).

Antimicrobial agents include **physical agents** (e.g. radiation) and **chemical compounds**. Chemical antimicrobials are most often derived from a living organism with or without modification (**semi-synthetic** or **natural** antimicrobials, respectively). Only a few antimicrobial drugs are wholly man-made (**synthetic**).

See appendix 7.2 for definitions and explanations of different types of microbes.

Antibiotics

During the late 1800s, German physician and scientist Paul Ehrlich began to systematically search for a chemical agent that would selectively kill bacteria, leaving humans unharmed. His search came to fruition in 1907 with the synthesis of arsenic-containing organic molecule arsphenamine, which had activity against the causative agent of syphilis (*Treponema pallidum)*. The drug became the first modern antimicrobial when it went to market in 1910 as Salvarsan. However, it was unstable, difficult to administer and had severe side effects – in some cases, death. Concerns around side effects including nausea and vomiting also applied for Neosalvarsan, a more water-soluble and less toxic alternative that was available from 1912.[30]

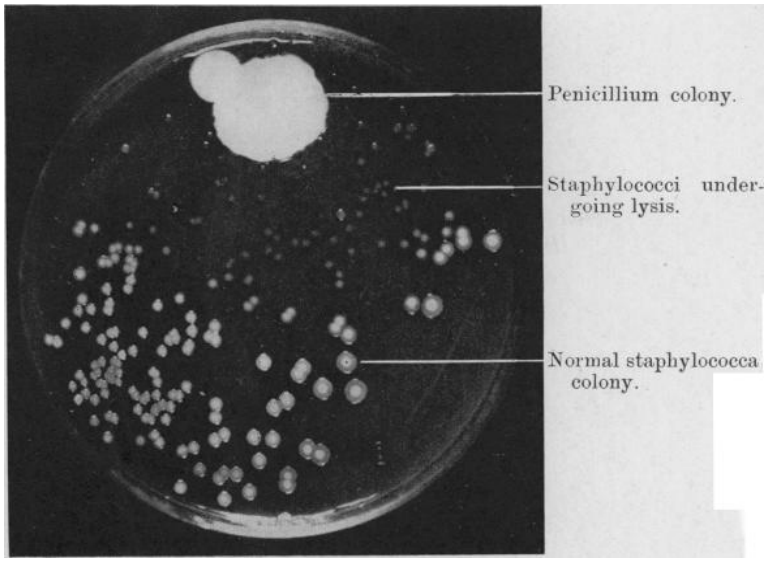

Figure 3: Alexander Fleming's plate with *Penicillium* mould growing at the top, an area of inhibited bacterial growth around the spot of mould, and normal bacterial colonies growing at the bottom of the plate.[31]

[30] Craig, C.B., & Collins, J. (1914). Four years' experience with salvarsan and neosalvarsan in the treatment of nervous disease due to syphilis. *Journal of the American Medical Association, LXII*(25), 1955-1963. https://doi.org/10.1001/jama.1914.02560500025005

[31] Fleming, A. (1929). On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzæ*. *British Journal of Experimental Pathology, 10*(3), 226-236.

In 1928, Scottish physician and microbiologist Alexander Fleming returned from holiday to find an odd pattern on one of his petri dishes: a fungus had contaminated one plate, and no bacteria were growing around the edges of the invading mould.[32] He isolated the mould and identified it as a member of the *Penicillium* genus. Fleming found that an extract of the *Penicillium* could restrict the growth of gram-positive bacteria. He named the active component 'penicillin' and published his findings in 1929.[33] However, Fleming was unable to isolate and purify penicillin.

In the meantime, German bacteriologist Gerhard Domagk discovered that a derivative of an oil dye, dubbed Prontosil, could kill bacteria when administered to animals (or his own child), but not in a test tube. In 1935, French scientists discovered that this was because Prontosil itself was not an antibiotic but was metabolised into the active compound sulfanilamide in the body. By the early 1940s, sulfanilamide and several derivatives were available on the market.[34]

By 1939, Howard Florey's group at the University of Oxford succeeded in extracting and purifying penicillin from cultures of *Penicillium* mould and demonstrated the drug's antibiotic effect in mice. By 1941, they had purified sufficient quantities to test in a human patient. On a nearby septic ward, a 43-year-old police officer was suffering from a severe infection; abscesses had developed on his face and in his lungs. This life-threatening septicaemia arose from a small sore on his lip sustained about four months prior. The police officer was injected with penicillin for five days and his condition improved, but the supply of penicillin was limited. Despite stretching the available medicine by collecting the patient's urine and purifying excreted penicillin for reuse, the supply was soon exhausted. The patient relapsed and died a month later.[35]

… scientists had witnessed the **striking temporary recovery brought about by penicillin**. Now, the challenge was to scale up production.

Nonetheless, the scientists had witnessed the striking temporary recovery brought about by penicillin. Now, the challenge was to scale up production. With World War II raging on Britain's doorstep, Florey turned to the US for assistance.

In the US, the principal mycologist at the US Department of Agriculture identified Fleming's *Penicillium* as *P. notatum*. The strain couldn't efficiently produce large amounts of penicillin, so a search for other strains began. The best strain, *P. chrysogenum,* was isolated from a mouldy rock melon from a fruit market near the lab. It produced six times more penicillin than Fleming's strain.

By the end of 1943, US scientists had optimised penicillin production via fermentation and could produce enough for the Allied Armed Forces. Thus began the 'golden age' of antibiotic discovery. Further naturally occurring antimicrobials, streptomycin and cephalosporins, were isolated from soil microbes in the 1940s, and by the mid-1950s, most of the major antibiotic families that we know today had been discovered (see Figure 5 for an overview of the different classes of antibiotics).[36]

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[32] Gaynes, R. (2017). The discovery of penicillin—New insights after more than 75 years of clinical use. *Emerging Infectious Diseases, 23*(5), 849-853. https://doi.org/10.3201/eid2305.161556

[33] Fleming, A. (1929). On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzæ*. *British Journal of Experimental Pathology, 10*(3), 226-236.

[34] Bentley, R. (2009). Different roads to discovery; Prontosil (hence sulfa drugs) and penicillin (hence β-lactams). *Journal of Industrial Microbiology and Biotechnology, 36*(6), 775-786. https://doi.org/10.1007/s10295-009-0553-8

[35] Fletcher, C. (1984). First clinical use of penicillin. *British Medical Journal (Clinical Research Edition), 289*(6460), 1721-1723. https://doi.org/10.1136/bmj.289.6460.1721

[36] Fong, I.W. (2018). Introduction: Coordinated global action is needed to combat antimicrobial resistance. In Fong, Shlaes and Drlica (Eds.), *Antimicrobial Resistance in the 21st Century* (pp. 1-10). Cham: Springer International Publishing.

While earlier gains in life expectancy in the 20th century likely came from rising living standards and improvements in hygiene, from 1950 onwards it was the power of medicine that propelled human longevity: primarily, antibiotics and mass vaccination campaigns (for more on vaccines, see section 5.3.2).

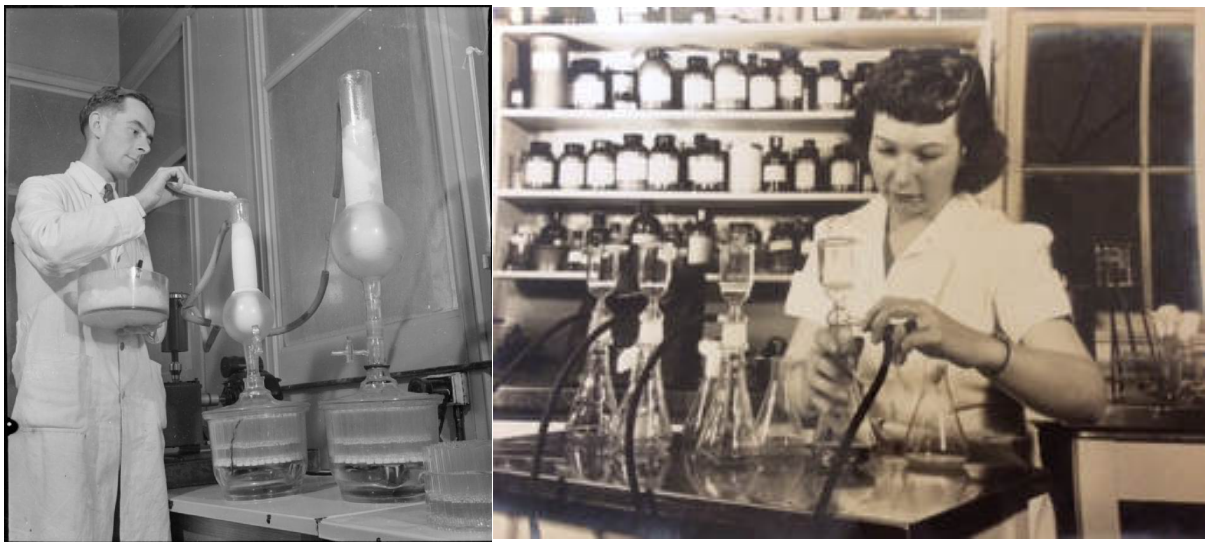

Figure 4: Left – A technician preparing penicillin in 1943. Right – Elizabeth Bugie Gregory, the biochemist who identified the antibiotic streptomycin, works in the lab. Image credit: Eileen Gregory/Scientista.

Antivirals

The success of the first antibiotics such as the sulphonamides led to them being tried against viral infections, without success. Given that viruses cause infection by invading human cells and using their machinery to replicate, it became a matter of dogma that there could be no antiviral that wouldn't harm the patient.[37] This was overturned by the discovery of interferons in the late 1950s and the development of the first nucleoside analogue, idoxyuridine, at the end of that decade.

Nucleoside analogues were initially developed to treat cancer, where they worked by disrupting DNA synthesis in rapidly dividing cancerous cells while causing less damage to more slowly dividing 'normal' cells. The transferability of this mechanism was quickly realised, and the drugs successfully tried against viral infections. Acyclovir is among the best known, still widely used to treat herpes. Molnupiarivir, the first oral antiviral to get emergency approval to treat COVID-19, is also a nucleoside analogue.

Receptor binding inhibitors, a class of antivirals that prevents binding of the virus to the host cell, were an early success in the quest to design specific molecules by understanding the 3D shapes of receptor interactions ('rational design'). This approach was used to design and synthesise a molecule to prevent interaction between the protein neuraminidase (found on the surface of influenza) and the host cell surface. The resulting treatment, zanamivir, suffered from being poorly bioavailable but a related molecule, osetamivir, is orally available and promoted as a treatment for pandemic influenza.

Nucleoside analogues can pose issues of toxicity, and both nucleoside analogues and receptor binding inhibitors are subject to issues of developing viral resistance. Looking for a solution to these problems, driven by the difficulties in treating HIV, led to the development of protease inhibitors. The assembly of the replicating virus particles within the host cell often requires an enzyme to

[37] Field, H.J., & De Clercq, E. (2004). Antiviral drugs – a short history of their discovery and development. *Microbiology Today, 31*, 58-61.

modify the viral proteins which is encoded in the viral genome. Inhibiting these enzymes can prevent viral assembly without affecting host-encoded protease enzymes essential for cell function. Four protease inhibitors are now in use against HIV: saquinavir, ritonavir, indinavir, and nelfinaivir.[38] A protease inhibitor, paxlovid, is currently being considered for use against COVID-19.[39]

Antifungals

Fewer antifungal compounds have been developed than antibiotics. This is partly because of the lower incidence of fungal infection and partly because fungal cells are more similar to human and animal cells, so there are fewer targets that would not lead to toxicity.

The main structural differences between fungal cells and human and animal cells are the fungal cell wall and membrane, making these structures the most attractive targets for antifungal drugs. The fungal cell wall is composed mainly of carbohydrates. The membrane beneath it contains ergosterol, a lipid related to cholesterol, that is essential for membrane flexibility and fluidity.

The first broad spectrum antifungal compounds to reach market were the polyenes, such as amphotericin B, which bind to ergosterol as their main mechanism of action. Over 200 different polyenes have been developed and are still widely used.

Azoles were discovered in the 1940s, but the first drug was not developed until 1958, with the introduction of chlormidazole.[40] Azoles block enzymes in the synthetic pathway of ergosterol. Allylamines, such as terbinafine – discovered in 1986 and approved by the US Food and Drug Administration (FDA) in 1996 – also inhibit the synthesis of ergosterol.[41]

Other classes of antifungals, including the echinocandins and polyoxins inhibit the synthesis of the cell wall itself. 5-Flucytosine was first synthesised in 1957 and in 1964 it was discovered that it was an antifungal, inhibiting DNA synthesis.[42]

Antiparasitics

Developing drugs for parasites is complicated by a number of factors: the wide range of parasites; the fact that they have similar cell structures as humans and animals; and the different life stages they may go through, including cysts which can resist drug entry.

Parasites are typically divided into ectoparasites (external parasites such as mites, ticks, and fleas) and endoparasites (internal parasites such as worms and protozoa). Ectoparasites are unpleasant, and may slow growth in animals, but are generally not life threatening, although they can pass on endoparasites or other pathogens. Endoparasites cause serious diseases in humans including Chagas disease, elephantiasis, river blindness, and malaria.

Antiparasitic compounds are widely used for production and companion animals. The global market size for animal antiparasitics is around US$7.5 billion per year,[43] slightly larger than the human

[38] Patick, A.K., & Potts, K.E. (1998). Protease inhibitors as antiviral agents. *Clinical Microbiology Reviews, 11*(4), 614-627. https://doi.org/10.1128/CMR.11.4.614
[39] Couzin-Frankel, J. (2021). Pfizer antiviral slashes COVID-19 hospitalizations. *Science, 374*(6569). Retrieved from https://www.science.org/content/article/pfizer-antiviral-slashes-covid-19-hospitalizations
[40] Shafiei, M., Peyton, L., Hashemzadeh, M.*, et al.* (2020). History of the development of antifungal azoles: A review on structures, SAR, and mechanism of action. *Bioorganic Chemistry, 104*, 104240. https://doi.org/10.1016/j.bioorg.2020.104240
[41] Abdel-Kader, M.S., & Muharram, M.M. (2017). New microbial source of the antifungal allylamine "Terbinafine". *Saudi Pharmaceutical Journal, 25*(3), 440-442. https://doi.org/10.1016/j.jsps.2016.06.006
[42] Scorzoni, L., de Paula e Silva, A.C.A., Marcos, C.M.*, et al.* (2017). Antifungal therapy: New advances in the understanding and treatment of mycosis. *Frontiers in Microbiology, 8*(36). https://doi.org/10.3389/fmicb.2017.00036
[43] Selzer, P.M., & Epe, C. (2021). Antiparasitics in animal health: Quo vadis? *Trends in Parasitology, 37*(1), 77-89. https://doi.org/10.1016/j.pt.2020.09.004

health market.[44] This represents around 23% of the animal drugs market against 0.5% of the human drugs market.

Most of the classes of antiparasitic compounds are more than 20 years old, with the exception of the isoxazolines (systemic insecticides used largely in the companion animal market but proposed for human use)[45] which first came to market in 2014.

Ivermectin, the first antiparasitic to show strong activity against both ecto- and endoparasites was first isolated from a soil organism in Japan in the late 1970s and commercialised for use in animals in 1981. It is effective against a wide range of parasites, including roundworms, lungworms, mites, ticks, lice, and hornflies.[46] It was first used in humans in 1988 to treat river blindness and is still widely used – although it has not been shown to be effective against COVID-19.[47]

[44] Coherent Market Insights. (2020). *Antiparasitic drugs market analysis*. Retrieved from https://www.coherentmarketinsights.com/market-insight/antiparasitic-drugs-market-3782

[45] Miglianico, M., Eldering, M., Slater, H.*, et al.* (2018). Repurposing isoxazoline veterinary drugs for control of vector-borne human diseases. *Proceedings of the National Academy of Sciences, 115*(29), E6920. https://doi.org/10.1073/pnas.1801338115

[46] Crump, A., & Omura, S. (2011). Ivermectin, 'wonder drug' from Japan: The human use perspective. *Proceedings of the Japan Academy, Series B, 87*(2), 13-28. https://doi.org/10.2183/pjab.87.13

[47] Popp, M., Stegemann, M., Metzendorf, M.I.*, et al.* (2021). Ivermectin for preventing and treating COVID-19. *Cochrane Database of Systematic Reviews, 7*. https://doi.org/10.1002/14651858.CD015017.pub2

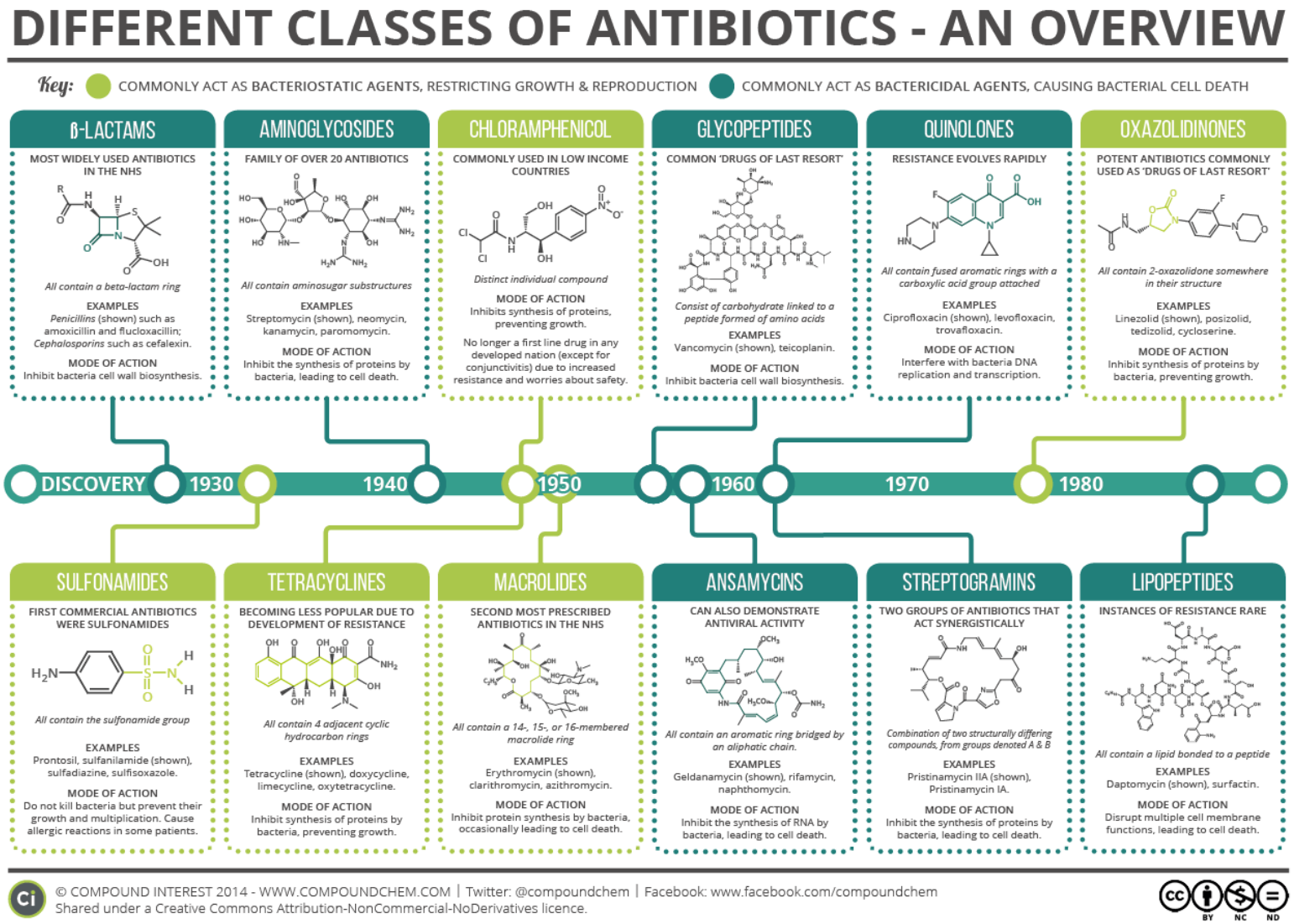

Figure 5: Infographic showing the different types of antibiotics. Only some of these are in widespread use in Aotearoa New Zealand. See appendix 7.3 for WHO's list of critical antimicrobials with Aotearoa New Zealand-specific commentary.

2.2.3 Emerging resistance and slowing discovery

By 1944, just three years after penicillin was used in humans, strains of *Staphylococcus aureus* with the ability to resist the effects of penicillin were detected. These resistant strains expressed an enzyme called penicillinase, which is able to break down penicillin.[48]

The 'H bug' epidemic in Aotearoa New Zealand 1955–1963

In November 1955, eight babies born at the same maternity hospital in Ōtautahi Christchurch died as a result of pneumonia caused by a strain of penicillin-resistant *S. aureus.* This was the beginning of the 'Hospital bug' (or 'H bug') epidemic, with multiple outbreaks of penicillin-resistant staphylococcal infection afflicting mostly babies, new mothers, and surgical patients across Aotearoa New Zealand. Babies developed skin lesions and serious respiratory infections while breastfeeding women developed mastitis (inflammation of breast tissue), breast abscesses, and infections of the genital tract.

Health officials promoted a range of non-pharmaceutical interventions to combat the outbreaks, including switching from communal care to 'rooming in' for mother and baby; investigating how transmission occurred; and increasing focus on IPC measures like handwashing. With these interventions and the development of penicillin derivatives, the last hospital-based outbreak of this particular resistant *S. aureus* strain was recorded in 1963.

New antimicrobials were needed to combat this resistance. In addition to scouring soil microbes for active compounds, scientists used structural modification of existing antibiotics to create new, albeit similar, drugs. However, bacteria quickly developed resistance to these so-called 'me too' compounds (Figure 6). For example, methicillin was created by slightly altering the chemical structure of penicillin, making it effective against penicillin-resistant strains of *S. aureus*. But the first instances of resistance to methicillin were observed within a year of its introduction.

In 1950, researchers demonstrated that resistant bacteria could evolve in turkeys fed with streptomycin – resistance wasn't just limited to humans.[49] Despite this, during the 1950s the use of antimicrobials in animals extended beyond treating and preventing disease, based on observations that adding certain antibiotics to animal feed promoted growth.[50] Antimicrobial growth promoters became popular worldwide, and continue to be used in some countries (this is covered in more detail in section 2.3.2). This likely further spurred AMR. Resistance was also detected in plant pathogens. For example, resistance to streptomycin began to appear in the 1960s, just a few years after it began to be used to protect crop health.[51]

Methicillin was created by slightly altering the chemical structure of penicillin, making it effective against penicillin-resistant strains of ***S. aureus***. **But the first instances of resistance to methicillin were observed within a year of its introduction.**

With some animal microbes able to infect humans, AMR in animals began to contribute to AMR in humans too. One

[48] Fong, I.W. (2018). Introduction: Coordinated global action is needed to combat antimicrobial resistance. In Fong, Shlaes and Drlica (Eds.), *Antimicrobial Resistance in the 21st Century* (pp. 1-10). Cham: Springer International Publishing.
[49] Starr, M.P., & Reynolds, D.M. (1951). Streptomycin resistance of coliform bacteria from turkeys fed streptomycin. *American Journal of Public Health and the Nations Health, 41*(11_Pt_1), 1375-1380. https://doi.org/10.2105/AJPH.41.11_Pt_1.1375
[50] Ma, F., Xu, S., Tang, Z.*, et al.* (2021). Use of antimicrobials in food animals and impact of transmission of antimicrobial resistance on humans. *Biosafety and Health, 3*(1), 32-38. https://doi.org/10.1016/j.bsheal.2020.09.004
[51] Vidaver, A.K. (2002). Uses of antimicrobials in plant agriculture. *Clinical Infectious Diseases, 34*(Supplement_3), S107-S110. https://doi.org/10.1086/340247

of the earliest documented crossover cases was reported in 1975.[52] Within one week of adding tetracycline to chicken feed, the intestinal flora of the chickens included tetracycline-resistant organisms. Within six months, nearly one-third of weekly faecal samples from farm dwellers contained more than 80% tetracycline-resistant bacteria.

In the 1990s, the advent of genome sequencing and advances in protein structure elucidation opened a new avenue for antimicrobial discovery. Sequencing of an organism's genetic code and resolving the structure of its proteins allowed identification of potential targets that drugs could act on. Targeted drug design eventually proved a successful approach for developing antiretroviral drugs to treat HIV (as described above).[53] But rational drug design has yielded few successes with antibiotics, predominantly because most of the promising drug candidates identified through rational design and screening were unable to penetrate the bacterial cell wall (particularly in gram-negative bacteria) and interact with their intended targets.[54]

AMR isn't just a problem for antibiotics … **Resistance to antifungals** is leading to a rise in deaths from invasive fungal infections.

AMR isn't just a problem for antibiotics (although at present this is where the bulk of AMR occurs and the area of greatest concern). Resistance to antifungals is leading to a rise in deaths from invasive fungal infections[55] and developing resistance against antiparasitics, including to Ivermectin, is a growing problem too. New classes of antifungal and antiparasitic compounds are urgently needed.[56] Among the antifungals, a large number of azoles have been developed to provide different treatment routes and help overcome issues of resistance.

For antivirals, vaccination is typically a very effective means of disease prevention. However, antivirals are still used in situations where there is no effective vaccine, such as for HIV; where chronic infection of cells leads to recurrence, such as shingles; or when the vaccine is not fully protective or can't be rolled out to all people, such as COVID-19. For antivirals, having classes of molecule with very different modes of action has helped to reduce the development of resistance, with antiviral drugs used in combination. This strategy has proved successful with HIV antivirals, while it is hoped that the use of combination therapies will be effective against COVID-19 too.

Over recent decades, it has become clear that regulatory and commercial barriers are making it difficult for new antimicrobials to enter the market (for details, see section 5.5.4), in addition to the technical challenges associated with drug discovery. As of December 2020, around 43 new antibiotics with the potential to treat serious bacterial infections were in clinical development,[57] but with high attrition rates from research and development through to market entry,[58] this is unlikely to

[52] Levy, S.B., FitzGerald, G.B., & Macone, A.B. (1976). Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. *New England Journal of Medicine, 295*(11), 583-588. https://doi.org/10.1056/nejm197609092951103
[53] Zhan, P., Pannecouque, C., De Clercq, E., *et al.* (2016). Anti-HIV drug discovery and development: Current innovations and future trends. *Journal of Medicinal Chemistry, 59*(7), 2849-2878. https://doi.org/10.1021/acs.jmedchem.5b00497
[54] Gajdács, M. (2019). The concept of an ideal antibiotic: Implications for drug design. *Molecules, 24*(5), 892.
[55] Rohde, R.E. (2021). Fungal infections worldwide are becoming resistant to drugs and more deadly. Retrieved from https://theconversation.com/fungal-infections-worldwide-are-becoming-resistant-to-drugs-and-more-deadly-161975
[56] Prichard, R.K. (2007). Ivermectin resistance and overview of the Consortium for Anthelmintic Resistance SNPs. *Expert Opinion on Drug Discovery, 2*(sup1), S41-S52. https://doi.org/10.1517/17460441.2.S1.S41
[57] The Pew Charitable Trusts. (2021). *Antibiotics currently in global clinical development*. Retrieved from: https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development
[58] The Pew Charitable Trusts. (2021, 9 March). Analysis shows continued deficiencies in antibiotic development since 2014. Retrieved 28 July, 2021, from https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2019/five-year-analysis-shows-continued-deficiencies-in-antibiotic-development

be enough to meet the world's need for drugs that can tackle resistant microbes. In addition, new treatments for multidrug-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Neisseria gonorrhoeae* are significant gaps in the development pipeline.[59] Additionally, none of the drug candidates aiming to treat gram-negative pathogens or WHO priority organisms (discussed in section 2.4.2) have novel mechanisms of action.[60]

As well as leading to accelerated development of vaccines, the COVID-19 pandemic has spurred research into antiviral drugs (as described above). Several antiviral drugs have been found to have no benefit to COVID-19 patients,[61] while others have shown promise in clinical trials.[62] In addition to antiviral drugs, antibody treatments and drugs that address the symptoms of COVID-19 (rather than targeting the virus) have also been explored and, in some cases, recommended for use by WHO.[63]

[59] Butler, M.S., & Paterson, D.L. (2020). Antibiotics in the clinical pipeline in October 2019. *The Journal of Antibiotics, 73*(6), 329-364. https://doi.org/10.1038/s41429-020-0291-8; World Health Organization. (2021). *2020 Antibacterial agents in clinical and preclinical development: An overview and analysis*. Geneva, Switzerland: Retrieved from https://www.who.int/publications/i/item/9789240021303

[60] World Health Organization. (2021). *2020 Antibacterial agents in clinical and preclinical development: An overview and analysis*. Geneva, Switzerland: Retrieved from https://www.who.int/publications/i/item/9789240021303

[61] World Health Organization. (2020, 20 November). *WHO recommends against the use of remdesivir in COVID-19 patients* [Press release]. Retrieved from https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients; World Health Organization. (2020, 4 July). *WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19* [Press release]. Retrieved from https://www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19

[62] Merck. (2021, 1 October). *Merck and Ridgeback's investigational oral antiviral molnupiravir reduced the risk of hospitalization or death by approximately 50 percent compared to placebo for patients with mild or moderate COVID-19 in positive interim analysis of phase 3 study* [Press release]. Retrieved from https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/; Pfizer. (2021, 5 November). *Pfizer's novel COVID-19 oral antiviral treatment candidate reduced risk of hospitalization or death by 89% in interim analysis of phase 2/3 EPIC-HR study* [Press release]. Retrieved from https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate

[63] World Health Organization. (2021). *Therapeutics and COVID-19: Living guideline*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3

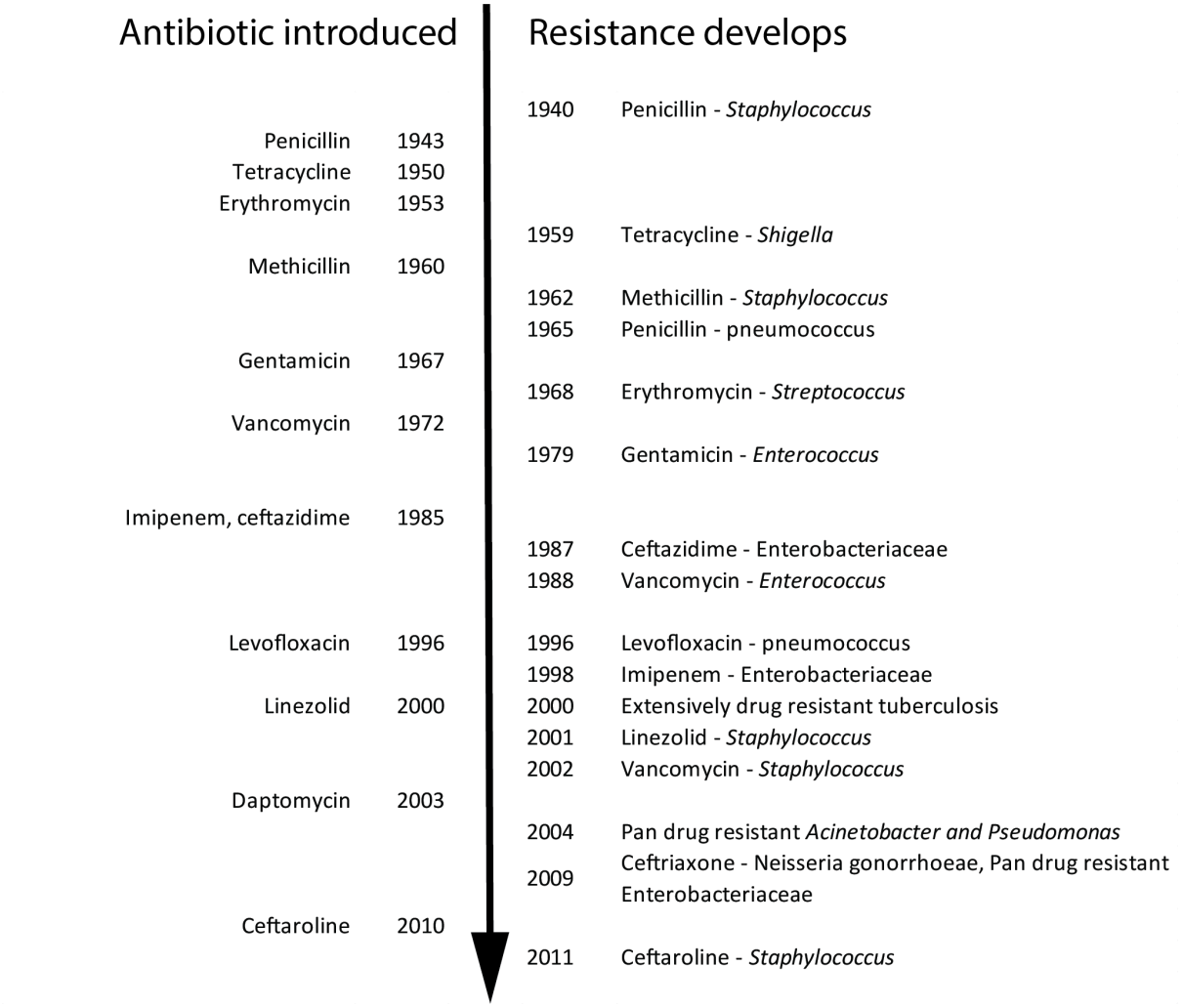

Figure 6: A timeline of antibiotic discovery and first records of resistance for different antibiotics. Information adapted from Ventola (2015).[64]

[64] Ventola, C.L. (2015). The antibiotic resistance crisis – Part 1: causes and threats. *Pharmacy and Therapeutics, 40*(4), 277.

2.3 Antimicrobial resistance basics

2.3.1 What is antimicrobial resistance?

AMR occurs when microbes develop the ability to resist the effects of the antimicrobials that are intended to kill them or suppress their growth. Microbes can be resistant to just one antimicrobial type or several. Microbes that are resistant to many antimicrobials are called multidrug-resistant organisms (MDROs).

It is important to note that resistance is a property of the microbe, not the infected person, animal, or plant. This has implications for the spread of antimicrobial-resistant microbes, discussed further in section 2.3.2 below.

A range of defences

The mechanisms by which microbes resist the effects of antimicrobial drugs are many and varied. Below is a list of common resistance mechanisms utilised by bacteria:

- Producing efflux pumps that quickly remove antibiotics from the cell.
- Producing enzymes that can break antibiotics down (e.g. penicillinase).
- Modifying the antimicrobial's target so the antibiotic is no longer effective.
- Producing so much of the target that the antimicrobial is rendered ineffective.
- Sequestering the antimicrobial.
- Developing an alternative process to replace the antimicrobial's target.
- Limiting uptake of the antimicrobial by reducing the number of entryways into the cell. [65]

In addition, bacteria may produce biofilms (complex structures of bacterial cells embedded in a sticky matrix of DNA, proteins, and carbohydrates) that can protect them against antibiotics by creating a physical barrier and through the presence of enzymes in the biofilm that can inactivate antibiotics.[66]

Some antibiotics only work against specific kinds of bacteria from the outset. For example, penicillin is effective against gram-positive bacteria, but is not active against many important gram-negative bacteria. This is because gram-negative bacteria have a relatively impermeable outer membrane that makes it harder for the antibiotic to penetrate. [67]

Resistance genes aren't necessarily expressed all the time. For example, some bacteria and fungi only express the genes that code for efflux pumps when exposed to low concentrations of antimicrobial drugs or other chemicals. The ability to switch resistance genes on in response to environmental cues is called adaptive resistance.[68]

Gram-positive vs gram-negative bacteria

Bacteria can either be gram positive or gram negative. Gram-positive bacteria have a cell wall made of a thick layer of proteins with sugars attached. Gram-negative bacteria have a cell wall with a thin layer of protein-sugar molecules, plus an outer layer of fatty sugars called lipopolysaccharides. This

[65] Reygaert, W.C. (2018). An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiology, 4*(3), 482-501. https://doi.org/10.3934/microbiol.2018.3.482

[66] Scientific Committe on Emerging and Newly Identified Health Risks. (2009). *Assessment of the antibiotic resistance effects of biocides*. European Commission. Retrieved from https://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_021.pdf

[67] Cox, G., & Wright, G.D. (2013). Intrinsic antibiotic resistance: Mechanisms, origins, challenges and solutions. *International Journal of Medical Microbiology, 303*(6), 287-292. https://doi.org/10.1016/j.ijmm.2013.02.009

[68] Sandoval-Motta, S., & Aldana, M. (2016). Adaptive resistance to antibiotics in bacteria: a systems biology perspective. *WIREs Systems Biology and Medicine, 8*(3), 253-267. https://doi.org/10.1002/wsbm.1335

extra layer provides gram-negative bacteria with additional protection against some antibiotics, detergents, and the immune system.

2.3.2 How does antimicrobial resistance develop?

Exposure to antimicrobials drives antimicrobial resistance

Microbes, like all living things, are genetically diverse. This diversity arises through the process of mutation, where changes in a microbe's genetic code are introduced by chance every time it replicates. Because bacteria and viruses can reproduce rapidly, they typically accrue mutations rapidly too, given that each reproduction cycle provides an opportunity for errors to be introduced into the genetic code. In additon, there is evidence to suggest that antibiotic exposure can induce higher rates of mutation by stressing bacteria.[69]

By chance, some mutations may enable a microbe to resist the impacts of an antimicrobial, coding for one of the defence mechanisms described in section 2.3.1 above. In the presence of antimicrobial compounds, only microbes that can resist the effects of the drug go on to reproduce, passing the genes that contributed to their survival on to their offspring. In this way, resistance is transmitted vertically (from a parent microbe to its offspring), leading to the proliferation of antimicrobial-resistant microbes.

Before humans developed antimicrobial drugs, naturally occurring antimicrobial compounds in the environment (e.g. produced by fungi) drove the evolution of AMR, and some AMR genes may have been selected for due to their ability to serve other functions like supporting protein synthesis.[70] But since the start of the antibiotic era in the mid-1900s, AMR has predominantly been selected for and driven by use of antimicrobial drugs,[71] albeit with pre-existing resistance genes likely contributing to the rapid observation of resistance against newly discovered classes of drugs.[72] For example, phylogenetic analysis suggests β-lactamases (including penicillinase) originated more than two billion years ago.[73]

Reversible resistance?

While antimicrobial exposure drives resistance, there is mixed evidence for whether cessation of antimicrobial exposure leads to the loss of resistance genes from a population of microbes.[74] Some studies have observed or predicted the long-term persistence of resistant microbes in the absence of antimicrobial use[75] (with resistance genes described as "easy to get and hard to lose"[76]), while others found or predicted a correlation between reduced antimicrobial use and declining

[69] Blazquez, J., Oliver, A., & Gomez-Gomez, J.-M. (2002). Mutation and evolution of antibiotic resistance: Antibiotics as promoters of antibiotic resistance? *Current Drug Targets, 3*(4), 345-349. https://doi.org/10.2174/1389450023347579

[70] Aminov, R.I., Garrigues-Jeanjean, N., & Mackie, R.I. (2001). Molecular ecology of tetracycline resistance: Development and validation of primers for detection of tetracycline resistance genes encoding ribosomal protection proteins. *Applied and Environmental Microbiology, 67*(1), 22-32. https://doi.org/10.1128/AEM.67.1.22-32.2001

[71] Holmes, A.H., Moore, L.S.P., Sundsfjord, A.*, et al.* (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet, 387*(10014), 176-187. https://doi.org/10.1016/S0140-6736(15)00473-0

[72] Forsberg, K.J., Patel, S., Gibson, M.K.*, et al.* (2014). Bacterial phylogeny structures soil resistomes across habitats. *Nature, 509*(7502), 612-616. https://doi.org/10.1038/nature13377

[73] Aminov, R.I. (2009). The role of antibiotics and antibiotic resistance in nature. *Environmental Microbiology, 11*(12), 2970-2988. https://doi.org/https://doi.org/10.1111/j.1462-2920.2009.01972.x

[74] Holmes, A.H., Moore, L.S.P., Sundsfjord, A.*, et al.* (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet, 387*(10014), 176-187. https://doi.org/10.1016/S0140-6736(15)00473-0; Heinemann, J.A., Ankenbauer, R.G., & Amábile-Cuevas, C.F. (2000). Do antibiotics maintain antibiotic resistance? *Drug Discovery Today, 5*(5), 195-204. https://doi.org/10.1016/s1359-6446(00)01483-5

[75] Baker, S., Duy, P.T., Nga, T.V.T.*, et al.* (2013). Fitness benefits in fluoroquinolone-resistant *Salmonella* Typhi in the absence of antimicrobial pressure. *eLife, 2*, e01229. https://doi.org/10.7554/eLife.01229; Marcusson, L.L., Frimodt-Møller, N., & Hughes, D. (2009). Interplay in the selection of fluoroquinolone resistance and bacterial fitness. *PLOS Pathogens, 5*(8), e1000541. https://doi.org/10.1371/journal.ppat.1000541

[76] Salyers, A.A., & Amábile-Cuevas, C.F. (1997). Why are antibiotic resistance genes so resistant to elimination? *Antimicrobial Agents and Chemotherapy, 41*(11), 2321-2325. https://doi.org/10.1128/AAC.41.11.2321

resistance.[77] This highlights the need to take urgent action against the threat of AMR – resistance that emerges while we delay action may not be reversible.

Bacteria can share transfer resistance genes with each other

Resistance genes can be transferred from a resistant microbe to its offspring (vertical transfer, as described above), as well as horizontally between bacteria. The exchange of genes or sections of DNA with other bacteria of the same or different species is called horizontal gene transfer (HGT). HGT is a major pathway by which bacteria acquire resistance genes.[78] There is evidence to suggest that use of antibiotics can stimulate HGT,[79] so not only do antimicrobials serve as a selector for drug resistance, but they can also promote the spread of resistance between bacteria. There are three main mechanisms for HGT (see Figure 7):

… not only do antimicrobials serve as a **selector** for drug resistance, but they can also promote the **spread** of resistance between bacteria.

- **Transformation**, where one bacterium releases 'naked' DNA that is taken up by another bacterium.
- **Transduction**, where DNA is transferred via phage viruses (viruses that infect bacteria).
- **Conjugation**, where DNA transfer results from cell-to-cell contact, with sections of DNA packaged for HGT delivery (called mobile genetic elements).[80]

There are different types of mobile genetic elements. Some mobile genetic elements important in resistance transmission include:

- **Plasmids** – Plasmids are sections of DNA, often circular, that replicate and are often transmitted via transformation or conjugation.
- **Transposons** – Transposons, also called 'jumping genes,' can move to different locations within a genome. They can also jump between chromosomes and plasmids in bacteria, facilitating the spread of resistance.[81]
- **Gene cassettes and integrons** – A gene cassette is (usually) a single gene accompanied by instructions for recombination. Sometimes this cassette exists as free-floating, circular DNA. Other times it is part of a collection of genes know as an integron that enables the correct integration and expression of the gene cassette into a genome, and its exchange between organisms. Integrons were first discovered due to their role in multidrug resistance.[82]

[77] Livermore, D.M., Hope, R., Reynolds, R.*, et al.* (2013). Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK: Links to prescribing change? *Journal of Antimicrobial Chemotherapy, 68*(11), 2667-2674. https://doi.org/10.1093/jac/dkt212

[78] Heinemann, J.A. (1999). How antibiotics cause antibiotic resistance. *Drug Discovery Today, 4*(2), 72-79. https://doi.org/10.1016/s1359-6446(98)01294-x

[79] Beaber, J.W., Hochhut, B., & Waldor, M.K. (2004). SOS response promotes horizontal dissemination of antibiotic resistance genes. *Nature, 427*(6969), 72-74. https://doi.org/10.1038/nature02241

[80] Furuya, E.Y., & Lowy, F.D. (2006). Antimicrobial-resistant bacteria in the community setting. *Nature Reviews Microbiology, 4*(1), 36-45. https://doi.org/10.1038/nrmicro1325

[81] Babakhani, S., & Oloomi, M. (2018). Transposons: The agents of antibiotic resistance in bacteria. *Journal of Basic Microbiology, 58*(11), 905-917. https://doi.org/10.1002/jobm.201800204

[82] Mazel, D. (2006). Integrons: Agents of bacterial evolution. *Nature Reviews Microbiology, 4*(8), 608-620. https://doi.org/10.1038/nrmicro1462

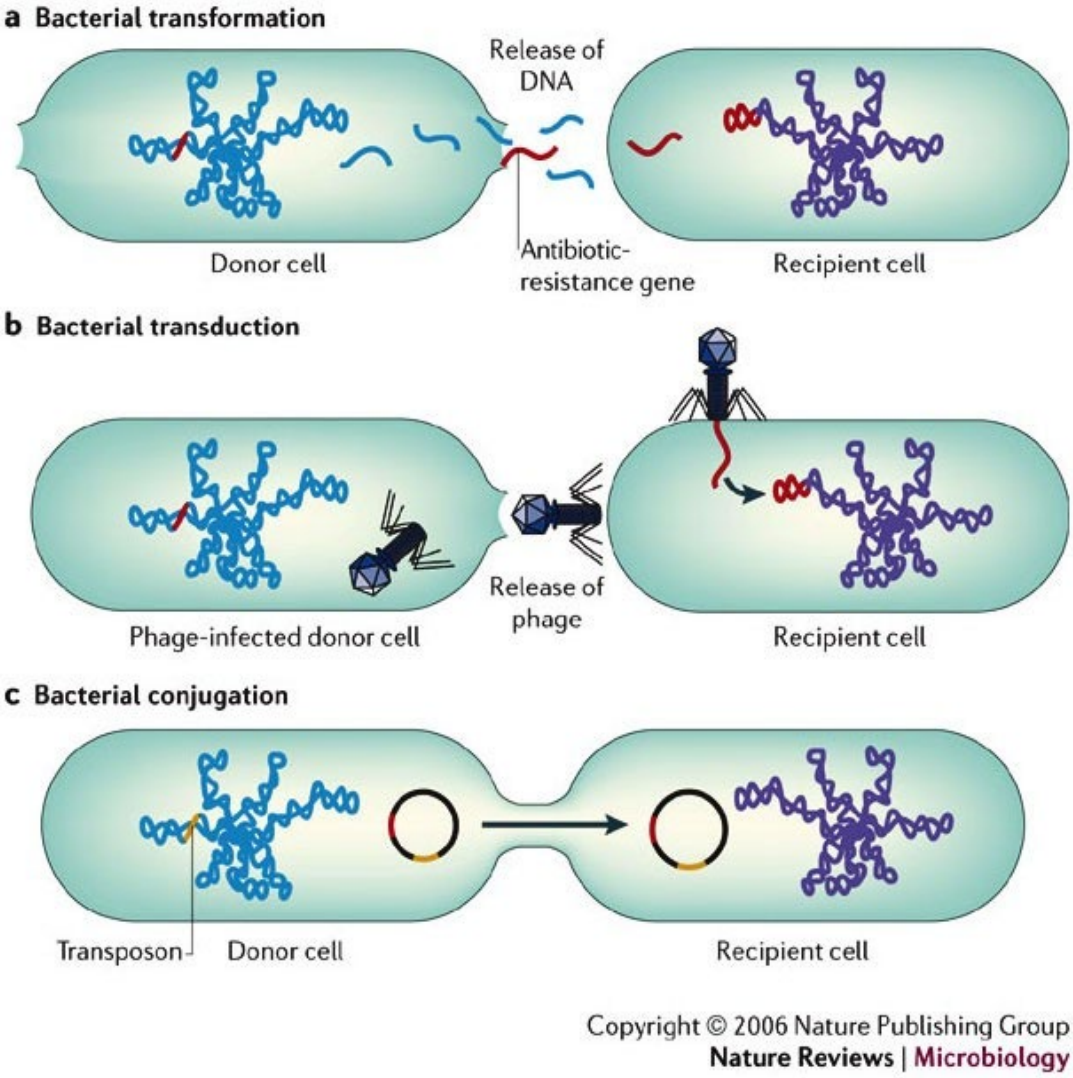

Figure 7: The three main mechanisms for HGT.

Where microbes are exposed to antimicrobials, resistance follows

Microbes are exposed to antimicrobials in a range of ways. Use of antimicrobial drugs in humans and animals is the most significant exposure route and most important intervention point to address when tackling AMR, given this is where most antimicrobial use occurs, and where antimicrobials exist in their highest concentrations.[83]

In human, animal, and plant health, microbes may be intentionally targeted through the use of antimicrobial drugs or other products as treatments, preventatives, or disinfectants. In the agricultural industry, antimicrobials are used to promote animal growth in some countries.

Microbes can also be exposed to antimicrobial residues that enter the environment (e.g. soil, water) as a result of excretion, run-off, and disposal of antimicrobials from the human, animal, and plant

[83] Holmes, A.H., Moore, L.S.P., Sundsfjord, A.*, et al.* (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet, 387*(10014), 176-187. https://doi.org/10.1016/S0140-6736(15)00473-0

worlds. The role of antimicrobials discharged into the environment in the emergence of AMR is a blind spot – more research is needed.[84]

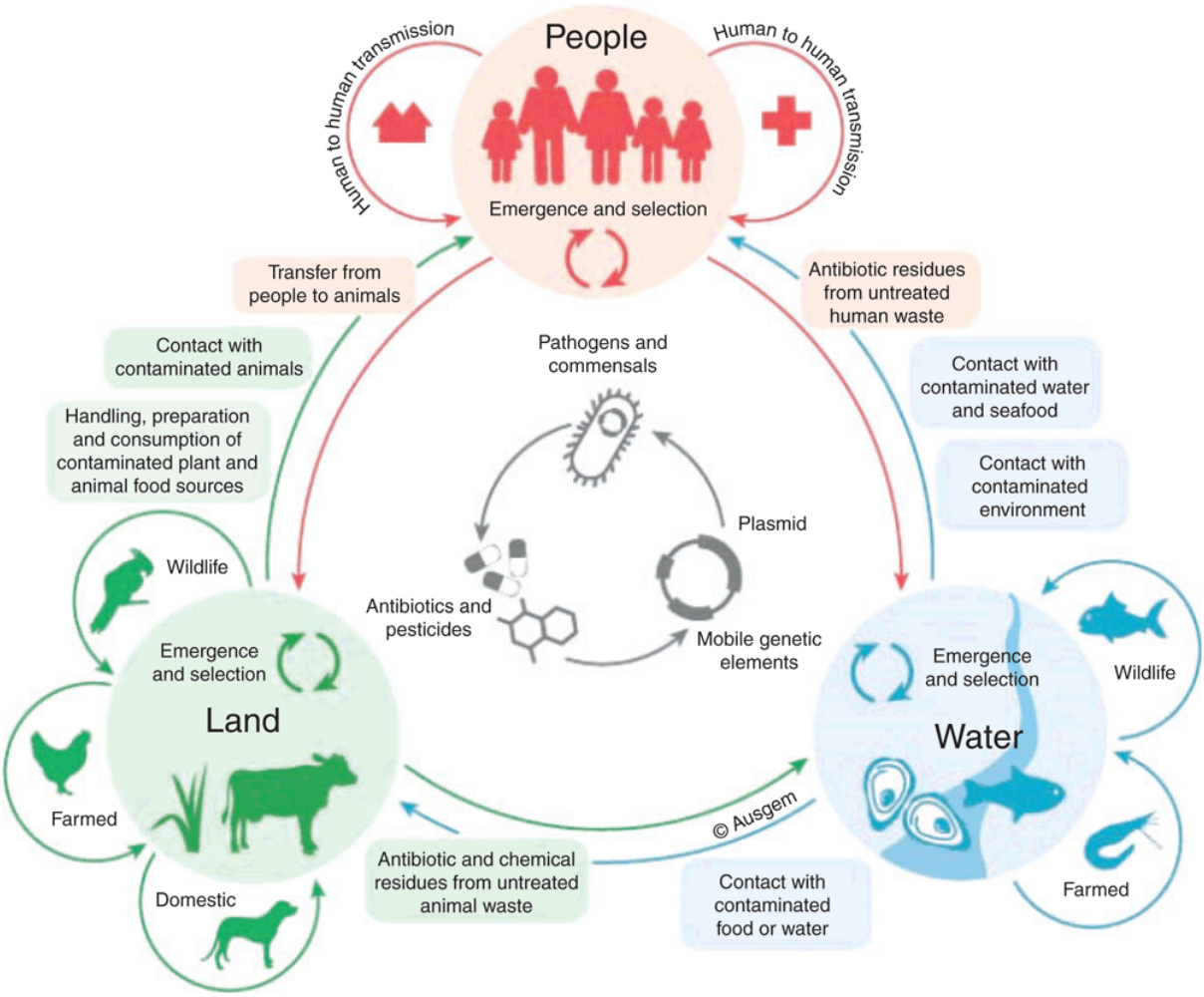

Figure 8: A diagram depicting AMR movements through humans, animals, plants, and the environment. Image credit: AusGem.[85]

Antimicrobials and AMR in humans

As described in section 2.2.3 above, resistant microbes are often detected soon after the introduction of new antimicrobials for human health (see Figure 6). Antimicrobial use in humans is dominated by antibiotics, the most commonly prescribed type of medicine around the world.[86] Global antibiotic use increased by 65% from 2000 to 2015, driven predominantly by rising use in lower income countries.[87] For details relating to key drug-resistant organisms of concern for human health, see section 2.4.2 below.

[84] Berkner, S., Konradi, S., & Schönfeld, J. (2014). Antibiotic resistance and the environment—there and back again. *EMBO reports, 15*(7), 740-744. https://doi.org/10.15252/embr.201438978

[85] Djordjevic, S.P., & Morgan, B.S. (2019). A One Health genomic approach to antimicrobial resistance is essential for generating relevant data for a holistic assessment of the biggest threat to public health. *Microbiology Australia, 40*(2), 73-76. https://doi.org/10.1071/MA19021

[86] Sriram, A., Kalanxhi, E., Kapoor, G., *et al.* (2021). *State of the world's antibiotics 2021: A global analysis of antimicrobial resistance and its drivers*. Washington DC, US: Center for Disease Dynamics, Economics & Policy. Retrieved from https://cddep.org/wp-content/uploads/2021/02/The-State-of-the-Worlds-Antibiotics-in-2021.pdf

[87] Klein, E.Y., Milkowska-Shibata, M., Tseng, K.K., *et al.* (2021). Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: An analysis of pharmaceutical sales data. *The Lancet Infectious Diseases, 21*(1), 107-115. https://doi.org/10.1016/S1473-3099(20)30332-7

Antimicrobials and AMR in animals

Antimicrobials are used widely in agriculture, both to maintain animal health and welfare, and to promote growth, including the use of some antimicrobials that are categorised by WHO as being critically important for use in humans. More antimicrobials are used in food production than in human beings.[88] A 2020 study estimated that antimicrobial sales could rise by 11.5% by 2030 compared to 2017 levels.[89] Globally, agricultural use of antimicrobials adjusted for weight is highest in chickens and pigs, followed by cattle.[90] The same general pattern is true for Aotearoa New Zealand too (see section 4.4.2 for more details).

Regulations to control antimicrobial use in food-producing animals are not consistent around the world.[91] In Aotearoa New Zealand, antimicrobials considered critical or highly important for human health are not permitted to be used for growth promotion in livestock. Antimicrobial use in animals and plants in Aotearoa New Zealand is explored further in section 4.4.

A complete ban on antimicrobials in agriculture is not desirable – **therapeutic use is essential** to treat disease and safeguard animal health, welfare, and productivity.

A complete ban on antimicrobials in agriculture is not desirable – therapeutic use is essential to treat disease and safeguard animal health, welfare, and productivity.[92] Banning or restricting use of antimicrobials for growth promotion is one approach to curbing excessive antimicrobial use in animals. Recognition of this has spurred some countries and jurisdictions to restrict or ban the use of antimicrobial growth promoters. There is evidence that this has made a difference to AMR levels in animals and animal products. In Denmark, which banned all antimicrobial growth promoters in 2000, AMR prevalence among zoonotic bacteria and indicator bacteria is lower in locally produced meat compared with imported meat.[93] In the mid-1970s, what is now the European Union (EU) banned tetracycline and a subsequent decline in tetracycline-resistant strains of *Salmonella* spp. was observed in both pigs and humans in the Netherlands.[94] The EU has since banned all antimicrobial growth promoters.[95]

Studies looking at exposure to AMR via food have been undertaken overseas. Source attribution and risk assessment have been widely used to provide evidence that can support strategies to reduce the burden of a number of foodborne pathogens, but the transmission and spread of antimicrobial-

[88] Holmes, A.H., Moore, L.S.P., Sundsfjord, A., *et al.* (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet, 387*(10014), 176-187. https://doi.org/10.1016/S0140-6736(15)00473-0

[89] Tiseo, K., Huber, L., Gilbert, M., *et al.* (2020). Global trends in antimicrobial use in food animals from 2017 to 2030. *Antibiotics, 9*(12), 918.

[90] Ma, F., Xu, S., Tang, Z., *et al.* (2021). Use of antimicrobials in food animals and impact of transmission of antimicrobial resistance on humans. *Biosafety and Health, 3*(1), 32-38. https://doi.org/10.1016/j.bsheal.2020.09.004

[91] World Health Organization. (2012). *The evolving threat of antimicrobial resistance: Options for action*. Geneva, Switzerland: Retrieved from http://apps.who.int/iris/bitstream/handle/10665/44812/9789241503181_eng.pdf

[92] Casewell, M., Friis, C., Marco, E., *et al.* (2003). The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. *Journal of Antimicrobial Chemotherapy, 52*(2), 159-161. https://doi.org/10.1093/jac/dkg313

[93] National Food Institute, Statens Serum Institut, & Danish Health Data Authority. (2019). *DANMAP 2019: Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark*. Denmark: Retrieved from https://www.danmap.org/reports/2019

[94] van Leeuwen, W.J., Guinée, P.A., Voogd, C.E., *et al.* (1986). Resistance to antibiotics in Salmonella. *Tijdschrift voor diergeneeskunde, 111*(1), 9-13.

[95] Ma, F., Xu, S., Tang, Z., *et al.* (2021). Use of antimicrobials in food animals and impact of transmission of antimicrobial resistance on humans. *Biosafety and Health, 3*(1), 32-38. https://doi.org/10.1016/j.bsheal.2020.09.004

resistant microbes adds an extra layer of complexity to this integrated food safety paradigm.[96] Overseas studies have tried to assess the source contribution to AMR,[97] but to our knowledge no such studies have been performed in Aotearoa New Zealand.

Making a far smaller contribution to antimicrobial use in animals, antimicrobials are also used to protect the health and welfare of companion animals like dogs and cats. Section 4.3.2 discusses evidence of AMR in animals and food in Aotearoa New Zealand.

Antimicrobials and AMR in aquaculture

Aquaculture is a fast-growing industry, which now accounts for 52% of all seafood consumed by humans worldwide.[98] Overseas, as a result of the intensification of aquaculture – including increased fish stocking density and poor sanitation – infections run rife among farmed fish, resulting in significant losses in annual production. Aotearoa New Zealand's aquaculture industry does not use antimicrobials (see section 4.4.2). In developing countries, prophylactic antimicrobials have been deployed in fish food in an attempt to mitigate the impact of diseases. This use of antimicrobials, including some important for human health, leads to environmental contamination, food residues, and increasing resistance among fish pathogens.[99]

Antimicrobials and AMR in plants

Antibiotics aren't widely used in plants given there are relatively few bacterial plant infections. However, plants are often susceptible to fungal infections, so the use of antifungals such as copper-based sprays is more widespread.[100]

Streptomycin, an antibiotic sometimes used on crops, including in Aotearoa New Zealand, has led to the development of AMR among plant pathogens.[101] A group of antifungals called azoles have been associated with the development of resistance among plant pathogens too.[102] Clinical and environmental isolates have shown cross-resistance between agricultural and medical azole antifungals (such as those used to treat athlete's foot, yeast infections, and ringworm), and cross-resistance between azoles and amphotericin B (which is used to treat fungal infections in humans). This cross resistance between azoles and amphotericin B is unsurprising

Globally, there is a paucity of data on antimicrobial use in plants and presence of drug-resistant plant pathogens.

[96] Pires, S.M., Duarte, A.S., & Hald, T. (2018). Source attribution and risk assessment of antimicrobial resistance. In Schwarz, Cavaco and Shen (Eds.), *Antimicrobial resistance in bacteria from livestock and companion animals* (pp. 619-635): ASM Press.
[97] Hald, T., Lo Fo Wong, D.M.A., & Aarestrup, F.M. (2007). The attribution of human infections with antimicrobial resistant *Salmonella* bacteria in Denmark to sources of animal origin. *Foodborne Pathogens and Disease, 4*(3), 313-326. https://doi.org/10.1089/fpd.2007.0002; Brown, A.C., Grass, J.E., Richardson, L.C., *et al.* (2017). Antimicrobial resistance in Salmonella that caused foodborne disease outbreaks: United States, 2003–2012. *Epidemiology and Infection, 145*(4), 766-774. https://doi.org/10.1017/s0950268816002867; Carmo, L.P., Nielsen, L.R., Da Costa, P.M., *et al.* (2014). Exposure assessment of extended-spectrum beta-lactamases/AmpC beta-lactamases-producing *Escherichia coli* in meat in Denmark. *Infection Ecology & Epidemiology, 4*(1), 22924. https://doi.org/10.3402/iee.v4.22924; Evers, E.G., Pielaat, A., Smid, J.H., *et al.* (2017). Comparative exposure assessment of ESBL-producing *Escherichia coli* through meat consumption. *PLOS One, 12*(1), e0169589. https://doi.org/10.1371/journal.pone.0169589
[98] Food and Agriculture Organization. (2020). *The state of world fisheries and aquaculture 2020: Sustainability in action*. Rome, Italy: Food and Agriculture Organization of the United Nations. Retrieved from https://doi.org/10.4060/ca9229en
[99] Cabello, F.C. (2006). Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment. *Environmental Microbiology, 8*(7), 1137-1144. https://doi.org/10.1111/j.1462-2920.2006.01054.x; Lulijwa, R., Rupia, E.J., & Alfaro, A.C. (2020). Antibiotic use in aquaculture, policies and regulation, health and environmental risks: A review of the top 15 major producers. *Reviews in Aquaculture, 12*(2), 640-663. https://doi.org/10.1111/raq.12344
[100] Vidaver, A.K. (2002). Uses of antimicrobials in plant agriculture. *Clinical Infectious Diseases, 34*(Supplement_3), S107-S110. https://doi.org/10.1086/340247
[101] Ibid.
[102] Schoustra, S., Debets, A.J.M., Rijs, A.J.M.M., *et al.* (2019). Environmental hotspots for azole resistance selection of *Aspergillus fumigatus*, the Netherlands. *Emerging Infectious Diseases, 25*(7), 1347. https://doi.org/10.3201/eid2507.181625

given both antifungals target ergosterol, a component the fungal membrane (see section 2.2.2).[103]

Globally, there is a paucity of data on antimicrobial use in plants and presence of drug-resistant plant pathogens. In a recent survey run by WHO and the FAO, only 3% of the 158 countries questioned indicated that they regularly assessed antibiotic use on crops, while 83% either didn't respond or said they had no means of assessing antimicrobial use on plants.[104] A recent study looking at low-to-middle income countries found that antibiotics were being used more frequently and on a much greater variety of crops than previously thought,[105] indicating that closer scrutiny could derive useful (and potentially concerning) insights about antimicrobial use and AMR in plants.

Antimicrobials and AMR in the environment

Antimicrobials can enter the environment as the result of use in humans, animals, and plants, as well as improper disposal. These residues can theoretically select for resistance among microbes in our soils and waterways, but this is understudied.[106] The level of pharmaceutical antimicrobial contamination in a particular environment depends on factors including: the size and nature of the local population; local levels of antimicrobial use; the size and nature of pharmaceutical manufacturing in the area; connectivity to wastewater treatment; local ecology (e.g. animal movements); local regulatory frameworks; and antimicrobial properties (e.g. stability).[107]

In addition, as noted earlier in this section, antimicrobial compounds exist naturally in the environment, meaning that even before the introduction of antimicrobial contaminants by humans, AMR traits existed among microbes in soil and waterways, with the collection of resistance genes present in environmental microbes known as the 'resistome.'[108]

There may be 'resistome hotspots' that result from human activities. For example, landfill leachate and groundwater near landfills are also known to contain resistance genes and pathogens.[109] More research is needed on environmental reservoirs of AMR and the extent to which resistance is driven by environmental contamination with antimicrobials as the result of human activities.

Homing in on overuse and inappropriate use

We can't stop all use of antimicrobials: they are an essential tool for controlling and, in some situations, preventing infections. We can, however, focus on reducing excessive use and inappropriate use of antimicrobials.[110] A correlation can be observed between the frequency and

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[103] Dalhoff, A. (2018). Does the use of antifungal agents in agriculture and food foster polyene resistance development? A reason for concern. *Journal of Global Antimicrobial Resistance, 13*, 40-48. https://doi.org/10.1016/j.jgar.2017.10.024; Brauer, V.S., Rezende, C.P., Pessoni, A.M.*, et al.* (2019). Antifungal agents in agriculture: Friends and foes of public health. *Biomolecules, 9*(10), 521. https://doi.org/10.3390/biom9100521

[104] Taylor, P., & Reeder, R. (2020). Antibiotic use on crops in low and middle-income countries based on recommendations made by agricultural advisors. *CABI Agriculture and Bioscience, 1*(1), 1. https://doi.org/10.1186/s43170-020-00001-y

[105] Ibid.

[106] Marshall, B.M., & Levy, S.B. (2011). Food animals and antimicrobials: Impacts on human health. *Clinical Microbiology Reviews, 24*(4), 718-733. https://doi.org/10.1128/cmr.00002-11

[107] Kookana, R.S., Williams, M., Boxall, A.B.A.*, et al.* (2014). Potential ecological footprints of active pharmaceutical ingredients: An examination of risk factors in low-, middle- and high-income countries. *Philosophical Transactions of the Royal Society B: Biological Sciences, 369*(1656), 20130586. https://doi.org/10.1098/rstb.2013.0586; Heinemann, J.A., Ankenbauer, R.G., & Amábile-Cuevas, C.F. (2000). Do antibiotics maintain antibiotic resistance? *Drug Discovery Today, 5*(5), 195-204. https://doi.org/10.1016/s1359-6446(00)01483-5

[108] Wright, G.D. (2007). The antibiotic resistome: the nexus of chemical and genetic diversity. *Nature Reviews Microbiology, 5*(3), 175-186. https://doi.org/10.1038/nrmicro1614

[109] Vikesland, P., Garner, E., Gupta, S.*, et al.* (2019). Differential drivers of antimicrobial resistance across the world. *Accounts of Chemical Research, 52*(4), 916-924. https://doi.org/10.1021/acs.accounts.8b00643

[110] Holmes, A.H., Moore, L.S.P., Sundsfjord, A.*, et al.* (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet, 387*(10014), 176-187. https://doi.org/10.1016/S0140-6736(15)00473-0

volume of antimicrobial use and the rate of resistance emergence, so even using less antimicrobials without completely curbing use will reduce resistance emergence.[111]

We can't stop all use of antimicrobial agents … We can, however, **focus on reducing excessive use** and inappropriate use of antimicrobials.

There is ample evidence for inappropriate antimicrobial use in human health across a range of settings and countries, although the extent of inappropriate use varies widely.[112] According to the US Centre for Disease Control and Prevention (CDC), up to 50% of the antibiotics prescribed in human health are not needed or are not optimally effective.[113] There are many reasons for inappropriate use, including: prescribing antimicrobials without a confirmed diagnosis to ensure the prescription is appropriate for the indication (often out of excessive caution);[114] exertion of pressure on prescribers by patients who feel an entitlement to access drugs regardless of whether they are likely to be suitable for a given illness;[115] legal and illegal access to antimicrobials without a prescription in some (mostly lower income) countries;[116] and use of substandard or counterfeit drugs that deliver a subtherapeutic antimicrobial dose.[117]

Combatting overuse and inappropriate use can be achieved by preventing infections using non-antimicrobial means: in this way, we don't have to reach for antimicrobial treatments in the first place, as well as ensuring that antimicrobials are only used when there are no suitable alternatives. When use is necessary, the details of use should be carefully considered, including the drug, dose, and duration of treatment. In addition, non-health uses (e.g. growth promotion in agriculture) represents a clear-cut target area to reduce use. However, it should be noted that reducing antimicrobial use shouldn't come at the expense of human, animal, and plant health – antimicrobials

[111] Goossens, H., Ferech, M., Vander Stichele, R., *et al.* (2005). Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. *The Lancet, 365*(9459), 579-587. https://doi.org/10.1016/s0140-6736(05)17907-0; Costelloe, C., Metcalfe, C., Lovering, A., *et al.* (2010). Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and meta-analysis. *BMJ, 340*, c2096. https://doi.org/10.1136/bmj.c2096

[112] Cusini, A., Rampini, S.K., Bansal, V., *et al.* (2010). Different patterns of inappropriate antimicrobial use in surgical and medical units at a tertiary care hospital in Switzerland: A prevalence survey. *PLOS One, 5*(11), e14011. https://doi.org/10.1371/journal.pone.0014011; Milani, R.V., Wilt, J.K., Entwisle, J., *et al.* (2019). Reducing inappropriate outpatient antibiotic prescribing: Normative comparison using unblinded provider reports. *BMJ Open Quality, 8*(1), e000351. https://doi.org/10.1136/bmjoq-2018-000351; Smieszek, T., Pouwels, K.B., Dolk, F.C.K., *et al.* (2018). Potential for reducing inappropriate antibiotic prescribing in English primary care. *Journal of Antimicrobial Chemotherapy, 73*(suppl_2), ii36-ii43. https://doi.org/10.1093/jac/dkx500; World Health Organization. (2018). *Antimicrobial resistance and primary health care*. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/326454/WHO-HIS-SDS-2018.56-eng.pdf

[113] Centers for Disease Control and Prevention. (2013). *Antibiotic resistance threats in the United States*. Retrieved from https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

[114] Kumar, S., Little, P., & Britten, N. (2003). Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. *BMJ, 326*(7381), 138. https://doi.org/10.1136/bmj.326.7381.138

[115] Llor, C., & Bjerrum, L. (2014). Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Therapeutic Advances in Drug Safety, 5*(6), 229-241. https://doi.org/10.1177/2042098614554919; O'Doherty, J., Leader, L.F.W., O'Regan, A., *et al.* (2019). Over prescribing of antibiotics for acute respiratory tract infections: A qualitative study to explore Irish general practitioners' perspectives. *BMC Family Practice, 20*(1), 27. https://doi.org/10.1186/s12875-019-0917-8

[116] Koji, E.M., Gebretekle, G.B., & Tekle, T.A. (2019). Practice of over-the-counter dispensary of antibiotics for childhood illnesses in Addis Ababa, Ethiopia: A simulated patient encounter study. *Antimicrobial Resistance & Infection Control, 8*(1), 119. https://doi.org/10.1186/s13756-019-0571-x; Belachew, S.A., Hall, L., & Selvey, L.A. (2021). Non-prescription dispensing of antibiotic agents among community drug retail outlets in Sub-Saharan African countries: A systematic review and meta-analysis. *Antimicrobial Resistance & Infection Control, 10*(1), 13. https://doi.org/10.1186/s13756-020-00880-w; Adhikari, B., Pokharel, S., Raut, S., *et al.* (2021). Why do people purchase antibiotics over-the-counter? A qualitative study with patients, clinicians and dispensers in central, eastern and western Nepal. *BMJ Global Health, 6*(5), e005829. https://doi.org/10.1136/bmjgh-2021-005829

[117] Bassat, Q., Tanner, M., Guerin, P.J., *et al.* (2016). Combating poor-quality anti-malarial medicines: A call to action. *Malaria Journal, 15*(1), 302. https://doi.org/10.1186/s12936-016-1357-8

should still be used when needed, including to protect the health of underserved patients who don't have access the medicines they need. These themes are explored further in section 4.4 and section 5.5.1.

Other products contribute to antimicrobial resistance too

While overuse and inappropriate use of antimicrobial drugs in humans and animals is the leading driver of AMR, other products can contribute to AMR emergence too.

Antimicrobial cleaning and hygiene products

Disinfectants used in healthcare settings and homes sometimes contain antimicrobial compounds and have implications for AMR emergence. Not only can this facilitate resistance to those cleaning and hygiene products, but it can also facilitate cross-resistance to antimicrobial medicines. However, more research is needed to identify the relative significance of this route to AMR emergence.[118]

Triclosan is an antimicrobial that is sometimes present in household products, including soap. Studies have found **no beneficial effects of triclosan-containing soaps compared with ordinary soap and water.**

In some situations the antimicrobials in these products support IPC – for example, antimicrobial disinfectants help to protect people in healthcare settings, and some are also used topically on people to help reduce the bacterial load on the skin prior to surgical procedure. But in other situations, there is no evidence to suggest that the inclusion of antimicrobials is necessary to promote health – therefore representing an example of inappropriate antimicrobial use that may contribute to AMR. For example, triclosan is an antimicrobial that is sometimes present in household products, including soap. Studies have found no beneficial effects of triclosan-containing soaps compared with ordinary soap and water. In addition, it has been demonstrated that microbes that develop resistance to triclosan may also be able to resist certain antimicrobial medicines.[119]

Non-antimicrobial drivers

Non-antimicrobial products and environmental contaminants may also play a role in the emergence of AMR. However, as with cleaning and hygiene products described above, more research is needed to identify the relative significance of these possible drivers of AMR.

Examples of early evidence indicating a possible role for non-antimicrobials in the development of AMR follow.

- Herbicides like glyphosate, 2,4-D (2,4-dichlorophenoxyacetic), and MCPA (methyl-4-chlorophenoxyacetic acid) can affect how bacteria respond to antibiotics, including accelerating the development of resistance to multiple antibiotics.[120]

[118] Scientific Committe on Emerging and Newly Identified Health Risks. (2009). *Assessment of the antibiotic resistance effects of biocides*. European Commission. Retrieved from https://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_021.pdf

[119] Giuliano, C.A., & Rybak, M.J. (2015). Efficacy of triclosan as an antimicrobial hand soap and its potential impact on antimicrobial resistance: A focused review. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 35*(3), 328-336. https://doi.org/10.1002/phar.1553

[120] Kurenbach, B., Hill, A.M., Godsoe, W.*, et al.* (2018). Agrichemicals and antibiotics in combination increase antibiotic resistance evolution. *PeerJ, 6*, e5801. https://doi.org/10.7717/peerj.5801; Kurenbach, B., Marjoshi, D., Amábile-Cuevas, C.F.*, et al.* (2015). Sublethal exposure to commercial formulations of the herbicides dicamba, 2,4-dichlorophenoxyacetic acid, and glyphosate cause changes in antibiotic susceptibility in *Escherichia coli* and *Salmonella enterica* serovar Typhimurium. *mBio, 6*(2), e00009-00015. https://doi.org/10.1128/mBio.00009-15

- A range of common medicines, including ibuprofen and the lipid-lowering drug gemfibrozil, can facilitate the transmission of resistance genes between bacteria.[121]
- A lab-based study found that artificial sweeteners can facilitate transfer of resistance genes between bacteria.[122]
- The 'inert' ingredients in common commercial formulations of herbicides, such as emulsifiers, may induce an adaptive response to antibiotics in bacteria, thereby increasing the chance of resistance developing.[123]
- In one study, strains of *S. aureus* became more resistant to certain antibiotics when exposed to cigarette smoke, and also demonstrated greater virulence.[124]
- Genes that code for AMR properties can be physically clustered together with genes that help protect microbes from heavy metals in the same mobile genetic element.[125] In this way, co-selection may lead to the emergence of resistant pathogens in environments contaminated with heavy metals like copper, zinc, nickel, and mercury.
- Plastic pollution may facilitate the spread of AMR genes. One study found that bacteria on the surface of microplastics engaged in higher frequencies of gene transfer.[126]

2.3.3 Drug-resistant microbes and genes can spread

Drug-resistant microbes are able to spread from host to host, bringing their resistant properties with them. For humans, drug-resistant microbes (and microbes generally) can spread both in healthcare facilities and the community; their spread is exacerbated by poor IPC practices; and microbes can spread across borders too.

Given some microbes are able to infect multiple different host types, this means AMR can spread both within and between species, including between animals and humans, and probably from environmental sources into humans and animals too. In addition, drug-resistant genes in bacteria can move horizontally between microbes, including into human-infecting microbes from a microbial source that doesn't ordinarily infect humans. This movement of drug-resistant microbes and genes means that any person, animal, or plant can be affected by a drug-resistant microbe, regardless of their history of antimicrobial exposure.

AMR spreads in healthcare facilities and communities

Drug resistant microbes can spread in healthcare settings and the community.[127] Drug-resistant skin infections, STIs, and foodborne pathogens may be acquired and spread in the community, while hospitals tend to have a somewhat unique set of AMR issues – for example, pathogens such as *Acinetobacter baumannii* are spread almost exclusively within hospitals.[128] The different character of AMR in hospitals may be attributed to:

- the concentrated use of antimicrobials that may promote acquisition of resistance,

[121] Wang, Y., Lu, J., Engelstädter, J., *et al.* (2020). Non-antibiotic pharmaceuticals enhance the transmission of exogenous antibiotic resistance genes through bacterial transformation. *The ISME Journal, 14*(8), 2179-2196. https://doi.org/10.1038/s41396-020-0679-2
[122] Yu, Z., Wang, Y., Lu, J., *et al.* (2021). Nonnutritive sweeteners can promote the dissemination of antibiotic resistance through conjugative gene transfer. *The ISME Journal, 15*(7), 2117-2130. https://doi.org/10.1038/s41396-021-00909-x
[123] Kurenbach, B., Hill, A.M., Godsoe, W., *et al.* (2018). Agrichemicals and antibiotics in combination increase antibiotic resistance evolution. *PeerJ, 6*, e5801. https://doi.org/10.7717/peerj.5801
[124] Lacoma, A., Edwards, A.M., Young, B.C., *et al.* (2019). Cigarette smoke exposure redirects *Staphylococcus aureus* to a virulence profile associated with persistent infection. *Scientific Reports, 9*(1), 10798. https://doi.org/10.1038/s41598-019-47258-6
[125] Martinez, J.L. (2009). The role of natural environments in the evolution of resistance traits in pathogenic bacteria. *Proceedings of the Royal Society B: Biological Sciences, 276*(1667), 2521-2530. https://doi.org/10.1098/rspb.2009.0320
[126] Arias-Andres, M., Klümper, U., Rojas-Jimenez, K., *et al.* (2018). Microplastic pollution increases gene exchange in aquatic ecosystems. *Environmental Pollution, 237*, 253-261. https://doi.org/10.1016/j.envpol.2018.02.058
[127] Bancroft, E.A. (2007). Antimicrobial resistance: It's not just for hospitals. *JAMA, 298*(15), 1803-1804. https://doi.org/10.1001/jama.298.15.1803
[128] Sefton, A.M. (2002). Mechanisms of antimicrobial resistance. *Drugs, 62*(4), 557-566. https://doi.org/10.2165/00003495-200262040-00001

- the potential for resistant pathogens to spread (e.g. through crowding together of people who share facilities including bathrooms and who come into close contact with many healthcare workers), and
- the population of vulnerable patients (especially in intensive care units, ICUs) who may be more susceptible to infection.

Healthcare settings and the community are not siloed settings but are strongly interconnected: patients with community-acquired infections may require hospitalisation while hospital-acquired microorganisms may subsequently spread to friends, whānau, and the wider community when a patient is discharged from hospital or visited by guests.[129]

There are Aotearoa New Zealand examples of resistant healthcare-associated infection (HAI) transmission. For example, transmission of carbapenemase-producing Enterobacterales (CPEs) in healthcare facilities in Aotearoa New Zealand has been identified,[130] and outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA)[131] and vancomycin-resistant enterococci[132] have also been detected (see section 4.3).

Inadequate infection prevention and control facilitates the spread of resistant organisms

Inadequate IPC measures drive transmission of all kinds of microbes, including resistant ones.[133] Good IPC practices, which can slow the spread of resistant organisms, are discussed in depth in section 5.3.1.

Examples of where suboptimal IPC measures can facilitate AMR dissemination follow.

- Inadequate sanitation,[134] and untreated wastewater[135] contribute to transmission of resistant organisms and genes via the faecal-oral route.
- Sexual activity without adequate protection, can spread drug-resistant pathogens like *Neisseria gonorrhoea*.
- Contamination of healthcare workers' hands contributes to transmission of MRSA in hospitals.[136]

[129] Dalton, K.R., Rock, C., Carroll, K.C*., et al.* (2020). One Health in hospitals: How understanding the dynamics of people, animals, and the hospital built-environment can be used to better inform interventions for antimicrobial-resistant gram-positive infections. *Antimicrobial Resistance & Infection Control, 9*(1), 78. https://doi.org/10.1186/s13756-020-00737-2

[130] Howard, J.C., Creighton, J., Heffernan, H*., et al.* (2016). Evidence of transmission of an NDM-5-producing *Klebsiella pneumoniae* in a healthcare facility in New Zealand. *Journal of Antimicrobial Chemotherapy*, dkw498. https://doi.org/10.1093/jac/dkw498)Counties Manukau Health. (2018, 20 December). *Multi-drug resistant organism identified at Middlemore Hospital* [Press release]. Retrieved from https://www.countiesmanukau.health.nz/news/multi-drug-resistant-organism-identified-at-middlemore-hospital/

[131] Akoorie, N. (2020, 30 November). Babies moved in superbug outbreak at Waikato Hospital, *Stuff*. Retrieved from https://www.stuff.co.nz/national/politics/local-democracy-reporting/300171348/babies-moved-in-superbug-outbreak-at-waikato-hospital

[132] Goodwin, E. (2016, 16 December). Superbug strikes Wakari Hospital, *Otago Daily Times*. Retrieved from https://www.odt.co.nz/news/dunedin/health/superbug-strikes-wakari-hospital

[133] Collignon, P., Beggs, J.J., Walsh, T.R*., et al.* (2018). Anthropological and socioeconomic factors contributing to global antimicrobial resistance: A univariate and multivariable analysis. *The Lancet Planetary Health, 2*(9), e398-e405. https://doi.org/10.1016/S2542-5196(18)30186-4

[134] Wellington, E.M.H., Boxall, A.B.A., Cross, P*., et al.* (2013). The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria. *The Lancet Infectious Diseases, 13*(2), 155-165. https://doi.org/10.1016/S1473-3099(12)70317-1

[135] Vikesland, P., Garner, E., Gupta, S*., et al.* (2019). Differential drivers of antimicrobial resistance across the world. *Accounts of Chemical Research, 52*(4), 916-924. https://doi.org/10.1021/acs.accounts.8b00643

[136] Chamchod, F., & Ruan, S. (2012). Modeling methicillin-resistant *Staphylococcus aureus* in hospitals: Transmission dynamics, antibiotic usage and its history. *Theoretical Biology and Medical Modelling, 9*(1), 25. https://doi.org/10.1186/1742-4682-9-25

Global connections facilitate the spread of AMR around the world

Resistant organisms can spread between and across countries via movement of people, animals, and goods, but more research is needed to identify how common this is, both for travel[137] and trade.[138]

There is evidence that travel is associated with an increased risk of carriage of a MDRO. For example, travel to AMR hotspots is associated with an increased risk of colonisation of the gut with organisms that produce extended spectrum β-lactamase (ESBL, see section 2.4.2)[139] and a real-time sampling study of European travellers in Laos found that they were colonised with ESBL organisms during their stay.[140] Wounded military personnel and tourists who travel overseas for medical treatment or are hospitalised while travelling may also be at increased risk of HAIs caused by drug-resistant pathogens and importing those pathogens back to their home country.[141]

In Aotearoa New Zealand, introduction of resistant microbes from overseas has been observed.

In Aotearoa New Zealand, introduction of resistant microbes from overseas has been observed too. This is discussed further in section 4.3.1.

Resistant microbes and genes can move between humans, animals, and the environment

There are links between the use of antimicrobials in humans, animals, and plants, and discharge into the environment. But these spheres aren't just interconnected because of the movement of antimicrobial drugs through ecosystems: drug-resistant organisms and genes that develop in one sphere can move to and contribute to resistance in another as well. However, the relative importance of AMR transmission pathways remains a critical knowledge gap.[142]

The relative importance of AMR transmission pathways remains **a critical knowledge gap**.

Resistant pathogens and AMR genes can be transferred between humans and animals, either through food, water, manure (used as fertiliser), or contact with live animals. There is ample evidence of such transfer occurring between food-producing animals and humans,[143] and some evidence for transfer between

[137] MacPherson, D.W., Gushulak, B.D., Baine, W.B., *et al.* (2009). Population mobility, globalization, and antimicrobial drug resistance. *Emerging Infectious Diseases, 15*(11), 1727-1732. https://doi.org/10.3201/eid1511.090419

[138] Jung, D., Morrison, B.J., & Rubin, J.E. A review of antimicrobial resistance in imported foods. *Canadian Journal of Microbiology, 0*(0), 1-15. https://doi.org/10.1139/cjm-2021-0234

[139] Karanika, S., Karantanos, T., Arvanitis, M., *et al.* (2016). Fecal colonization with extended-spectrum beta-lactamase-producing Enterobacteriaceae and risk factors among healthy individuals: A systematic review and metaanalysis. *Clinical Infectious Diseases, 63*(3), 310-318. https://doi.org/10.1093/cid/ciw283

[140] Kantele, A., Kuenzli, E., Dunn, S.J., *et al.* (2021). Dynamics of intestinal multidrug-resistant bacteria colonisation contracted by visitors to a high-endemic setting: A prospective, daily, real-time sampling study. *The Lancet Microbe, 2*(4), e151-e158. https://doi.org/10.1016/S2666-5247(20)30224-X

[141] MacPherson, D.W., Gushulak, B.D., Baine, W.B., *et al.* (2009). Population mobility, globalization, and antimicrobial drug resistance. *Emerging Infectious Diseases, 15*(11), 1727-1732. https://doi.org/10.3201/eid1511.090419

[142] Pires, S.M., Duarte, A.S., & Hald, T. (2018). Source attribution and risk assessment of antimicrobial resistance. In Schwarz, Cavaco and Shen (Eds.), *Antimicrobial resistance in bacteria from livestock and companion animals* (pp. 619-635): ASM Press.

[143] Ma, F., Xu, S., Tang, Z., *et al.* (2021). Use of antimicrobials in food animals and impact of transmission of antimicrobial resistance on humans. *Biosafety and Health, 3*(1), 32-38. https://doi.org/10.1016/j.bsheal.2020.09.004; Lazarus, B., Paterson, D.L., Mollinger, J.L., *et al.* (2015). Do human extraintestinal *Escherichia coli* infections resistant to expanded-spectrum cephalosporins originate from food-producing animals? A systematic review. *Clinical Infectious Diseases, 60*(3), 439-452. https://doi.org/10.1093/cid/ciu785; Shen, Z., Wang, Y., Shen, Y., *et al.* (2016). Early emergence of *mcr-1* in *Escherichia coli* from food-producing animals. *The Lancet Infectious Diseases, 16*(3), 293.

companion animals and humans too.[144] As well as evidence for transfer from food animals to humans through the food chain, there is also evidence for transfer from food animals to companion animals through raw meat.[145] However, more work is needed to understand the details of these animal-human AMR transmission pathways and quantify their relative impact.[146]

There is little research clearly linking resistant microbes in plants or the environment to resistance in humans – more research is needed here.[147] However, limited available evidence suggests that is possible for AMR genes in environmental microbes to mobilise and transfer from innocuous environmental microbes into human pathogens. For example, researchers screened soil bacteria for AMR gene cassettes, and found several with identical nucleotide sequences to those found in clinical pathogens.[148] In another example, it has been suggested that patients infected with azole-resistant *Aspergillus fumigatus* may have become infected through exposure to environmental sources of the fungus following treatment with antifungal plant sprays.[149] Noentheless, direct evidence of environment-to-human transmission routes is scarce.[150]

Even if spread of resistant microbes and genes from plants and animals plays a relatively minor role in AMR in human health (compared to overuse and inappropriate use of antimicrobial medicines), AMR in plants and animals can impact agricultural productivity and animal welfare, so is problematic in its own right.

2.3.4 Kotahitanga: A holistic approach

Because of the flows of antimicrobials, resistant pathogens, and resistance genes between humans, animals, plants, and the environment, a transdisciplinary and collaborative approach is needed to tackle AMR.

Overseas and here in Aotearoa New Zealand, the term 'One Health' is used to describe a collaborative, transdisciplinary approach to combating health hazards, including infectious disease and AMR, across

Our approach emphasises kaitiakitanga: the need to be kaitiaki (guardians) of our antimicrobial medicines to ensure they are available for future generations.

https://doi.org/10.1016/S1473-3099(16)00061-X; Marshall, B.M., & Levy, S.B. (2011). Food animals and antimicrobials: Impacts on human health. *Clinical Microbiology Reviews, 24*(4), 718-733. https://doi.org/10.1128/cmr.00002-11

[144] Joosten, P., Ceccarelli, D., Odent, E.*, et al.* (2020). Antimicrobial usage and resistance in companion animals: A cross-sectional study in three European countries. *Antibiotics, 9*(2). https://doi.org/10.3390/antibiotics9020087; Toombs-Ruane, L.J., Benschop, J., French, N.P.*, et al.* (2020). Carriage of extended-spectrum-beta-lactamase- and *AmpC* beta-lactamase-producing *Escherichia coli* strains from humans and pets in the same households. *Applied and Environmental Microbiology, 86*(24). https://doi.org/10.1128/aem.01613-20; Ljungquist, O., Ljungquist, D., Myrenås, M.*, et al.* (2016). Evidence of household transfer of ESBL-/pAmpC-producing Enterobacteriaceae between humans and dogs – a pilot study. *Infection Ecology & Epidemiology, 6*(1), 31514. https://doi.org/10.3402/iee.v6.31514

[145] Nüesch-Inderbinen, M., Treier, A., Zurfluh, K.*, et al.* (2019). Raw meat-based diets for companion animals: A potential source of transmission of pathogenic and antimicrobial-resistant Enterobacteriaceae. *Royal Society Open Science, 6*(10), 191170. https://doi.org/10.1098/rsos.191170

[146] Priest, P., Toombs-Ruane, L., Benschop, J.*, et al.* (2017). A One Health future to meet the AMR challenge? *New Zealand Veterinary Journal, 65*(2), 60-61. https://doi.org/10.1080/00480169.2016.1270651

[147] Chatterjee, A., Modarai, M., Naylor, N.R.*, et al.* (2018). Quantifying drivers of antibiotic resistance in humans: A systematic review. *The Lancet Infectious Diseases, 18*(12), e368-e378. https://doi.org/10.1016/S1473-3099(18)30296-2

[148] Forsberg, K.J., Reyes, A., Wang, B.*, et al.* (2012). The shared antibiotic resistome of soil bacteria and human pathogens. *Science, 337*(6098), 1107. https://doi.org/10.1126/science.1220761

[149] Burks, C., Darby, A., Gómez Londoño, L.*, et al.* (2021). Azole-resistant *Aspergillus fumigatus* in the environment: Identifying key reservoirs and hotspots of antifungal resistance. *PLOS Pathogens, 17*(7), e1009711. https://doi.org/10.1371/journal.ppat.1009711; Snelders, E., Veld, R.A.G.H.i.t., Rijs, A.J.M.M.*, et al.* (2009). Possible environmental origin of resistance of *Aspergillus fumigatus* to medical triazoles. *Applied and Environmental Microbiology, 75*(12), 4053-4057. https://doi.org/10.1128/AEM.00231-09

[150] Chatterjee, A., Modarai, M., Naylor, N.R.*, et al.* (2018). Quantifying drivers of antibiotic resistance in humans: A systematic review. *The Lancet Infectious Diseases, 18*(12), e368-e378. https://doi.org/10.1016/S1473-3099(18)30296-2

the human health, animal health and environmental sectors.[151]

For this project, we have chosen to use the term 'kotahitanga,' meaning unity or togetherness in te reo Māori, to capture the same concepts embodied in One Health, adapted for the Aotearoa New Zealand context and with an added focus on equity of health outcomes across our diverse communities. Different communities – including Māori and Pacific peoples, people living in rural and remote areas, and refugees and migrants – all have different contexts and challenges when it comes to health and wellbeing. These need to be accounted for in any solutions related to combatting infections disease and AMR. To enact meaningful change to mitigate AMR and the impact of infectious diseases, we need to consider the whole system and all people. Our approach also emphasises kaitiakitanga: the need to be kaitiaki (guardians) of our antimicrobial medicines to ensure they are available for future generations.

One Health operational definition

The One Health High Level Expert Panel has developed an operational definition of One Health, endorsed by the FAO, World Organisation for Animal Health (OIE), United Nations Environment Programme and WHO:[152]

> "One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and inter-dependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change, and contributing to sustainable development."

[151] McEwen Scott, A., Collignon Peter, J., Aarestrup Frank, M.*, et al.* (2018). Antimicrobial resistance: A One Health perspective. *Microbiology Spectrum, 6*(2), 6.2.10. https://doi.org/10.1128/microbiolspec.ARBA-0009-2017

[152] Food and Agriculture Organization of the United Nations, World Organisation for Animal Health (OIE), World Health Organization*, et al.* (2021, 1 December). *Tripartite and UNEP support OHHLEP's definition of "One Health"* [Press release]. Retrieved from https://www.oie.int/en/tripartite-and-unep-support-ohhleps-definition-of-one-health/

2.4 Global state of play

2.4.1 Global status of infectious disease

In the last 30 years, global health has steadily improved. Disease burden has shifted away from infectious disease towards noncommunicable conditions such as heart disease and cancer (Figure 9) – although there is significant global variation in this trend (Figure 10).

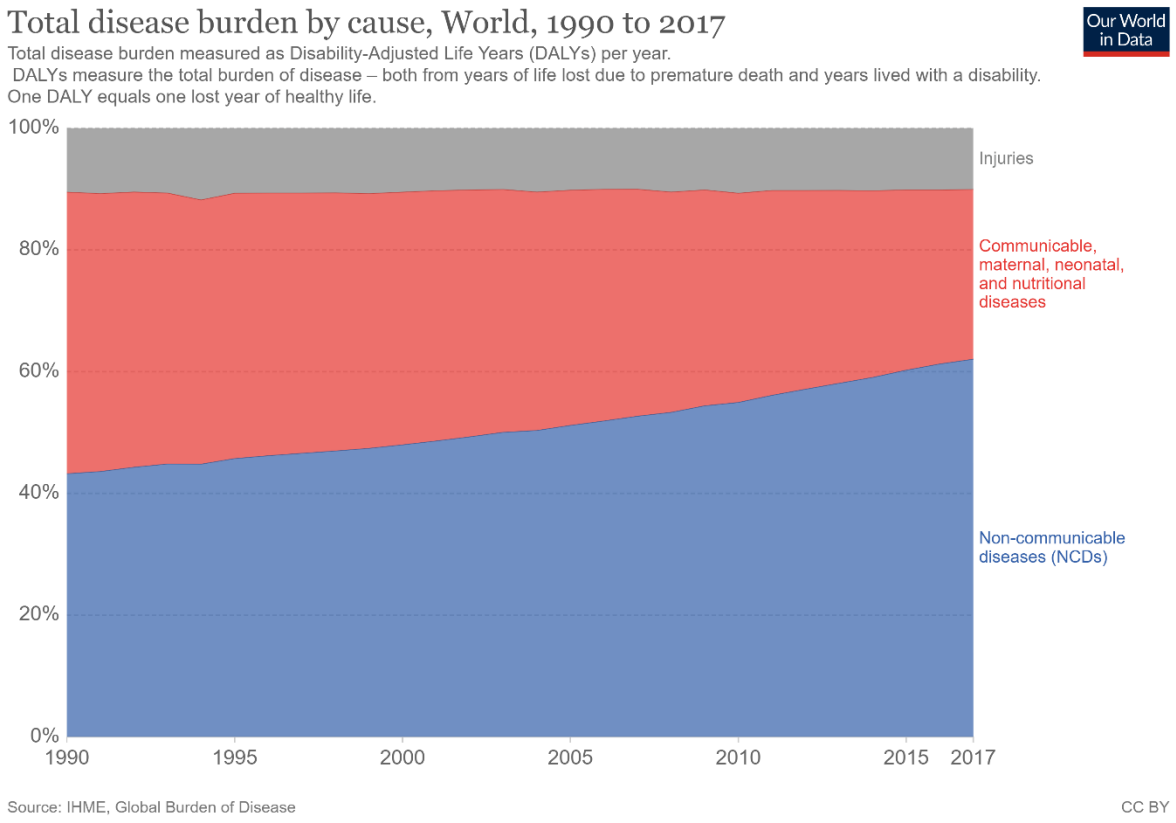

Figure 9: Total disease burden measured in DALYs over time. Image credit: Our World in Data (CC BY 4.0).

Nonetheless, infectious diseases still cause significant loss of life and wellbeing. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) measures disability-adjusted life-years (DALYs) due to 369 diseases and injuries.[153] Statistics from the most recent GBD (2019) relevant to infectious disease are summarised in Table 1. In 2019, over 7 million people died from infectious diseases. With an estimated 17 million people killed by COVID-19 as at October 2021,[154] the toll taken by infectious diseases for 2020 and 2021 will be considerably greater.

[153] Vos, T., Lim, S.S., Abbafati, C.*, et al.* (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet, 396*(10258), 1204-1222. https://doi.org/10.1016/S0140-6736(20)30925-9

[154] IHME. (n.d.). COVID-19 projections. Retrieved 24 November, 2021, from https://covid19.healthdata.org/; The Economist. (2021, 22 November). Tracking COVID-19 excess deaths across countries. Retrieved 24 November, 2021, from https://www.economist.com/graphic-detail/coronavirus-excess-deaths-tracker

Table 1: Deaths and DALYs in 2019 attributed to infectious disease. Data accessed from the Global Health Data Exchange on 23 July 2021.[155]

Disease group	Number of deaths	% of all deaths	Number of DALYs
Respiratory infections	3.68 million	6.51%	153 million
TB	*1.18 million*	*2.09%*	*47 million*
Enteric (intestinal) infections	1.75 million	3.09%	96.8 million
STIs	954,000	1.69%	56.2 million
HIV/AIDS	*864,000*	*1.53%*	*47.6 million*
Other STIs	*90,000*	*0.16%*	*8.57 million*
Other infectious diseases (e.g. whooping cough, measles, tetanus)	730,000	1.29%	51.4 million
Neglected tropical diseases (incl. malaria)	747,000	1.32%	62.9 million
Total	7.86 million	13.9%	420 million

Some key conclusions from the 2019 GBD analysis[156] follow:

- **Infectious diseases are a significant cause of harm among children.** Six infectious diseases were among the top ten causes of DALYs in children younger than 10 years in 2019: lower respiratory infections (ranked second), diarrhoeal diseases (third), malaria (fifth), meningitis (sixth), whooping cough (ninth), and STIs (which, in this age group, is fully accounted for by congenital syphilis; ranked tenth).
- **The burden of infectious disease is not spread equally across the world** (Figure 10). The burden is concentrated in developing countries in sub-Saharan Africa and South and Southeast Asia. There are also inequities within countries, with some groups more affected by infectious diseases than other.
- **HIV/AIDS is the biggest contributor to the burden of STIs.** Of the aggregated DALYs caused by STIs, 97.2% were attributable to HIV/AIDS. The majority of this burden was in sub-Saharan Africa. Note that HIV/AIDS can also be transmitted by routes other than sexual contact – for example, through blood transfusions and intravenous (IV) injections.
- **Infections of the intestine are also a major cause of death and disability.** There were 6.6 billion new cases and 98.8 million ongoing cases in 2019. This includes infections such as campylobacteriosis and salmonellosis.

What is a DALY?

According to WHO, "Mortality does not give a complete picture of the burden of disease borne by individuals in different populations. The overall burden of disease is assessed using the DALY, a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health, or years of healthy life lost due to disability. One DALY represents the loss of the equivalent of one year of full health. Using DALYs, the burden of diseases that cause premature death but little disability (such as drowning or measles) can be compared to that of diseases that do not cause death but do cause disability (such as cataract causing blindness)."

[155] IHME. (2020). *Global Burden of Disease 2019*. Retrieved from: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/195510a3e8223860c35341922e74ecbf

[156] Vos, T., Lim, S.S., Abbafati, C.*, et al.* (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet, 396*(10258), 1204-1222. https://doi.org/10.1016/S0140-6736(20)30925-9

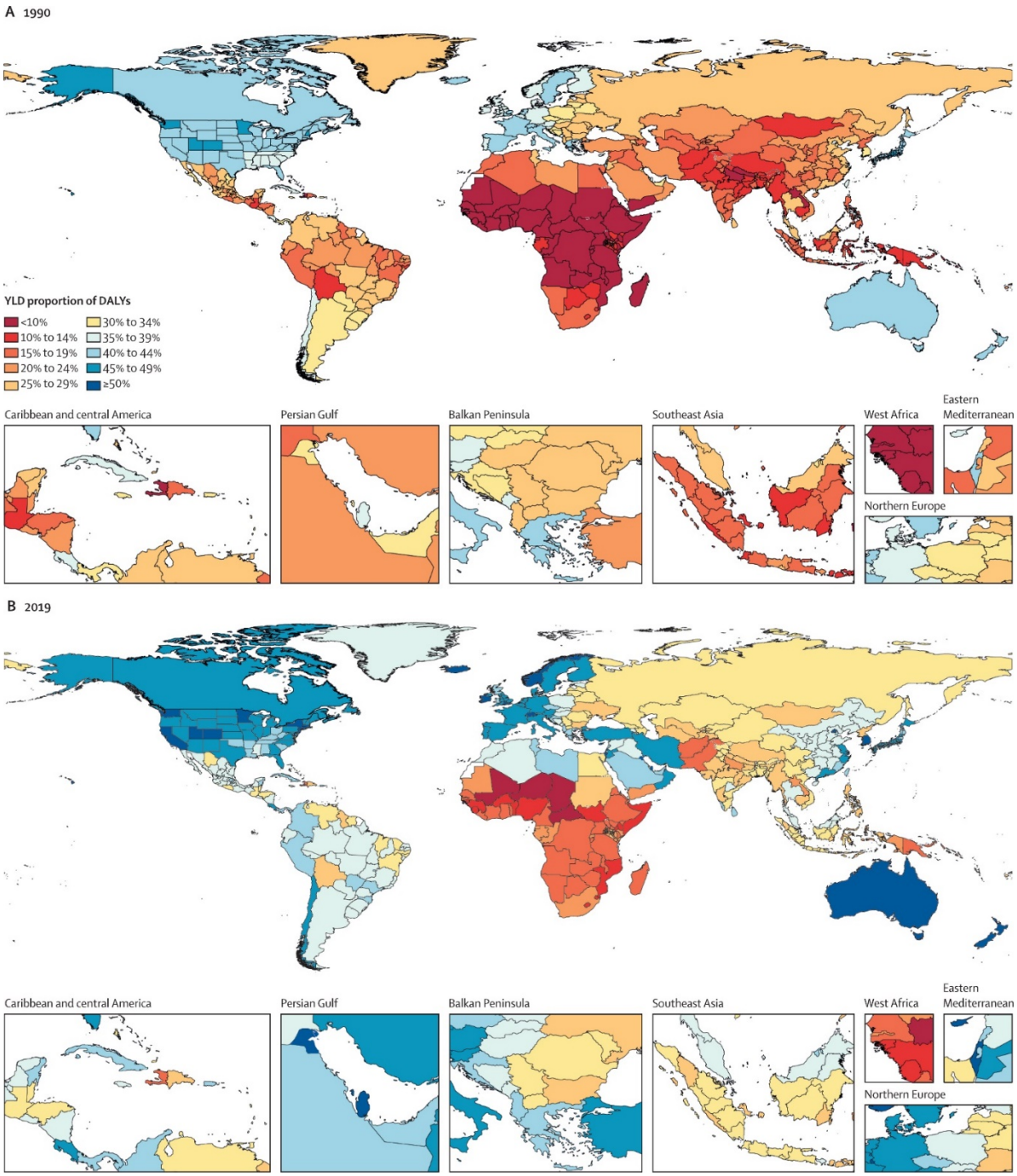

Figure 10: Map showing age-standardised DALY rates per 100,000 by location in 1990 and 2019 (CC BY 4.0).[157] To explore this dataset on an interactive map, go to the GBD Compare Viz Hub.[158]

[157] Ibid.

[158] IHME. (2019). GBD Compare Viz Hub. Retrieved 26 November, 2021, from https://vizhub.healthdata.org/gbd-compare/

Respiratory diseases are a leading cause of death and disability

Infectious respiratory diseases are responsible for considerable loss of life and health.[159] About one-quarter of the world's population is infected with TB. Those infected with TB have a 5-10% lifetime risk of developing active disease. In 2019, an estimated 10 million people contracted TB, resulting in around 1.2 million deaths among HIV-negative people, and a further 208,000 deaths in people with HIV.[160] Pre-COVID, TB was the most lethal infectious pathogen worldwide. Ninety percent of all TB cases are concentrated in 30 high-burden countries.

Acute lower respiratory infections and pneumonia, caused by a range of viral and bacterial pathogens, are a leading infectious cause of mortality among both children and adults, resulting in millions of fatalities every year.[161] Examples of causative pathogens include *Streptococcus pneumoniae*, the influenza virus, and respiratory syncytial virus (RSV).

Unsafe food costs lives

WHO estimates that one in ten people fall ill after consuming unsafe food every year.[162] From 2007 to 2015, the WHO Foodborne Disease Burden Epidemiology Reference Group was tasked with estimating the worldwide burden of 32 foodborne diseases caused by various viruses, bacteria, parasites, and some chemicals.[163]

One in ten people fall ill after consuming unsafe food every year.

The Reference Group found that in 2010, there were 600 million cases of foodborne illness resulting in 420,000 deaths. The most common causes of foodborne illness were norovirus and *Campylobacter* spp., while *Salmonella* spp. and hepatitis A were among those pathogens responsible for the greatest number of deaths. An estimated 33 million years of healthy life were lost, with 40% of this burden falling on children aged five or younger. Low-to-middle income countries bear a greater share of the burden, particularly Africa, South East Asia, and the Eastern Mediterranean.

Healthcare-associated infections are a hidden burden

Worldwide, an estimated 10% of patients receiving healthcare develop an infection related to this care. The risk of acquiring an infection rises to around 30% for ICU patients, and patients with invasive devices such as catheters and ventilators suffer more frequent infections. HAIs result in longer hospital stays, higher costs, increased AMR, long-term disabilities, and excess deaths.[164]

[159] Forum of International Respiratory Societies. (2017). *The global impact of respiratory disease*. Sheffield, UK: European Respiratory Society. Retrieved from https://theunion.org/sites/default/files/2020-08/The_Global_Impact_of_Respiratory_Disease.pdf
[160] World Health Organization. (2020). *Global tuberculosis report 2020*. Geneva, Switzerland: Retrieved from https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf
[161] Murdoch, D.R., & Howie, S.R.C. (2018). The global burden of lower respiratory infections: Making progress, but we need to do better. *The Lancet Infectious Diseases, 18*(11), 1162-1163. https://doi.org/10.1016/S1473-3099(18)30407-9
[162] World Health Organization. (n.d.). Estimating the burden of foodborne diseases. Retrieved 25 July, 2021, from https://www.who.int/activities/estimating-the-burden-of-foodborne-diseases
[163] World Health Organization Foodborne Disease Burden Epidemiology Reference Group 2007–2015. (2015). *WHO estimates of the global burden of foodborne diseases*. Geneva, Sitzerland: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/199350/9789241565165_eng.pdf?sequence=1
[164] World Health Organization. (2011). *Report on the burden of endemic health care-associated infection worldwide*. Geneva, Switzerland: Retrieved from https://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf

2.4.2 Global status of AMR

AMR is like a series of small fires, rather than the raging firestorm of a pandemic. But left too long, these fires can coalesce into something much bigger and more serious. If we act now, we can prevent a full-scale conflagration. But to do this, we need to treat antimicrobial medicines like fire extinguishers: they are ready on the shelf when needed, but they aren't used every day indiscriminately.

AMR is like a series of small fires, rather than the raging firestorm of a pandemic.

But left too long, these fires can coalesce into something much bigger and more serious.

If we act now, we can prevent a full-scale conflagration.

It is estimated that infections caused by drug-resistant pathogens currently cause 700,000 deaths worldwide every year.[165] This includes deaths in developed countries with modern health systems, like Aotearoa New Zealand. In the US, there are an estimated 2.8 million infections caused by drug-resistant pathogens every year, causing 35,000 fatalities.[166] In the EU, an estimated 25,000 people die from infections caused by drug-resistant pathogens every year.[167]

In the foreword to a 2019 US CDC report titled *Antibiotic Resistance Threats in the United States*, the director of the CDC Robert Redfield wrote:

> "Stop referring to a coming post-antibiotic era – it's already here. You and I are living in a time when some miracle drugs no longer perform miracles and families are being ripped apart by a microscopic enemy. The time for action is now and we can be part of the solution."[168]

The economic cost is huge, with multidrug-resistant bacteria costing NZ$2.5 billion in lost productivity and extra healthcare expenses in the EU, Iceland, and Norway alone.[169] A 2018 analysis found that, if no action is tackle to tackle AMR across 33 EU and Organisation for Economic Co-operation and Development (OECD) countries, up to roughly NZ$5 billion (adjusted for purchasing power parity) is expected to be spent yearly between 2015 and 2050 on AMR-related complications, corresponding to 10% of healthcare costs associated with infectious diseases in those countries.[170]

AMR does not affect everyone equally. As with infectious diseases generally, AMR disproportionately affects old and young people, and those in ill-health, including people with compromised immune systems. The burden of AMR is also greater in low- and middle-income

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[165] O'Neill, J. (2016). *Tackling drug-resistant infections globally: Final report and recommendations*. UK: HM Government and Wellcome Trust. Retrieved from https://amr-review.org/

[166] Centers for Disease Control and Prevention. (2019). *Antibiotic resistance threats in the United States*. Atlanta, Georgia, USA: CDC. Retrieved from https://www.cdc.gov/drugresistance/biggest-threats.html

[167] European Commission. (2017). *AMR: A major European and global challenge*. Retrieved from https://ec.europa.eu/health/sites/default/files/antimicrobial_resistance/docs/amr_2017_factsheet.pdf

[168] Centers for Disease Control and Prevention. (2019). *Antibiotic resistance threats in the United States*. Atlanta, Georgia, USA: CDC. Retrieved from https://www.cdc.gov/drugresistance/biggest-threats.html

[169] European Centre for Disease Prevention and Control, & European Medicines Agency. (2009). *The bacterial challenge: Time to react*. Stockholm, Sweden: Retrieved from https://www.ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf

[170] OECD. (2018). *Stemming the superbug tide: Just a few dollars more*. Retrieved from https://www.oecd.org/health/health-systems/Stemming-the-Superbug-Tide-Policy-Brief-2018.pdf

countries compared with high-income countries.[171] Global predictions of AMR abundance based on wastewater surveillance reveal hotspots in South America, Africa and South East Asia (Figure 11).[172]

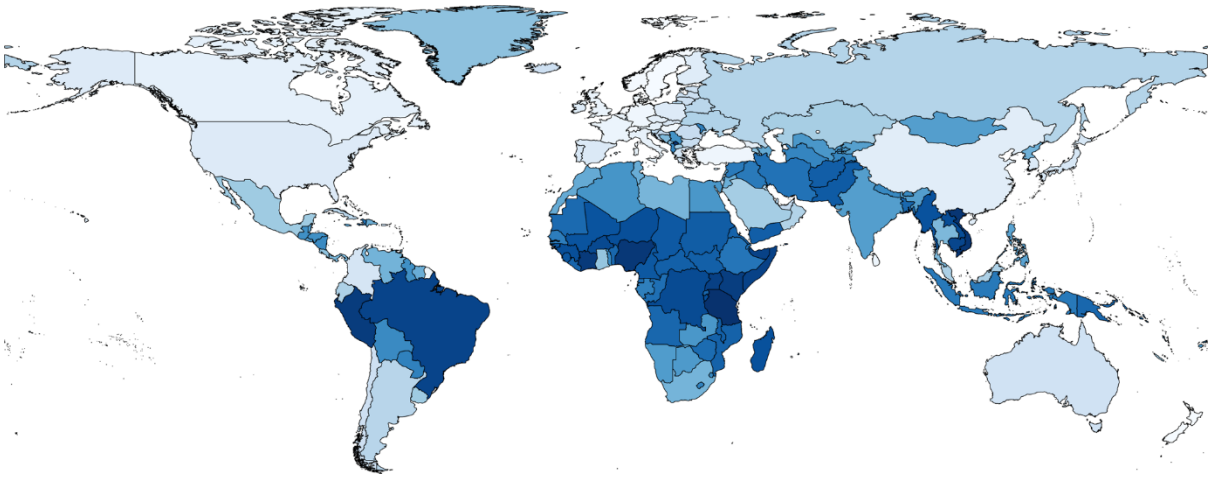

Figure 11: Global predictions of AMR abundance with light blue indicating low abundance and dark blue indicating high abundance.[173] (CC BY 4.0).

In recent years, AMR has garnered attention on the world policy stage. The annual World Economic Forum Global Risks report has consistently mentioned or featured AMR in its last ten reports (since 2013).[174] Earlier this year, WHO listed combatting drug resistance as a 'global health issue to track' for 2021.[175]

Most unwanted: Drug-resistant pathogens

In 2017, WHO published a list of antibiotic-resistant pathogens (Table 2).[176] They are grouped into three tiers – critical, high and medium – according to how urgently new treatments are needed.

ESKAPE pathogens

ESKAPE is a common acronym used to refer to six pathogens characterised by their ability to cause severe disease and death, high levels of multidrug resistance, and role in fatal hospital-acquired infections.[177] The ESKAPE pathogens are:

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter* spp.

The ESKAPE pathogens are all included as high or critical priority on the WHO list above. All of these pathogens are present in Aotearoa New Zealand. For more details see section 4.3.1.

[171] Vikesland, P., Garner, E., Gupta, S., *et al.* (2019). Differential drivers of antimicrobial resistance across the world. *Accounts of Chemical Research, 52*(4), 916-924. https://doi.org/10.1021/acs.accounts.8b00643
[172] Hendriksen, R.S., Munk, P., Njage, P., *et al.* (2019). Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nature Communications, 10*(1), 1124. https://doi.org/10.1038/s41467-019-08853-3
[173] Ibid.
[174] World Economic Forum. (2021, 19 January). Global risks: Archive. Retrieved 19 May, 2021, from https://www.weforum.org/global-risks/archive
[175] World Health Organization. (2020, 24 December). 10 global health issues to track in 2021. Retrieved 24 May, 2021, from https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021
[176] World Health Organization. (2017). *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*. Retrieved from https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf
[177] Mulani, M.S., Kamble, E.E., Kumkar, S.N., *et al.* (2019). Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: A review. *Front Microbiol, 10*, 539. https://doi.org/10.3389/fmicb.2019.00539

Table 2: WHO list of priority antibiotic-resistant pathogens.

	Organism	Resistance profile	Selected infection types
Priority 1: CRITICAL	*Acinetobacter baumannii*	Carbapenem resistant.	Hospital acquired. Can cause pneumonia, bloodstream infections/sepsis, meningitis, UTIs, SSIs and wound infections.
	Pseudomonas aeruginosa	Carbapenem resistant.	Hospital acquired. Can cause bloodstream infections/sepsis, pneumonia and SSIs.
	Enterobacterales (Includes *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp.)	Carbapenem resistant, third generation cephalosporin resistant.	Some species can be present naturally in gut flora. Can cause UTIs, diarrhoea and bloodstream infections/sepsis.
Priority 2: HIGH	*Enterococcus faecium*	Vancomycin resistant.	Can cause neonatal meningitis, endocarditis (heart inflammation), infections associated with medical devices such as catheters, UTIs, bloodstream infections/sepsis, SSIs and wound infections.
	Staphylococcus aureus	Methicillin resistant, vancomycin intermediate and resistant.	Found naturally on skin and in upper respiratory tract. Can cause minor skin and respiratory infections, and food poisoning. Can also cause life-threatening infections such as toxic shock syndrome, bloodstream infections/sepsis, meningitis, pneumonia and endocarditis.
	Helicobacter pylori	Clarithromycin resistant.	Causes stomach ulcers.
	Campylobacter spp.	Fluoroquinolone resistant.	Causes campylobacteriosis, a type of food poisoning.
	Salmonella spp.	Fluoroquinolone resistant.	Causes salmonellosis, a gastrointestinal disease.
	Neisseria gonorrhoeae	Third generation cephalosporin resistant, fluoroquinolone resistant.	Causes gonorrhoea, an STI.
Priority 3: MEDIUM	*Streptococcus pneumoniae*	Penicillin non-susceptible.	Can cause pneumonia and meningitis in children and the elderly.
	Haemophilus influenzae	Ampicillin resistant.	Can cause a range of infections, from mild ear infections through to serious bloodstream infections, meningitis, pneumonia and cellulitis.
	Shigella spp.	Fluoroquinolone resistant.	Causes shigellosis, a type of food poisoning.

Below we briefly examine the characteristics of WHO's three critical pathogens, underscoring the seriousness of these pathogens and how important it is for Aotearoa New Zealand to act before they become prevalent here. See section 4.3.1 for evidence of these pathogens in Aotearoa New Zealand.

Acinetobacter baumannii, carbapenem resistant

Identified in some patients in Aotearoa New Zealand, but not yet endemic.

Bloodstream infections caused by carbapenem-resistant ***A. baumannii*** can have **mortality rates as high as 50-60%.**

A. baumannii is a gram-negative bacterium that is harmless for most people but opportunistically pathogenic in some situations. We don't know where *A. baumannii* naturally occurs; it has largely been isolated from hospital settings.[178] It is particularly prevalent in ICUs, where it is more likely to infect people undergoing treatment that requires use of invasive devices such as ventilators or catheters. It most commonly causes ventilator-associated pneumonia or bloodstream infections.

It is extremely difficult to treat carbapenem-resistant *A. baumannii* infection, with current treatment options relatively ineffective and displaying significant toxicity and side effects.[179] Bloodstream infections caused by carbapenem-resistant *A. baumannii* can have mortality rates as high as 50-60%.[180] In the US in 2017, carbapenem-resistant *A. baumannii* caused an estimated 8,500 infections and 700 deaths in 2017.[181]

Rates of carbapenem-resistant *A. baumannii* vary widely around the world. For example, a recent study from Germany found carbapenem resistance rates among hospitalised patients of just 4.4% in 2018.[182] In other countries, such as Greece and Turkey, the prevalence of carbapenem resistance in *A. baumannii* exceeds 90%.[183] Overall, the global proportion of carbapenem resistance has increased from less than 4% in 2000, to greater than 60% in 2016.[184]

A. baumannii is notable for its:

- propensity to acquire and swap genes that confer resistance, including a reservoir of 45 known resistance genes within its genome[185] and the ability to develop resistance in the midst of a course of antibiotics,[186]

[178] Antunes, L.C.S., Visca, P., & Towner, K.J. (2014). *Acinetobacter baumannii*: Evolution of a global pathogen. *Pathogens and Disease, 71*(3), 292-301. https://doi.org/10.1111/2049-632X.12125

[179] Isler, B., Doi, Y., Bonomo, R., A*., et al.* (2018). New treatment options against carbapenem-resistant *Acinetobacter baumannii* infections. *Antimicrobial Agents and Chemotherapy, 63*(1), e01110-01118. https://doi.org/10.1128/AAC.01110-18

[180] Wong, D., Nielsen, T.B., Bonomo, R., A*., et al.* (2017). Clinical and pathophysiological overview of Acinetobacter infections: A century of challenges. *Clinical Microbiology Reviews, 30*(1), 409-447. https://doi.org/10.1128/CMR.00058-16

[181] Centers for Disease Control and Prevention. (2019). *Antibiotic resistance threats in the United States*. Atlanta, Georgia, USA: CDC. Retrieved from https://www.cdc.gov/drugresistance/biggest-threats.html

[182] Said, D., Willrich, N., Ayobami, O*., et al.* (2021). The epidemiology of carbapenem resistance in *Acinetobacter baumannii* complex in Germany (2014–2018): An analysis of data from the national Antimicrobial Resistance Surveillance system. *Antimicrobial Resistance & Infection Control, 10*(1), 45. https://doi.org/10.1186/s13756-021-00909-8

[183] Xie, R., Zhang, X.D., Zhao, Q*., et al.* (2018). Analysis of global prevalence of antibiotic resistance in *Acinetobacter baumannii* infections disclosed a faster increase in OECD countries. *Emerging Microbes & Infections, 7*(1), 1-10. https://doi.org/10.1038/s41426-018-0038-9

[184] Wong, D., Nielsen, T.B., Bonomo, R., A*., et al.* (2017). Clinical and pathophysiological overview of Acinetobacter infections: A century of challenges. *Clinical Microbiology Reviews, 30*(1), 409-447. https://doi.org/10.1128/CMR.00058-16

[185] Ibid.

[186] Shields, R.K., Clancy, C.J., Gillis, L.M*., et al.* (2012). Epidemiology, clinical characteristics and outcomes of extensively drug-resistant *Acinetobacter baumannii* infections among solid organ transplant recipients. *PLOS One, 7*(12), e52349. https://doi.org/10.1371/journal.pone.0052349

- inherent resistance to a range of antibiotics, due to its low-permeability membrane and high efflux making it difficult for antibiotics to diffuse into the cell,[187] and
- ability to survive on surfaces – resisting desiccation and disinfectants.[188]

Pseudomonas aeruginosa, carbapenem resistant

Identified in some patients in Aotearoa New Zealand, but not yet endemic.

P. aeruginosa is a gram-negative bacterium that is opportunistically pathogenic. It is associated with HAIs, particularly in patients fitted with invasive devices, or open wounds from surgery or burns. *P. aeruginosa* is found in soil and water, but also spreads via surfaces, hands and equipment in healthcare settings.

P. aeruginosa can acquire resistance to one or more carbapenems through different mechanisms, such as producing enzymes to break down the drugs, or enhancing its ability to pump carbapenems out of the cell.[189] The type of carbapenem resistance affects how an infection can be treated – for example, strains of *P. aeruginosa* that produce metallo-β-lactamase enzymes often need to be treated with colistin, a last-resort antibiotic that is very difficult to use effectively and is very toxic to humans, especially to the kidneys and nervous system, including the brain.[190]

In the US in 2017, there were an estimated 32,600 cases of multidrug-resistant *P. aeruginosa*, resulting in an estimated 2,700 deaths.[191] Carbapenem-resistant strains of *P. aeruginosa* are associated with increased mortality risk.[192]

Rates of carbapenem resistance in *P. aeruginosa* vary around the world. According to Pfizer's Atlas surveillance tool, isolates from South American hospitals display 20-40% resistance, while rates of resistance in some parts of Eastern Europe and Southeast Asia approach or exceed 50%.[193]

Enterobacterales, carbapenem resistant, third generation cephalosporin resistant

Identified in some patients in Aotearoa New Zealand, with a carbapenem-resistant cluster in the Te Whanganui-a-Tara Wellington region and fairly widespread presence of cephalosporin resistance.

Includes *Klebsiella pneumoniae, Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp.

Enterobacterales are an order of bacteria that commonly inhabit the gut without causing any problems. But if they get into a place where they're not supposed to be, such as the bladder or bloodstream, they can cause a serious infection that needs to be treated with antibiotics.

An increasing number of people are carrying Enterobacterales that are resistant to antibiotics. Infections caused by these resistant Enterobacterales are particularly difficult to treat and can result

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[187] Wong, D., Nielsen, T.B., Bonomo, R., A*., et al.* (2017). Clinical and pathophysiological overview of Acinetobacter infections: A century of challenges. *Clinical Microbiology Reviews, 30*(1), 409-447. https://doi.org/10.1128/CMR.00058-16

[188] Chapartegui-González, I., Lázaro-Díez, M., Bravo, Z*., et al.* (2018). *Acinetobacter baumannii* maintains its virulence after long-time starvation. *PLOS One, 13*(8), e0201961-e0201961. https://doi.org/10.1371/journal.pone.0201961

[189] Meletis, G., Exindari, M., Vavatsi, N*., et al.* (2012). Mechanisms responsible for the emergence of carbapenem resistance in *Pseudomonas aeruginosa*. *Hippokratia, 16*(4), 303-307.

[190] Kazmierczak, K.M., Rabine, S., Hackel, M*., et al.* (2016). Multiyear, multinational survey of the incidence and global distribution of metallo-beta-lactamase-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa*. *Antimicrobial Agents and Chemotherapy, 60*(2), 1067-1078. https://doi.org/10.1128/AAC.02379-15

[191] Centers for Disease Control and Prevention. (2019). *Antibiotic resistance threats in the United States*. Atlanta, Georgia, USA: CDC. Retrieved from https://www.cdc.gov/drugresistance/biggest-threats.html

[192] Liu, Q., Li, X., Li, W*., et al.* (2015). Influence of carbapenem resistance on mortality of patients with *Pseudomonas aeruginosa* infection: A meta-analysis. *Scientific Reports, 5*(1), 11715. https://doi.org/10.1038/srep11715

[193] Pfizer. (2021). Atlas surveillance heatmap. Retrieved 16 July 2021 https://atlas-surveillance.com/

in death. Some carbapenem-resistant Enterobacterales (CRE) are resistant to all available antibiotics and are associated with high mortality rates.[194]

CRE are concerning for their tendency to spread.[195] There are different enzymes capable of hydrolysing carbapenem antibiotics including the New Delhi metallo-β-lactamase enzyme (NDM), *Klebsiella pneumoniae* carbapenemase (KPC), and OXA-48. CRE infection is mostly in hospital settings, although there have been some reported community-acquired cases.[196] Countries with high CRE rates include Greece, Italy, Brazil, the US, and China. CRE rates among *K. pneumoniae* reach 62% in Greece. India may also have higher CRE prevalence driven by the NDM carbapenemase, but data are scarce. In the US, CRE caused an estimated 13,100 cases and 1,100 deaths in 2017.[197]

Enterobacterales resistant to cephalosporins have acquired the ability to produce ESBL, a type of enzyme capable of breaking down β-lactam antibiotics. Patients with an infection caused by an ESBL-producing Enterobacterales may not be able to take oral antibiotics at home and may require more complex treatment including IV antibiotics in hospital. In 2017, there were an estimated 197,400 cases of ESBL-producing Enterobacterales in the US, and an estimated 9,100 deaths.[198] ESBL-producing Enterobacterales have been present in Aotearoa New Zealand since the late 1990s with a steadily growing prevalence; the local situation is explored further in section 4.3.1.

Resistance mechanisms can be tracked in addition to pathogens

Rather than tracking pathogens, we can also track types of resistance mechanisms that can be shared between different bacteria species via HGT. For example, the ESBL resistance mechanism has swept around the world in recent years. Currently, average global colonisation with ESBL-producing organisms is 14% and growing 5.4% annually.[199] In some parts of the world, there is up to 50% prevalence of faecal colonisation with ESBL-producing Enterobacterales.

Emerging mechanisms to resist carbapenem antibiotics are particularly worrying given that some are resistant to all available antibiotics and are associated with high mortality rates.[200]

In 2015, a gene encoding resistance to colistin, a last-resort antibiotic used to treat CRE, was discovered in humans, food and food animals in China.[201] Called *mcr-1*, the gene has since been detected in isolates of various organisms around the world.[202] Ten subtypes of the *mcr* gene have since been identified.[203]

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[194] Tumbarello, M., Viale, P., Viscoli, C.*, et al.* (2012). Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: Importance of combination therapy. *Clinical Infectious Diseases, 55*(7), 943-950. https://doi.org/10.1093/cid/cis588

[195] Iovleva, A., & Doi, Y. (2017). Carbapenem-resistant Enterobacteriaceae. *Clinics in Laboratory Medicine, 37*(2), 303-315. https://doi.org/10.1016/j.cll.2017.01.005

[196] Kelly, A.M., Mathema, B., & Larson, E.L. (2017). Carbapenem-resistant Enterobacteriaceae in the community: A scoping review. *International Journal of Antimicrobial Agents, 50*(2), 127-134. https://doi.org/10.1016/j.ijantimicag.2017.03.012

[197] Centers for Disease Control and Prevention. (2019). *Antibiotic resistance threats in the United States*. Atlanta, Georgia, USA: CDC. Retrieved from https://www.cdc.gov/drugresistance/biggest-threats.html

[198] Ibid.

[199] Karanika, S., Karantanos, T., Arvanitis, M.*, et al.* (2016). Fecal colonization with extended-spectrum beta-lactamase-producing Enterobacteriaceae and risk factors among healthy individuals: A systematic review and metaanalysis. *Clinical Infectious Diseases, 63*(3), 310-318. https://doi.org/10.1093/cid/ciw283

[200] Holmes, A.H., Moore, L.S.P., Sundsfjord, A.*, et al.* (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet, 387*(10014), 176-187. https://doi.org/10.1016/S0140-6736(15)00473-0

[201] Liu, Y.-Y., Wang, Y., Walsh, T.R.*, et al.* (2016). Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. *The Lancet Infectious Diseases, 16*(2), 161-168. https://doi.org/10.1016/S1473-3099(15)00424-7

[202] Xiaomin, S., Yiming, L., Yuying, Y.*, et al.* (2020). Global impact of mcr-1-positive Enterobacteriaceae bacteria on "one health". *Critical Reviews in Microbiology, 46*(5), 565-577. https://doi.org/10.1080/1040841X.2020.1812510

[203] Wang, C., Feng, Y., Liu, L.*, et al.* (2020). Identification of novel mobile colistin resistance gene mcr-10. *Emerging Microbes & Infections, 9*(1), 508-516. https://doi.org/10.1080/22221751.2020.1732231

2.4.3 International initiatives

The issue of AMR has received significant global attention in the past decade, with a large number of international initiatives, although it has been overshadowed by COVID-19 since early 2020. As AMR is a global problem, we need international collaborations and connections to tackle it. Aotearoa New Zealand can tap into the knowledge, lessons and ideas captured by these initiatives, as well as actively participate and connect to do our bit to collectively combat AMR. This section briefly outlines key reports and initiatives that form the global response to AMR.

The initiatives are grouped based on their common areas of focus:

International reports and reviews – Work from WHO and a review from the UK have been particularly influential in shaping global discourse on AMR.

Policy, analysis and advocacy – Organisations such as The Pew Charitable Trusts and the Wellcome Trust have AMR workstreams that integrate knowledge to influence policy.

Boosting the antibiotic pipeline – Several initiatives have emerged in recent years with significant funding to bring new antibiotics to market.

Funding general/other research and development – In addition to funding to support antibiotic development, funding has been made available support other kinds of AMR research and work, including exploring diagnostics and non-antimicrobial interventions.

Data sharing – Platforms and initiatives have been created to make AMR data more accessible.

International reports and reviews

Tripartite Global Action Plan on Antimicrobial Resistance, 2015

Worldwide discussion ramped up in 2015 with the endorsement of a *Tripartite Global Action Plan on Antimicrobial Resistance* at the World Health Assembly.[204] This plan is administered jointly by WHO, OIE and FAO. Member states committed to developing national action plans aligned with this global action plan by May 2017. Aotearoa New Zealand developed an action plan but has not implemented it. The *Global Action Plan on AMR* was endorsed at the UN General Assembly as part of a political declaration on AMR in 2016.[205] See appendix 7.4 for a selection of different countries' AMR action plans and how they align with the *Tripartite Global Action Plan*.

Interagency Coordination Group on Antimicrobial Resistance

The 2016 declaration also led to the formation of an inter-agency coordination group tasked with providing guidance to the UN Secretary General to ensure sustained global action on AMR. The Group on AMR released its report *No time to wait: Securing the future from drug-resistant infections* in 2019.[206] This report made five overarching recommendations:

- Accelerate progress on tackling AMR.
- Innovate to secure the future.

[204] World Health Organization. (2015). *Global action plan on antimicrobial resistance*. Geneva, Switzerland: Retrieved from https://www.who.int/publications/i/item/9789241509763
[205] United Nations General Assembly. (2016). *Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance*. Retrieved from https://digitallibrary.un.org/record/842813?ln=en
[206] Interagency Coordination Group on Antimicrobial Resistance. (2019). *No time to wait: Securing the future from drug-resistant infections*. Retrieved from https://www.who.int/docs/default-source/documents/no-time-to-wait-securing-the-future-from-drug-resistant-infections-en.pdf

- Collaborate for more effective action.
- Invest for a sustainable response.
- Strengthen accountability and global governance.

UK review on antimicrobial resistance, 2014–2016

In 2014, the UK Prime Minister commissioned economist Jim O'Neill to analyse the global problem of drug-resistant pathogens. The review was jointly supported by the UK Government Department of Health and the Wellcome Trust.

Its findings and recommendations were published in 2016, in the report *Tackling drug-resistant infections globally: Final report and recommendations*, often referred to as the O'Neill report. It includes nine interventions:

- A global public awareness campaign.
- Improve sanitation and prevent the spread of infection.
- Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment.
- Improve global surveillance of drug resistance and antimicrobial consumption in humans and animals.
- Promote new, rapid diagnostics to reduce unnecessary use of antimicrobials.
- Promote development and use of vaccines and alternatives.
- Improve the number, pay and recognition of people working in infectious disease.
- A global innovation fund for early stage and non-commercial research and development.
- Better incentives to promote investment for new drugs and improving existing ones.

Royal Society Te Apārangi expert advice paper

The issue of AMR has previously been contextualised to Aotearoa New Zealand by the Royal Society Te Apārangi, who produced an expert advice paper in 2017.[207] This was accompanied by fact sheets in both English and Te Reo Māori, and a series of short informative videos.

Policy, analysis and advocacy

The Pew Charitable Trusts Antibiotic Resistance Project

This project from US-based non-profit organisation The Pew Charitable Trusts focuses on three areas: antibiotic innovation, antibiotic use in food animals, and antibiotic use in human healthcare.[208] The project aims to support policies that:

- spur the creation of new antibiotics by removing the regulatory, economic, and scientific obstacles that impede antibiotic discovery and development,
- establish stewardship programs to ensure that antibiotics are prescribed only when necessary in human healthcare settings, and
- reduce the need for antibiotics in food animals through use of alternative products, improved management practices, and effective stewardship.

Since 2014, the project has tracked the development of new antibiotics and publishes progress annually.[209]

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[207] Royal Society Te Apārangi. (2017). *Antimicrobial Resistance – Implications for New Zealanders Evidence Update*. Wellington, New Zealand:

[208] The Pew Charitable Trusts. (n.d.). Antibiotic resistance project. Retrieved 19 July, 2021, from https://www.pewtrusts.org/en/projects/antibiotic-resistance-project

[209] The Pew Charitable Trusts. (2021, 9 March). Tracking the global pipeline of antibiotics in development, March 2021. Retrieved 19 July, 2021, from https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development

The Wellcome Trust

This UK-based organisation has a workstream dedicated to 'transforming the global response' to AMR.[210] This workstream has three objectives:

- Advancing a sustainable pipeline of antibiotics, so that new antibiotics are available around the world.
- Encouraging appropriate use of antibiotics, so that the emergence and spread of drug resistance slows down.
- Mobilising national action on AMR so that countries can effectively respond at a national level.

The Wellcome Trust has produced several publications related to AMR, including the November 2020 report *The global response to AMR*, which sets out a two-phase 'critical path' to impact.[211] The first phase, 2020-30, focuses on risk mitigation and plugging evidence gaps. The second phase, beyond 2030, moves into maintaining control of resistance and scaling up best practice.

Partnership to Fight Infectious Disease

The Partnership to Fight Infectious Disease is a US-based group working to raise awareness of the threats posed by infectious disease, comprising patients, community organisations, academic researchers and infectious disease experts, among others.[212] The Partnership is especially focused on pandemic preparedness, AMR, and COVID-19 vaccination. The Partnership produces a range of public-facing resources such as fact sheets and explainer videos on these topics, in addition to policy and advocacy work.

ReAct

Founded in 2005, ReAct is an independent international network operating across Africa, the Asia pacific, Europe, Latin America and North America.[213] They compile and share scientific evidence related to AMR, work to influence policy and encourage action to address AMR.

COMBAT-AMR

An initiative supported by Australia's Department of Foreign Affairs and Trade, bringing together organisations from across Australia, Aotearoa New Zealand and the wider Asia-Pacific region to partner with governments and National AMR Committees in Samoa, Fiji, Solomon Islands and Papua New Guinea.[214] COMBAT-AMR implements capacity building and training activities to support the prevention, diagnosis, surveillance and management of AMR pathogens in these Pacific countries. Their initial work programme covers 2019-2022 and includes activities across antimicrobial stewardship, infection prevention and control, laboratory capacity and surveillance, and animal health.

Boosting the antibiotic pipeline

Global Antibiotic Research and Development Partnership

The Global Antibiotic Research and Development Partnership is a non-profit organisation borne out of the WHO's Global Action Plan.[215] The partnership mobilises partners to develop new antibiotics, supports access to treatments and promotes responsible use of antibiotics. For example,

[210] Wellcome Trust. (n.d.). Drug-resistant infections: Transforming the global response. Retrieved 19 July, 2021, from https://wellcome.org/what-we-do/our-work/drug-resistant-infections
[211] Wellcome Trust. (2020). *The global response to AMR: Momentum, success, and critical gaps*. Retrieved from https://wellcome.org/reports/global-response-amr-momentum-success-and-critical-gaps
[212] Partnership to Fight Infectious Disease. (n.d.). About PFID. Retrieved July 19, 2021, from https://www.fightinfectiousdisease.org/about
[213] ReAct. (n.d.). About us. Retrieved 28 July, 2021, from https://www.reactgroup.org/about-us/
[214] COMBAT-AMR. (n.d.). About us. Retrieved 9 September, 2021, from https://www.combatamr.org.au/about-us
[215] GARDP. (n.d.). About GARDP. Retrieved 23 August, 2021, from https://www.gardp.org/who-we-are/about-gardp/

the partnership is supporting the late-stage development of a novel, first-in-class treatment for drug-resistant gonorrhoea.

AMR Action Fund

The AMR Action Fund was launched in July 2020.[216] The Fund expects to invest more than US$1 billion in small biotech companies targeting novel AMR treatments as they enter late-stage development. The Fund aims to bring 2-4 novel antibiotics to patients by 2030.

Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator

The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) is a global partnership investing US$480 million over 2016-2022 in early development of new antibiotics, vaccines, rapid diagnostics and other products to prevent, diagnose and treat bacterial infections.[217]

The partnership is based at Boston University and includes the US Department of Health and Human Services Biomedical Advanced Research and Development Authority, the Wellcome Trust, Germany's federal Ministry of Education and Research, the UK's Global Antimicrobial Resistance Innovation Fund, the Bill and Melinda Gates Foundation, and the National Institute of Allergy and Infectious Diseases.

New Drugs for Bad Bugs

A programme of the world's biggest public-private partnership in the life sciences, Innovative Medicines Initiative, New Drugs for Bad Bugs brings together industry, academia and biotech organisations to combat AMR in Europe.[218] Funded with €650 million, eight projects are aiming to address scientific, regulatory, and business barriers to the development of new antibiotics.

Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR) Impact Fund

The REPAIR Impact Fund was established in February 2018 by Novo Holdings, a Danish private limited liability company.[219] The Fund has US$165 million to invest in start-ups, early-stage companies, and corporate spin-outs involved in discovering and developing therapies to target resistant pathogens. They plan to invest US$20-40 million per year over five years in around 20 projects, hoping to yield at least one new therapy on the market.

Community for Open Antimicrobial Drug Discovery

The Community for Open Antimicrobial Drug Discovery is a non-profit initiative led by academics at the University of Queensland in Australia aiming to help scientists discover new and diverse antibiotics.[220] They screen compounds for antimicrobial activity on behalf of research groups for free.

Funding general/other research and development

Joint Programming Initiative on AMR

The Joint Programming Initiative on AMR is a collaborative platform bringing together 28 countries and the European Commission to deliver €100 million in funding across 118 projects and

[216] AMR Action Fund. (n.d.). About us. Retrieved 26 July, 2021, from https://amractionfund.com/about-us/
[217] CARB-X. (n.d.). About CARB-X. Retrieved 26 July, 2021, from https://carb-x.org/about/overview/
[218] Innovative Medicines Initiative. (n.d.). ND4BB. Retrieved 26 July, 2021, from https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb
[219] Repair Impact Fund, & Novo Holdings. (n.d.). Repair Impact Fund. Retrieved 28 July, 2021, from https://www.repair-impact-fund.com/
[220] CO-ADD. (n.d.). Open-access antimicrobial screening program. Retrieved 28 July, 2021, from https://co-add.org/

networks to curb AMR using a 'one health' approach.[221] The initative has a shared Strategic Research and Innovation Agenda that provides alignment and coordination to member countries.

AMR Industry Alliance

The AMR Industry Alliance is a coalition of more than 100 private sector pharmaceutical and biotechnology companies and associations.[222] They aim to help curb AMR by focusing on four priority areas:

- Investing in research and development for innovative diagnostics and treatments
- Supporting appropriate use
- Improving access to antibiotics – both existing and new
- Reducing the environmental impact of manufacturing

Global Research Collaboration for Infectious Disease Preparedness

The Global Research Collaboration for Infectious Disease Preparedness brings together research funding organisations from around the world to facilitate rapid research when a pandemic, epidemic or outbreak of a new or emerging infectious disease occurs.[223] They are also involved in enhancing preparedness and building frameworks to share data and connect clinical trials.

Ineos Oxford Institute for AMR Research

Established in 2021 with a £100 million donation from global petrochemicals manufacturer INEOS, this research institute will carry out research to address AMR.[224] One of their top priorities is to develop animal-specific antibiotics for agriculture.

International Centre for Antimicrobial Resistance Solutions

The International Centre for Antimicrobial Resistance Solutions partners with low- and middle-income countries to assist their efforts to combat AMR, co-designing and implementing solutions that build on national AMR action plans.[225]

Foundation for Innovative New Diagnostics

The Foundation for Innovative New Diagnostics is a global non-profit alliance working to accelerate the development, evaluation and delivery of affordable diagnostic tests for poverty-related diseases such as TB and malaria.[226] Twenty-four new diagnostic technologies have been developed with the foundation's support since 2003.

Data sharing

Global Antimicrobial Resistance and Use Surveillance System

An initiative of the WHO resulting from the Global Action Plan, the Global Antimicrobial Resistance and Use Surveillance System (GLASS) is the first global effort to standardise AMR surveillance[227] across collection, analysis, interpretation, and data sharing. GLASS aims to support capacity building and shifts to systems that incorporate lab, epidemiological, clinical and population-level data. Aotearoa New Zealand does not currently participate in GLASS.

[221] JPIAMR. (n.d.). About. Retrieved 27 July, 2021, from https://www.jpiamr.eu/about-jpiamr/
[222] AMR Industry Alliance. (n.d.). AMR Industry Alliance. Retrieved 26 July, 2021, from https://www.amrindustryalliance.org/
[223] GloPID-R. (n.d.). About us. Retrieved 28 July, 2021, from https://www.glopid-r.org/about-us/
[224] INEOS. (n.d.). The INEOS Oxford Institute. Retrieved 26 July, 2021, from https://www.ineos.com/about/foundations/education/the-ineos-oxford-institute/
[225] International Centre for Antimicrobial Resistance Solutions. (n.d.). From evidence to action. Retrieved 28 July, 2021, from https://icars-global.org/
[226] FIND. (n.d.). About us. Retrieved 28 July, 2021, from https://www.finddx.org/about/
[227] World Health Organization. (n.d.). Global Antimicrobial Resistance and Use Surveillance (GLASS). Retrieved 14 July, 2021, from https://www.who.int/initiatives/glass

Shared Platform for Antibiotic Research

The Pew Charitable Trusts runs the Shared Platform for Antibiotic Research,[228] a public-facing, interactive tool that integrates data from published studies and other sources. This 'virtual laboratory' aims for scientists working on new antibiotics to share data and insights, learn from past research, and collaborate in real-time.

The Fleming Fund

The Fleming Fund is an aid programme established by the UK Government in 2015 that supports 24 low- and middle-income countries across Asia and Africa to generate, share, and use AMR data.[229] The Fleming Fund, worth over NZ$500 million, is mostly used to develop AMR workforce capacity and establish lab capacity and surveillance systems. It resulted from the UK review on AMR (see above).

[228] The Pew Charitable Trusts. (2021, 31 March). The Shared Platform for Antibiotic Research and Knowledge (SPARK). Retrieved 27 July, 2021, from https://www.pewtrusts.org/en/research-and-analysis/articles/2018/09/21/the-shared-platform-for-antibiotic-research-and-knowledge

[229] The Fleming Fund. (n.d.). The Fleming Fund. Retrieved 26 July, 2021, from https://www.flemingfund.org/

2.5 Future context

Failing to mitigate AMR will cost the world socially, economically, and in lost health and lives. AMR threatens the safety of many healthcare interventions, such as chemotherapy, hip replacements, and intensive care – these may become unethically dangerous in the future. In Aotearoa New Zealand, the burden will fall disproportionately on Māori and Pacific peoples, who shoulder more of the infectious diseases burden in this country (see section 3.4 for more details). AMR also threatens our agriculture and the health of production animals. If we don't act now, it is estimated that by 2050:

AMR **threatens the safety** of many healthcare interventions, such as chemotherapy, hip replacements, and intensive care – these may become unethically dangerous in the future.

- 10 million people will die every year due to infections caused by drug-resistant pathogens – more than will die of cancer.[230]
- Cumulative lost global production will total US$100 trillion.[231]
- The annual reduction in global GDP could be equivalent to having a 2008 global financial crisis every year.[232]
- 28.3 million people will be plunged into poverty – mostly in low-income countries.[233]
- Livestock production will decline by 2.6-7.5% per year.[234]
- Additional healthcare expenditures will total US$1.2 trillion annually.

A number of factors will impact the future global AMR and infectious diseases landscape. Demographic change, COVID-19's legacy, and climate change are explored below.

2.5.1 Demographic change

Shifting demographics and population density will affect the dissemination of infectious diseases and AMR. When people move, they bring diseases and AMR with them.[235] As people move from rural to urban areas, they encounter more crowded living and working conditions and greater risk of infectious disease. At the same time, they may have reduced contact with livestock, reducing the risk of zoonoses, and typically have easier access to healthcare.

In Aotearoa New Zealand, our ageing population means we will need to figure out how to safely care for the elderly. With declining immune function associated with ageing, older people are more likely to be adversely affected by drug-resistant pathogens[236] while aged residential care (ARC) facilities provide an environment where pathogens can easily spread.[237] In addition, elderly people are more likely to need hip or knee replacement surgeries than younger people, meaning there will be increasing demand for antimicrobials to protect against infections associated with these surgeries.[238]

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[230] O'Neill, J. (2016). *Tackling drug-resistant infections globally: Final report and recommendations*. UK: HM Government and Wellcome Trust. Retrieved from https://amr-review.org/

[231] Ibid.

[232] World Bank. (2017). *Drug-resistant infections: A threat to our economic future*. Washington DC: World Bank. Retrieved from https://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf

[233] Ibid.

[234] Ibid.

[235] Vikesland, P., Garner, E., Gupta, S., *et al.* (2019). Differential drivers of antimicrobial resistance across the world. *Accounts of Chemical Research, 52*(4), 916-924. https://doi.org/10.1021/acs.accounts.8b00643

[236] Aw, D., Silva, A.B., & Palmer, D.B. (2007). Immunosenescence: Emerging challenges for an ageing population. *Immunology, 120*(4), 435-446. https://doi.org/10.1111/j.1365-2567.2007.02555.x

[237] Lim, C., Stuart, R., & Kong, D. (2015). Antibiotic use in residential aged care facilities. *Australian Family Physician, 44*, 192-196.

[238] The New Zealand Joint Registry. (2020). *Twenty-one year report: January 1999 to December 2019*. Retrieved from https://www.nzoa.org.nz/sites/default/files/DH8426_NZJR_2020_Report_v5_30Sep.pdf

2.5.2 COVID-19 impacts

COVID-19 has led to the emergence of both risks and opportunities related to global efforts to tackle AMR and infectious disease. This section outlines some of these impacts, noting that exact outcomes are yet to crystallise.

Antimicrobial use in hospitals

Despite evidence suggesting that bacterial or fungal co-infections among COVID-19 patients are relatively uncommon (although highly variable between countries and contexts),[239] there has been widespread use of antimicrobial drugs among hospitalised COVID-19 patients.

Despite low incidence of bacterial co-infection, there has been wide use of broad-spectrum antibiotics among hospitalised COVID-19 patients.

- One meta-analysis conducted in mid-2020 found that roughly 7% of hospitalised COVID-19 patients present with or subsequently develop bacterial co-infections.[240]
- A different meta-analysis concurred with the 7% co-infection finding, and further noted that co-infection is more likely among patients in ICU (at 14%).[241] This meta-analysis was conducted before dexamethasone, a corticosteroid drug, was demonstrated to be effective against COVID-19 in critically ill patients.[242] Corticosteroids suppress the immune system, so may contribute to increased co-infection risk among severely ill patients.
- A third meta-analysis looking at bacteria and fungi found coinfection in 8% of hospitalised COVID-19 patients.[243]

Despite low co-infection incidence, several studies have found that the majority of hospitalised COVID-19 patients are given antimicrobial drugs. For example, 52% of hospitalised patients were given at least one antibiotic according to a US study,[244] while an English language meta-analysis found that 72% of patients were given antibiotics and/or antifungals.[245]

[239] Ghosh, S., Bornman, C., & Zafer, M.M. (2021). Antimicrobial resistance threats in the emerging COVID-19 pandemic: Where do we stand? *Journal of Infection and Public Health, 14*(5), 555-560. https://doi.org/10.1016/j.jiph.2021.02.011

[240] Langford, B.J., So, M., Raybardhan, S., *et al.* (2020). Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. *Clinical Microbiology and Infection, 26*(12), 1622-1629. https://doi.org/10.1016/j.cmi.2020.07.016; Lansbury, L., Lim, B., Baskaran, V., *et al.* (2020). Co-infections in people with COVID-19: A systematic review and meta-analysis. *Journal of Infection, 81*(2), 266-275. https://doi.org/10.1016/j.jinf.2020.05.046; Rawson, T.M., Moore, L.S.P., Zhu, N., *et al.* (2020). Bacterial and fungal coinfection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. *Clinical Infectious Diseases, 71*(9), 2459-2468. https://doi.org/10.1093/cid/ciaa530

[241] Lansbury, L., Lim, B., Baskaran, V., *et al.* (2020). Co-infections in people with COVID-19: A systematic review and meta-analysis. *Journal of Infection, 81*(2), 266-275. https://doi.org/10.1016/j.jinf.2020.05.046

[242] The RECOVERY Collaborative Group. (2020). Dexamethasone in hospitalized patients with COVID-19. *New England Journal of Medicine, 384*(8), 693-704. https://doi.org/10.1056/NEJMoa2021436

[243] Langford, B.J., So, M., Raybardhan, S., *et al.* (2020). Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. *Clinical Microbiology and Infection, 26*(12), 1622-1629. https://doi.org/10.1016/j.cmi.2020.07.016; Lansbury, L., Lim, B., Baskaran, V., *et al.* (2020). Co-infections in people with COVID-19: A systematic review and meta-analysis. *Journal of Infection, 81*(2), 266-275. https://doi.org/10.1016/j.jinf.2020.05.046; Rawson, T.M., Moore, L.S.P., Zhu, N., *et al.* (2020). Bacterial and fungal coinfection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. *Clinical Infectious Diseases, 71*(9), 2459-2468. https://doi.org/10.1093/cid/ciaa530

[244] The Pew Charitable Trusts. (2021). Could efforts to fight the coronavirus lead to overuse of antibiotics? Retrieved from https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/could-efforts-to-fight-the-coronavirus-lead-to-overuse-of-antibiotics

[245] Langford, B.J., So, M., Raybardhan, S., *et al.* (2020). Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. *Clinical Microbiology and Infection, 26*(12), 1622-1629. https://doi.org/10.1016/j.cmi.2020.07.016; Lansbury, L., Lim, B., Baskaran, V., *et al.* (2020). Co-infections in people with COVID-19: A systematic review and meta-analysis. *Journal of Infection, 81*(2), 266-275. https://doi.org/10.1016/j.jinf.2020.05.046; Rawson, T.M., Moore, L.S.P., Zhu, N., *et al.* (2020). Bacterial and

With initial uncertainty about the risk posed by co-infection and knowledge that patients with co-infections suffer worse outcomes,[246] the practice of using antimicrobials in hospitalised COVID-19 patients has likely been driven by an abundance of caution.

The impacts of telemedicine on antimicrobial use

Outside of the hospital setting, lockdowns around the world significantly reduced access to routine in-person healthcare, with a corresponding boom in telemedicine (virtual consultations). The shift to telemedicine in primary care may also affect antimicrobial prescribing, in part due to the difficulties of assessing a patient remotely.[247] There is some limited evidence that telemedicine is associated with increased rates of antimicrobial use.[248]

For example, in the UK, general practice antibiotic prescription numbers were 15% lower across April-August 2020 compared with the same period in 2019.[249] However, when adjusted for the significantly lower number of consultations, antibiotic prescribing rates were actually 6.7% higher than expected. This needs to be considered as increased utilisation of telemedicine looks set to persist throughout and beyond the pandemic.[250]

Increased use of antimicrobial household products

While increased handwashing with 'plain' soap and water may reduce the spread of drug-resistant pathogens, using antimicrobial soaps and other household products may actually exacerbate AMR without providing an appreciable health benefit (see section 2.3.2). The increased use of these products during and after the pandemic may impact AMR emergence.[251]

Changes in infection prevention and control

While the pandemic has engendered a heightened awareness of hand hygiene and the use of personal protective equipment (PPE) in healthcare settings and the community, other aspects of IPC may have loosened in healthcare settings overwhelmed by COVID-19.[252]

For example, in March 2020, a surge in COVID-19 hospitalisations compounded by staff and PPE shortages disrupted normal IPC practices in a hospital in New Jersey, US.[253] An outbreak of carbapenem-resistant *A. baumannii* resulted, with a cluster of 34 cases over five months (see section 2.4.2 for more information on carbapenem-resistant *A. baumannii*). When the COVID-19 wave subsided, IPC practices returned to normal and the number of *A. baumannii* cases returned to baseline levels. Similar outbreaks have occurred in Israel, Spain, Mexico, Brazil and Italy.[254] However,

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fungal coinfection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. *Clinical Infectious Diseases, 71*(9), 2459-2468. https://doi.org/10.1093/cid/ciaa530

[246] Garcia-Vidal, C., Sanjuan, G., Moreno-García, E., *et al.* (2021). Incidence of co-infections and superinfections in hospitalized patients with COVID-19: A retrospective cohort study. *Clinical Microbiology and Infection, 27*(1), 83-88. https://doi.org/10.1016/j.cmi.2020.07.041

[247] Wellcome Trust. (2020). *The global response to AMR: Momentum, success, and critical gaps*. Retrieved from https://wellcome.org/reports/global-response-amr-momentum-success-and-critical-gaps

[248] Rawson, T.M., Moore, L.S.P., Castro-Sanchez, E., *et al.* (2020). COVID-19 and the potential long-term impact on antimicrobial resistance. *Journal of Antimicrobial Chemotherapy, 75*(7), 1681-1684. https://doi.org/10.1093/jac/dkaa194

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[250] Koonin, L.M., Hoots, B., Tsang, C.A., *et al.* (2020). Trends in the use of telehealth during the emergence of the COVID-19 pandemic — United States, January–March 2020. *Morbidity and Mortality Weekly Report, 69*(43), 1595-1599. https://doi.org/10.15585/mmwr.mm6943a3

[251] Murray, A.K. (2020). The novel coronavirus COVID-19 outbreak: Global implications for antimicrobial resistance. *Frontiers in Microbiology, 11*(1020). https://doi.org/10.3389/fmicb.2020.01020

[252] Tomczyk, S., Taylor, A., Brown, A., *et al.* (2021). Impact of the COVID-19 pandemic on the surveillance, prevention and control of antimicrobial resistance: A global survey. *Journal of Antimicrobial Chemotherapy, 76*(11), 3045-3058. https://doi.org/10.1093/jac/dkab300

[253] Perez, S., Innes, G.K., Walters, M.S., *et al.* (2020). Increase in hospital-acquired carbapenem-resistant *Acinetobacter baumannii* infection and colonization in an acute care hospital during a surge in COVID-19 admissions - New Jersey, February-July 2020. *Morbidity and Mortality Weekly Report, 69*(48), 1827-1831. https://doi.org/10.15585/mmwr.mm6948e1

[254] O'Toole, R.F. (2021). The interface between COVID-19 and bacterial healthcare-associated infections. *Clinical Microbiology and Infection*. https://doi.org/https://doi.org/10.1016/j.cmi.2021.06.001

other hospitals in Singapore, Los Angeles and Taiwan have found reduced rates of HAIs caused by drug-resistant organisms during the pandemic, attributed to more stringent IPC including hand washing and use of alcohol-based sanitiser.[255] These experiences underscore the importance of maintaining IPC to protect patients. For more details on IPC, see section 5.3.1.

Changes in prevalence of infectious diseases

Public health measures designed to curb the spread of COVID-19 have also reduced the prevalence of other infectious diseases in many countries. In Aotearoa New Zealand, 2020 saw a 99.9% reduction in confirmed influenza cases between April and August, compared with previous years.[256]

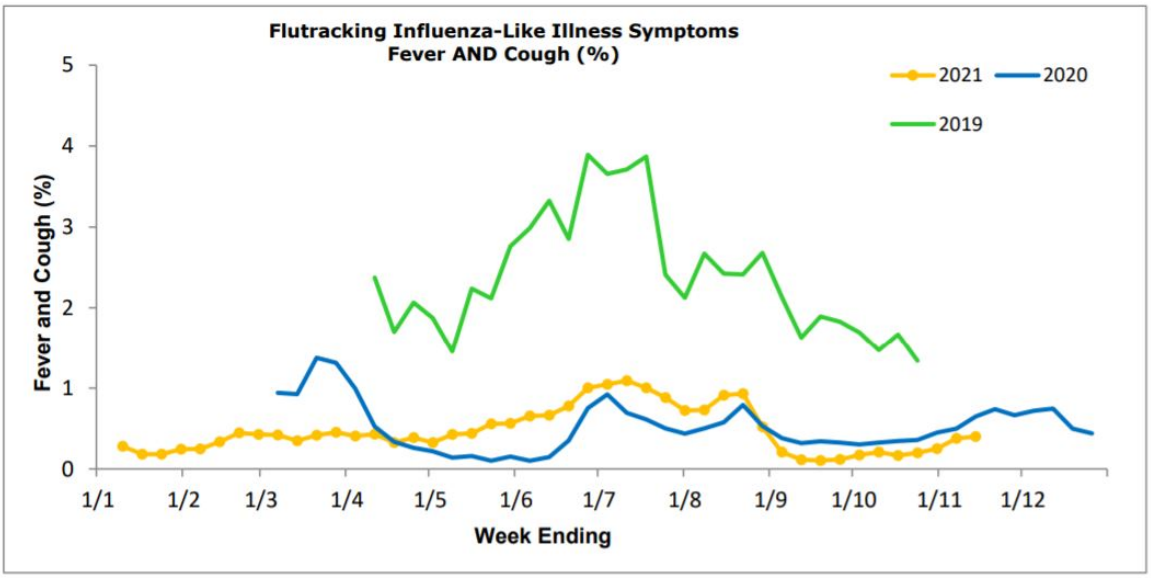

Figure 12: FluTracking comparison for 2019, 2020 and 2021 shows reduced numbers of people in Aotearoa New Zealand reporting fever and cough symptoms since the COVID-19 pandemic.[257]

In 2020, the rates of RSV decreased by 98% in Aotearoa New Zealand.[258] This lack of cases can be attributed to Aotearoa New Zealand's border controls, alert levels three and four, and other practices such as physical distancing and increased handwashing. However, 2021 has seen a large outbreak of RSV among children and infants. As of the week ending 3 October 2021, there have been 6,327 RSV cases recorded by ESR.[259] This spike is thought to have been seeded by people travelling between Australia and Aotearoa New Zealand.[260] The RSV outbreak has affected a larger number of children in 2021 compared with years pre-COVID-19 due to 'immunity debt,' with the absence of

[255] Ibid.
[256] Huang, Q.S., Wood, T., Jelley, L., *et al.* (2021). Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. *Nature Communications, 12*(1), 1001. https://doi.org/10.1038/s41467-021-21157-9
[257] FluTracking. (2021). *Weekly interim report New Zealand: Week ending 14 November 2021*. Retrieved from https://info.flutracking.net/reports-2/new-zealand-reports/
[258] Huang, Q.S., Wood, T., Jelley, L., *et al.* (2021). Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. *Nature Communications, 12*(1), 1001. https://doi.org/10.1038/s41467-021-21157-9
[259] Institute of Environmental Science and Research Limited (ESR). (2021). *Laboratory-based virology weekly report: Week 39 ending 3 October, 2021*. Upper Hutt, NZ: ESR. Retrieved from https://www.esr.cri.nz/assets/SHIVERS/Reports/Virology-report/Virology-Weekly-report_2021_39.pdf
[260] Williams, K. (2021, 7 July). Wellington hospital sees 'sharp, exponential increase' in RSV cases, *The Dominion Post*. Retrieved from https://www.stuff.co.nz/national/health/125663628/wellington-hospital-sees-sharp-exponential-increase-in-rsv-cases

circulating virus in 2020 meaning that there is now a larger cohort of susceptible children, so we are seeing two seasons' worth of infections bunched together in one season.[261]

Another pathogen absent in Aotearoa New Zealand in 2020 was the intestinal parasite *Cryptosporidium hominis* that causes gastrointestinal disease. No cases were recorded between 14 February 2020 up to the beginning of 2021 (when the analysis was published).[262] *C. hominis* is spread via human-to-human transmission, and the researchers speculate that stringent lockdowns combined with border controls have stopped the parasite in its tracks and prevented reintroductions from overseas. In contrast, numbers of infections due to the zoonotic *Cryptosporidium parvus*, which can infect both ruminant animals (e.g. cows) and humans, followed its typical transmission pattern.

In an international study that included data from Aotearoa New Zealand, *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis* were less prevalent in 2020 than in the preceding two years, an observation attributed to COVID-19 public health measures.[263] The authors provided evidence to rule out the possibility that this reduced number of observed cases was the result of reduced surveillance.

Diverted attention

The urgent crisis of the COVID-19 pandemic has seen funding and political attention diverted, and researchers pivoting away from their usual areas of interest – sometimes at the expense of other pressing issues and infectious diseases of concern, including AMR.

'Covidisation' of research

'Covidisation' is a term used to describe the scientific communities' shift towards COVID-19-related research, at the expense of research into other areas. This shift may continue for some time, with experts consulted by the Wellcome Trust suggesting that this may result in a more viral-focused infectious diseases agenda, and junior research talent enticed by viral topics.[264]

In a *Nature Medicine* article, TB researcher Madhukar Pai neatly summarises the issue, "As a scientific community, we need to acknowledge that all health research cannot be about a pandemic, or infectious threats, and all infectious disease research cannot be about COVID-19…diversity in research will prepare us better for the next crisis."[265]

COVID-19 also led to delays in research projects. In Aotearoa New Zealand, all non-COVID-19 lab and clinical research in the health sciences was suspended during levels three and four, with researchers at the University of Otago estimating that 95% of research projects have been impacted, and with research funders indicating that no additional funding will be provided to support researchers affected by delays.[266]

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[261] Cohen, R., Ashman, M., Taha, M.-K.*, et al.* (2021). Pediatric Infectious Disease Group (GPIP) position paper on the immune debt of the COVID-19 pandemic in childhood, how can we fill the immunity gap? *Infectious Diseases Now, 51*(5), 418-423. https://doi.org/10.1016/j.idnow.2021.05.004

[262] Knox, M.A., Garcia-R, J.C., Ogbuigwe, P.*, et al.* (2021). Absence of *Cryptosporidium hominis* and dominance of zoonotic *Cryptosporidium* species in patients after COVID-19 restrictions in Auckland, New Zealand. *Parasitology*, 1-5. https://doi.org/10.1017/S0031182021000974

[263] Brueggemann, A.B., Jansen van Rensburg, M.J., Shaw, D.*, et al.* (2021). Changes in the incidence of invasive disease due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: A prospective analysis of surveillance data. *The Lancet Digital Health, 3*(6), e360-e370. https://doi.org/10.1016/S2589-7500(21)00077-7

[264] Wellcome Trust. (2020). *The global response to AMR: Momentum, success, and critical gaps*. Retrieved from https://wellcome.org/reports/global-response-amr-momentum-success-and-critical-gaps

[265] Pai, M. (2020). Covidization of research: What are the risks? *Nature Medicine, 26*(8), 1159-1159. https://doi.org/10.1038/s41591-020-1015-0

[266] Stamp, L.K., Cameron, V.A., Woodfield, T.B.F.*, et al.* (2021). Impact of COVID-19 on health research in New Zealand: A case study of a research-intensive campus. *Journal of the Royal Society of New Zealand, 51*(sup1), S75-S85. https://doi.org/10.1080/03036758.2020.1867202

Important clinical issues on the backburner

It's not just the research agenda that has been skewed by COVID-19 – routine healthcare work has also been disrupted, including elective surgeries,[267] cancer[268] and cardiovascular diagnosis and care, diagnosis of other infectious diseases like TB, HIV and malaria,[269] and delivery of non-COVID-19 vaccines, with 23 million children worldwide missing out on basic childhood vaccines in 2020.[270]

In addition, a survey of 73 countries found that the majority of responding countries experienced a reduction in availability of nursing, medical and public health staff to support AMR-related work (such as AMS, outbreak response, and reporting) as well as reduced capacity to train lab staff in AMR susceptibility testing, and 40% reported an increase in the time taken to turn around susceptibility test results.[271]

Medical product supply chains exposed

COVID-19 has exposed long-standing vulnerabilities in global medical product supply chains. Throughout the pandemic, supply of medical products has struggled to meet demand. At the start of the pandemic, supply shortages were most significant for PPE and ventilators. In the case of face masks, limited supplies at the start of the pandemic forced healthcare workers to extend the use of their masks, reuse masks after sterilisation, find alternatives, or go without.[272] As drugs and vaccines have become available, demand outstripped supply here too, disproportionately impacting lower income countries given their limited ability to engage in advance purchase agreements to position themselves favourably for early vaccine access.[273]

A lack of spare manufacturing capacity, raw material shortages, manufacturing disruptions caused by COVID-19 lockdowns, and depleted emergency medical supply stockpiles in various countries contributed to shortages.[274] For countries relying on imports, export bans imposed by countries prioritising national needs further jeopardised access. In the early months of 2020, 80 countries temporarily restricted the export of COVID-19-related products.[275] India's ban on COVID-19 vaccine exports seriously limited vaccine access in the developing world, while the EU's threat of vaccine export bans introduced considerable uncertainty for countries relying on Europe for access, and US restrictions on the export of key raw materials for the manufacture of vaccines may have reduced manufacturing outputs in other vaccine-manufacturing countries.[276]

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[267] Uimonen, M., Kuitunen, I., Paloneva, J., *et al.* (2021). The impact of the COVID-19 pandemic on waiting times for elective surgery patients: A multicenter study. *PLOS One, 16*(7), e0253875. https://doi.org/10.1371/journal.pone.0253875

[268] Lai, A.G., Pasea, L., Banerjee, A., *et al.* (2020). Estimated impact of the COVID-19 pandemic on cancer services and excess 1-year mortality in people with cancer and multimorbidity: near real-time data on cancer care, cancer deaths and a population-based cohort study. *BMJ Open, 10*(11), e043828. https://doi.org/10.1136/bmjopen-2020-043828

[269] Venkatesan, P. (2020). COVID-19 diagnostics—not at the expense of other diseases. *The Lancet Microbe, 1*(2), e64. https://doi.org/https://doi.org/10.1016/S2666-5247(20)30041-0

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[271] Tomczyk, S., Taylor, A., Brown, A., *et al.* (2021). Impact of the COVID-19 pandemic on the surveillance, prevention and control of antimicrobial resistance: A global survey. *Journal of Antimicrobial Chemotherapy, 76*(11), 3045-3058. https://doi.org/10.1093/jac/dkab300

[272] Miller, F.A., Young, S.B., Dobrow, M., *et al.* (2021). Vulnerability of the medical product supply chain: The wake-up call of COVID-19. *BMJ Quality & Safety, 30*(4), 331-335. https://doi.org/10.1136/bmjqs-2020-012133

[273] Duan, Y., Shi, J., Wang, Z., *et al.* (2021). Disparities in COVID-19 vaccination among low-, middle-, and high-income countries: The mediating role of vaccination policy. *Vaccines, 9*(8), 905. https://doi.org/10.3390/vaccines9080905

[274] Bhaskar, S., Tan, J., Bogers, M.L.A.M., *et al.* (2020). At the epicenter of COVID-19: The tragic failure of the global supply chain for medical supplies. *Frontiers in Public Health, 8*(821). https://doi.org/10.3389/fpubh.2020.562882

[275] Gereffi, G. (2021). Increasing resilience of medical supply chains during the COVID-19 pandemic. Retrieved from https://iap.unido.org/articles/increasing-resilience-medical-supply-chains-during-covid-19-pandemic

[276] Ibrahim, I.A. (2021). Overview of export restrictions on COVID-19 vaccines and their components. *ASIL Insights, 25*(10).

As countries identify lessons from the COVID-19 pandemic, many seem to be seeking to enhance their ability to make medical products at home in order to give them greater control over access to essential supplies. This includes increasing exploration of vaccine manufacturing capacity in Africa, where there is currently almost no vaccine manufacturing capacity.[277]

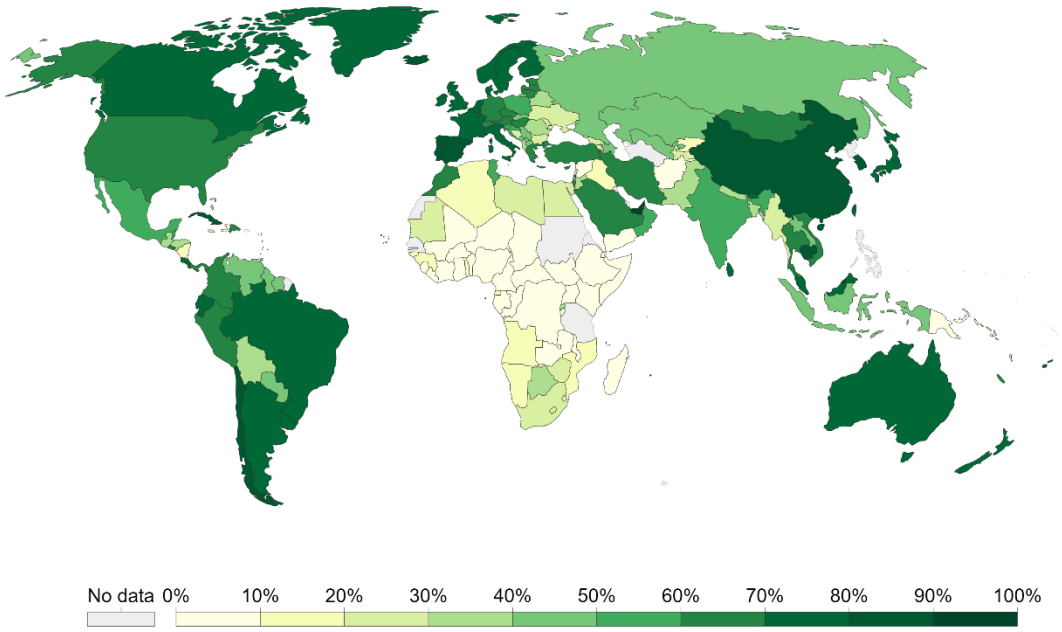

Figure 13: Share of people who have received at least one dose of COVID-19 vaccine as at 23 November 2021. Image credit: Our World in Data (CC BY 4.0).

Silver linings

Awareness and understanding

The COVID-19 pandemic has enhanced the general public's awareness and understanding of infectious disease. It has also induced some positive behaviour changes and social norms. For example, it's less socially acceptable to go to work with a cold, and there is renewed emphasis on hand hygiene.[278] There is perhaps greater social licence to act in the interests of public health, with the opportunity to embed initiatives such as surveillance and whole genome sequencing (WGS) into our standard practice.

Global pandemic preparedness efforts

COVID-19 has highlighted the perilous state of global pandemic preparedness and response capacity. The Independent Panel for Pandemic Preparedness and Response and Global Preparedness Monitoring Board made a range of recommendations on this topic, including strengthening WHO and adequately funding it to allow it to perform its functions.[279] A report by the United Nations Environment Programme takes a prevention approach, exploring how we can reduce the odds of a novel pathogen jumping from animals to humans and sparking the next epidemic or pandemic. The

[277] African Union, & Africa CDC. (2021). African Union and Africa CDC launches Partnerships for African Vaccine Manufacturing (PAVM), framework to achieve it and signs 2 MoUs. Retrieved from https://africacdc.org/news-item/african-union-and-africa-cdc-launches-partnerships-for-african-vaccine-manufacturing-pavm-framework-to-achieve-it-and-signs-2-mous/

[278] Poon, L. (2020). What our post-pandemic behaviour might look like. Retrieved from https://www.bloomberg.com/news/features/2020-05-26/how-our-behavior-will-change-after-the-pandemic

[279] The Independent Panel. (2021). *COVID-19: Make it the last pandemic*. Retrieved from https://theindependentpanel.org/mainreport/; Global Preparedness Monitoring Board. (2021). *From worlds apart to a world prepared: Global Preparedness Monitoring Board report 2021*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.gpmb.org/docs/librariesprovider17/default-document-library/gpmb-annual-report-2021.pdf?sfvrsn=44d10dfa_9

report points to the role played by biodiversity loss and ecological encroachment as drivers of disease emergence and spread.[280]

Already, a number of actions have been taken. For example, a new WHO hub for Pandemic and Epidemic Intelligence was opened in Berlin in September 2021, which will serve to support global disease monitoring, risk analysis and management, and data sharing.[281] In addition, the World Health Assembly met in late November/early December 2021 to discuss a 'pandemic treaty'.[282] Member states have agreed to start work on drafting and negotiating a WHO convention, agreement, or other international instrument on pandemic prevention, preparedness and response.[283]

Vaccine research, development, and manufacturing

COVID-19 stimulated vaccine research and development and led to a massive expansion of global vaccine manufacturing capacity. This has potential to assist with the research, development, and manufacturing of other vaccines, beyond COVID-19. For more details on this theme, see section 5.3.2.

2.5.3 Climate change impacts

Global warming and our changing climate, driven by anthropogenic fossil fuel use and greenhouse gas emissions, have ramifications for AMR and infectious disease.

Increased temperatures could mean more antimicrobial-resistant pathogens

A recent study in the US found that increasing local temperature correlates with higher percentage rates of AMR.[284] A similar study in Europe detected this association and further found that warmer minimum temperatures were linked to faster rates of increasing resistance.[285] This connection to environmental temperature was echoed in a Europe-wide wastewater surveillance study.[286] Increased temperatures may increase the rate of bacterial growth and enhance horizontal gene transfer between bacteria, facilitating the spread of AMR genes.[287] There is also an observed relationship between temperature and rates of bacterial infection, including for *Acinetobacter* spp., *Salmonella* spp., and gram-negative bloodstream infections.[288]

[280] United Nations Environment Programme, & International Livestock Research Institute. (2020). *Preventing the next pandemic: Zoonotic diseases and how to break the chain of transmission.* Nairobi, Kenya: Retrieved from https://www.cbd.int/doc/c/084c/e8fd/84ca7fe0e19e69967bb9fb73/unep-sa-sbstta-sbi-02-en.pdf

[281] World Health Organization. (2021, 1 September). *WHO, Germany open hub for pandemic and epidemic intelligence in Berlin* [Press release]. Retrieved from https://www.who.int/news/item/01-09-2021-who-germany-open-hub-for-pandemic-and-epidemic-intelligence-in-berlin

[282] World Health Organization. (2021). WHASS2: Special session of the World Health Assembly referred to in decision WHA74(16). Retrieved 24 November, 2021, from https://www.who.int/news-room/events/detail/2021/11/29/default-calendar/second-special-session-of-the-world-health-assembly

[283] World Health Organization. (2021, 1 December). *World Health Assembly agrees to launch process to develop historic global accord on pandemic prevention, preparedness and response* [Press release]. Retrieved from https://www.who.int/news/item/01-12-2021-world-health-assembly-agrees-to-launch-process-to-develop-historic-global-accord-on-pandemic-prevention-preparedness-and-response

[284] MacFadden, D.R., McGough, S.F., Fisman, D., *et al.* (2018). Antibiotic resistance increases with local temperature. *Nature Climate Change, 8*(6), 510-514. https://doi.org/10.1038/s41558-018-0161-6

[285] McGough, S.F., MacFadden, D.R., Hattab, M.W., *et al.* (2020). Rates of increase of antibiotic resistance and ambient temperature in Europe: A cross-national analysis of 28 countries between 2000 and 2016. *Eurosurveillance, 25*(45), 1900414. https://doi.org/doi:https://doi.org/10.2807/1560-7917.ES.2020.25.45.1900414

[286] Pärnänen, K.M.M., Narciso-da-Rocha, C., Kneis, D., *et al.* (2019). Antibiotic resistance in European wastewater treatment plants mirrors the pattern of clinical antibiotic resistance prevalence. *Science Advances, 5*(3), eaau9124. https://doi.org/10.1126/sciadv.aau9124

[287] Burnham, J.P. (2021). Climate change and antibiotic resistance: A deadly combination. *Therapeutic Advances in Infectious Disease, 8*, 2049936121991374. https://doi.org/10.1177/2049936121991374

[288] Ibid.

Climate change is shifting the distribution of pathogens and vectors

Changing climatic conditions are likely to affect the distribution and prevalence of disease vectors such as mosquitoes that spread malaria.[289] A 2017 Royal Society report on the impacts of climate change on health in Aotearoa New Zealand noted that, while most disease-spreading mosquitoes aren't present in the country (e.g. those that carry malaria, dengue fever, and Ross River virus), these mosquitoes have been intercepted at the border multiple times. With rising temperatures and changing precipitation patterns, these species will become more likely to be able to establish in the future.[290]

Changing climatic conditions may also allow pathogens themselves to exploit new environments. For example, the recent spread of the emergent drug-resistant fungus *Candida auris* may have been facilitated by climate change, as warming temperatures lead to adaptations to heat across fungi.[291]

Climate change – and environmental degradation and ecological encroachment more generally (e.g. deforestation) increases interactions between humans and wildlife vectors of disease, potentially sparking novel zoonotic infections.[292]

Other climate change impacts may cascade with implications for AMR

Climate change-induced extreme weather events may lead to disaster-associated outbreaks of infectious disease. Flooding waters can spread waterborne pathogens, while displacement may result in overcrowding, which in turn increases infection rates.[293]

The increased risk of drought, displacement, and wider economic impacts of climate change may result in increased poverty and poorer living conditions, including reduced access to clean water. A worldwide analysis of wastewater surveillance for AMR genes found that poor sanitation and limited access to clean water was strongly positively correlated with higher prevalence of AMR genes in wastewater.[294]

[289] Rodríguez-Verdugo, A., Lozano-Huntelman, N., Cruz-Loya, M., *et al.* (2020). Compounding effects of climate warming and antibiotic resistance. *iScience, 23*(4), 101024. https://doi.org/10.1016/j.isci.2020.101024
[290] Royal Society Te Apārangi. (2017). *Human health impacts of climate change for New Zealand*. Retrieved from https://www.royalsociety.org.nz/assets/documents/Report-Human-Health-Impacts-of-Climate-Change-for-New-Zealand-Oct-2017.pdf
[291] Casadevall, A., Kontoyiannis, D.P., Robert, V., *et al.* (2019). On the emergence of *Candida auris*: Climate change, azoles, swamps, and birds. *mBio, 10*(4), e01397-01319. https://doi.org/doi:10.1128/mBio.01397-19
[292] Burnham, J.P. (2021). Climate change and antibiotic resistance: A deadly combination. *Therapeutic Advances in Infectious Disease, 8*, 2049936121991374. https://doi.org/10.1177/2049936121991374
[293] Ibid.
[294] Hendriksen, R.S., Munk, P., Njage, P., *et al.* (2019). Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nature Communications, 10*(1), 1124. https://doi.org/10.1038/s41467-019-08853-3

2.6 Summary

Part two has highlighted that infectious diseases remain a very real threat to human, animal, and plant health. In addition, the 'slow-burning pandemic' of AMR is already making us more vulnerable to the effects of infectious disease, as our antimicrobial options for treating and preventing infectious diseases narrow. While Aotearoa New Zealand isn't as badly impacted by AMR as other countries (see part four for details), the longer we wait to act, the worse the situation will become.

… infectious diseases remain **a very real threat** to human, animal, and plant health.

Given that microbes know no borders – a lesson reinforced by the COVID-19 experience – we can't tackle these threats alone. Ensuring we take lessons from overseas jurisdictions and align our efforts with international initiatives will enhance our ability to effectively tackle infectious disease and AMR. Part two has highlighted the breadth of global activity to address AMR – a rich source of expertise and knowledge that Aotearoa New Zealand can tap into. It has also sketched out some potential intersections with other global threats – the COVID-19 pandemic and climate change – that could compound the negative impacts of AMR in the future.

With the global stage set, the next two parts focus on the specific situation in Aotearoa New Zealand: first, with a brief overview of our unique infectious disease profile – the local context in which AMR will develop – and then on AMR itself. In part five, we outline the evidence for solutions and interventions within a holistic framework.

3 Part three: Infectious diseases in Aotearoa New Zealand

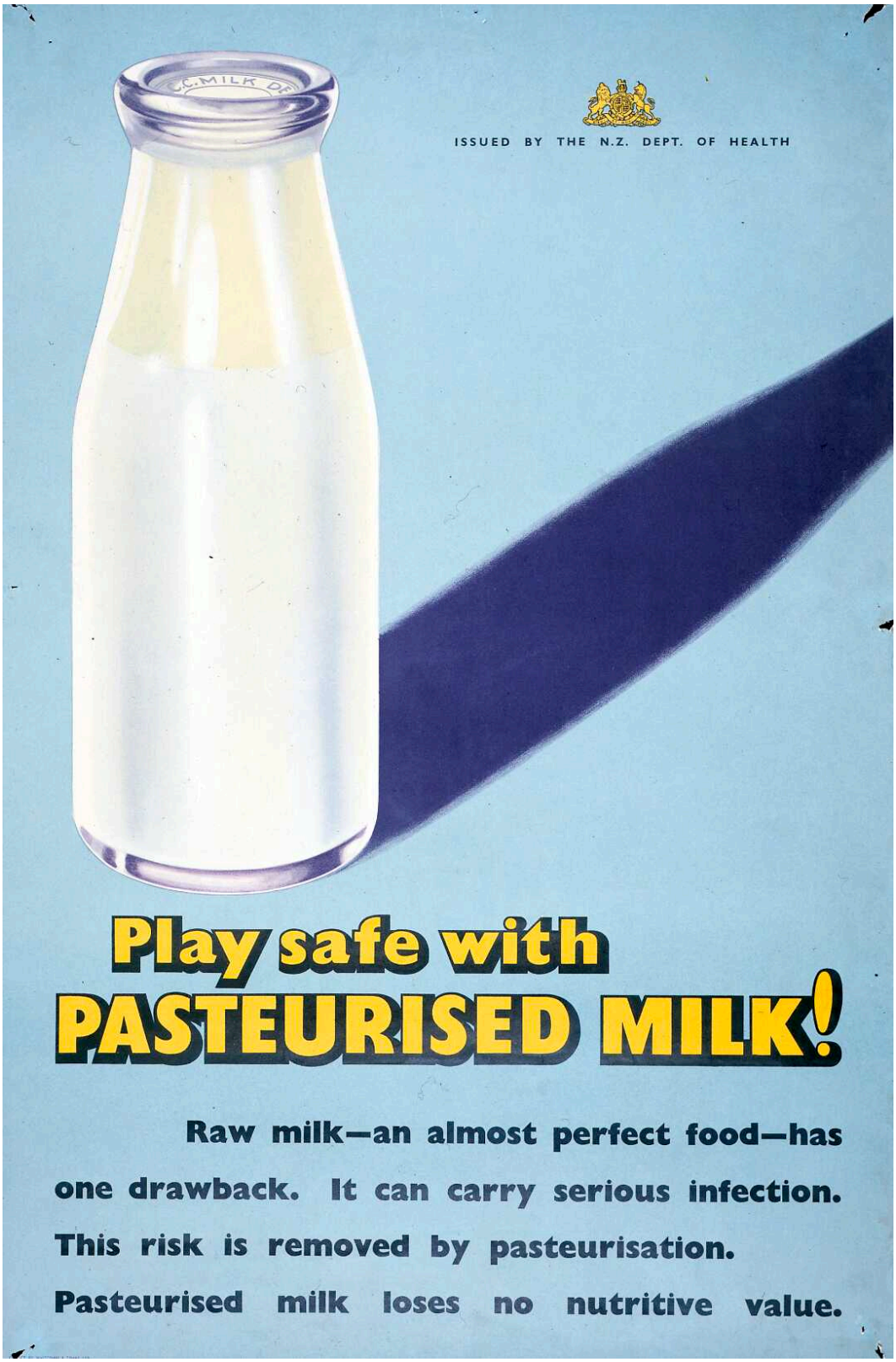

Figure 14: A New Zealand government Department of Health poster from the 1940s. Imager credit: New Zealand Department of Health / Alexander Turnbull Library Ref: Eph-D-HEALTH-1946-01.

3.1 Overview

AMR and action taken to address it occurs in the wider context of infectious disease. If we reduce infections in Aotearoa New Zealand, we will also reduce the need to use antimicrobials. This is important because selection pressure resulting from use of antimicrobials is the primary driver of AMR (see section 2.3.2).

In this way, actions taken to combat infectious diseases in Aotearoa New Zealand (regardless of whether the causative pathogen exhibits AMR) will help to combat AMR too. However, we can't combat infectious diseases simply by looking within our own borders. Pathogens (including drug-resistant ones) can enter Aotearoa New Zealand from overseas, so addressing infectious diseases also requires us to maintain our stringent border controls and contribute to global efforts to combat infectious disease and AMR.

AMR aside, addressing infectious disease threats has many advantages including promoting human health and wellbeing, preserving agricultural productivity and animal welfare, protecting our natural and cultural heritage, and growing our economy.

Part three outlines the state of play of infectious disease in Aotearoa New Zealand. It is not intended to be comprehensive, but rather serves to highlight a range of infectious diseases that affect our people, animals, and plants – or have scope to affect us through border incursions.

Part three serves to highlight a range of infectious diseases that affect our people, animals, and plants – or have scope to affect us through border incursions.

First, we lay out the local context, describing the characteristics that make us vulnerable and resilient to infectious disease threats. Next, we discuss the costs of infectious diseases in humans: the harm – both acute and long-term – caused by infectious disease, and the inequity that accompanies it. These health impacts and inequitable burdens are illustrated by three case studies: healthcare-associated infections, sepsis, and rheumatic fever.

Infectious disease impacts our agricultural industry, with infections affecting the welfare of farm animals and the productivity of crops. *Pseudomonas syringae pv. actinidiae* (Psa) in kiwifruit is used to demonstrate the economic costs of plant pathogens as well as the AMR consequences of disease management. *Mycoplasma bovis* in cattle is provided as an example of a pathogen we managed to exclude from the country through strict border controls for many years and have been working to eliminate since it was detected in the country in 2017. Pathogens impact our natural and cultural heritage, with myrtle rust provided as an example of a pathogen that infects our taonga species.

Some infectious diseases are transmitted across the human-animal-environment interface. We provide an overview of zoonotic, foodborne, and waterborne infectious diseases, with brief case studies on Shiga toxin-producing *Escherichia coli* (STEC) and *Salmonella*, and a close look at *Campylobacter* to illustrate the connections between human, animal, and environmental health. These examples illustrate the need for timely surveillance that integrates data from different sectors to meaningfully inform evidence-based action.

3.2 Key messages

- While 82% of lost life and health in Aotearoa New Zealand is attributable to non-communicable diseases like cancer and cardiovascular disease, infectious diseases remain a present and pressing threat, from the toll taken by well-established infectious diseases like campylobacteriosis to novel infectious diseases like COVID-19.

- Examples of the threats to human health posed by infectious diseases in Aotearoa New Zealand (besides COVID-19) include our high incidence of food- and waterborne illnesses relative to other developed countries, high incidence of rheumatic fever and rheumatic heart disease among Māori and Pacific peoples, and the continued occurrence of sepsis and HAIs. The impacts go beyond acute illness and death, with some infectious diseases having long-lasting health impacts leading to life disruptions, including time away from work or school.

- The burden of infectious disease falls most heavily on the shoulders of Māori and Pacific peoples, who are at greater risk of acquiring many infectious diseases, developing health complications, and being admitted to hospital.

- Infectious disease also places a greater burden on old and young people, people with underlying health conditions, and pregnant women. In addition, people who live in remote rural areas in Aotearoa New Zealand and those living in material hardship regardless of ethnicity are less likely to have ready access to affordable and quality healthcare.

- For animals and plants, both in agriculture and nature, infectious diseases pose a threat too. Being geographically isolated has its advantages, with many infectious diseases excluded from the country using strict biosecurity measures. But incursions can and do occur, causing economic, cultural, social, and environmental losses – as seen with *Mycoplasma bovis*, Psa, and myrtle rust.

- Our understanding of the incidence of infectious diseases in Aotearoa New Zealand, as well as risk factors, exposure routes, and intervention points, is impeded by incomplete data collection and analysis, and poor connectivity between the human, animal, plant, and environment sectors, despite infectious disease threats (e.g. zoonotic diseases) spanning these sectors.

3.3 Our context

3.3.1 Infectious diseases remain a prominent feature of the human health landscape

In Aotearoa New Zealand, non-communicable diseases such as cardiovascular disease and cancer drive most of our collective health loss, contributing 82% of disability-adjusted life years (DALYs, defined in section 2.4.1).[295] However, infectious diseases remain a prominent feature of the health landscape and can have substantial, wide-reaching consequences. While the COVID-19 pandemic is the most salient reminder of the harm and disruption that infectious diseases can cause, there are many other infectious diseases that impact us as well.

Some infectious diseases are **notably prevalent** in Aotearoa New Zealand.

Some infectious diseases are notably prevalent in Aotearoa New Zealand. We continue to have outbreaks of vaccine-preventable illnesses such as measles[296] and whooping cough (also known as pertussis).[297] Enteric infectious diseases such as campylobacteriosis are more prevalent in Aotearoa New Zealand than many other developed countries.[298] Other infectious diseases or related conditions of concern include acute rheumatic fever, meningococcal disease, childhood pneumonia, and skin infections, due to their high prevalence here.[299]

Infectious diseases do not affect everyone equally: specific subsets of the Aotearoa New Zealand population are affected more than others. The burden of infectious disease falls most heavily on the shoulders of Māori and Pacific peoples, who are at greater risk of acquiring many infectious diseases, developing health complications, and being admitted to hospital. Health inequities are explored in section 3.4.2 below.

3.3.2 We can eliminate some diseases

Aotearoa New Zealand has unique characteristics that shape our ability to manage infectious diseases. We are a remote island nation with strict biosecurity measures at our borders, making it possible to keep some infectious diseases out and eliminate others that find their way here, even as they continue to spread overseas.

For example, we managed to eliminate COVID-19 in the community on two occasions in the past two years, through quarantine facilities at the border and non-pharmaceutical interventions including lockdowns, mask use, and physical distancing.[300] This bought us valuable time to prepare the health system and roll vaccines out in the community. We are also currently working to eliminate two

[295] Ministry of Health. (2020). *Longer, healthier lives: New Zealand's health 1990-2017*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/system/files/documents/publications/longer-healthier-lives-new-zealands-health-1990-2017.pdf

[296] Turner, N. (2019). A measles epidemic in New Zealand: Why did this occur and how can we prevent it occurring again? *The New Zealand Medical Journal, 132*(1504), 8-12.

[297] The Immunisation Advisory Centre. (2020, September). Pertussis. Retrieved 16 September, 2021, from https://www.immune.org.nz/diseases/pertussis

[298] Lal, A., Lill, A.W.T., Mcintyre, M.*, et al.* (2015). Environmental change and enteric zoonoses in New Zealand: A systematic review of the evidence. *Australian and New Zealand Journal of Public Health, 39*(1), 63-68. https://doi.org/10.1111/1753-6405.12274

[299] Baker, M.G., Barnard, L.T., Kvalsvig, A.*, et al.* (2012). Increasing incidence of serious infectious diseases and inequalities in New Zealand: A national epidemiological study. *The Lancet, 379*(9821), 1112-1119. https://doi.org/10.1016/S0140-6736(11)61780-7

[300] Baker, M.G., Wilson, N., & Blakely, T. (2020). Elimination could be the optimal response strategy for COVID-19 and other emerging pandemic diseases. *BMJ, 371*, m4907. https://doi.org/10.1136/bmj.m4907; Douglas, J., Geoghegan, J., Hadfield, J.*, et al.* (2021). Real-time genomics for tracking severe acute respiratory syndrome coronavirus 2 border incursions after virus elimination, New Zealand. *Emerging Infectious Diseases, 27*(9), 2361. https://doi.org/10.3201/eid2709.211097; Jefferies, S., French, N., Gilkison, C.*, et al.* (2020). COVID-19 in New Zealand and the impact of the national response: A descriptive epidemiological study. *The Lancet Public Health, 5*(11), e612-e623. https://doi.org/10.1016/S2468-2667(20)30225-5

pathogens that cause disease in cattle: *Mycoplasma bovis*[301] (see section 3.5.1 for details) and *Mycobacterium bovis*.[302] Historically, we have eliminated two zoonoses, *Brucella abortus* (last case 1989, regarded as being free of this pathogen)[303] and hydatid disease (declared provisionally free in 2002).[304] We also successfully eliminated polio in 1962,[305] and join the rest of the world in being free from rinderpest and smallpox, the only two pathogens to have been globally eradicated so far.[306]

We are a remote island nation with strict biosecurity measures at our borders, making it possible to keep some infectious diseases out and eliminate others.

3.3.3 International connections

Our high level of international travel is another characteristic that impacts our infectious diseases landscape. In 2019 (before the COVID-19 pandemic), New Zealanders made more than three million international trips, with particularly strong connections to the Asia-Pacific region.[307] A highly mobile human population is accompanied by the risk of importing additional cases of established diseases and as well as exotic diseases that may become established here. This includes drug-resistant pathogens, a theme that is explored further in part four.

A highly mobile human population is accompanied by the risk of importing additional cases of established diseases and as well as exotic diseases that may become established here.

For example, in 2016 nearly 80% of TB notifications in Aotearoa New Zealand were in people born overseas, likely representing reactivation of latent TB acquired overseas.[308] Similarly, the majority of shigellosis cases are likely contracted overseas and diagnosed upon arrival here.[309] In some cases, there may be a delay between the emergence of a

[301] Ministry for Primary Industries. (n.d.). What is MPI doing about *M. bovis*? Retrieved 10 September, 2021, from https://www.mpi.govt.nz/biosecurity/mycoplasma-bovis/what-is-mpi-doing/

[302] Livingstone, P.G., Hancox, N., Nugent, G.*, et al.* (2015). Development of the New Zealand strategy for local eradication of tuberculosis from wildlife and livestock. *New Zealand Veterinary Journal, 63*(sup1), 98-107. https://doi.org/10.1080/00480169.2015.1013581; Nugent, G., Gormley, A.M., Anderson, D.P.*, et al.* (2018). Roll-back eradication of bovine tuberculosis (TB) from wildlife in New Zealand: Concepts, evolving approaches, and progress. *Frontiers in Veterinary Science, 5*(277). https://doi.org/10.3389/fvets.2018.00277

[303] Davidson, R.M. (2002). Control and eradication of animal diseases in New Zealand. *New Zealand Veterinary Journal, 50*(sup3), 6-12. https://doi.org/10.1080/00480169.2002.36259; Zohrab, T. (2021). *Self-declaration by New Zealand of historical freedom from Brucella abortus*. World Organisation for Animal Health. Retrieved from https://www.oie.int/app/uploads/2021/06/2021-04-new-zealand-brucella-abortus-self-declaration.pdf

[304] Ministry of Health. (2018, 4 April). Hydatid disease. Retrieved 16 September, 2021, from https://www.health.govt.nz/our-work/diseases-and-conditions/communicable-disease-control-manual/hydatid-disease

[305] Wilson, N., & Baker, M.G. (2012). Celebrating 50 years of polio elimination in New Zealand: But inadequate progress in eliminating other vaccine-preventable diseases. *The New Zealand Medical Journal, 125*(1365), 67-74.

[306] Centers for Disease Control and Prevention. (2021, 20 February). History of smallpox. Retrieved 1 December, 2021, from https://www.cdc.gov/smallpox/history/history.html; World Organisation for Animal Health (OIE). (n.d.). Rinderpest. Retrieved 1 December, 2021, from https://www.oie.int/en/disease/rinderpest/#ui-id-4

[307] Stats NZ. (2020). International travel: December 2019. Retrieved 16 September, 2021, from https://www.stats.govt.nz/information-releases/international-travel-december-2019

[308] Verrall, A.J., Hill, P.C., Thorburn, D.*, et al.* (2020). Towards elimination of tuberculosis in New Zealand. *The New Zealand Medical Journal, 133*(1513), 89-96.

[309] Heffernan, H., Woodhouse, R., Hewison, C.*, et al.* (2018). Antimicrobial resistance among *Shigella* in New Zealand. *New Zealand Medical Journal, 131*(1477), 56-62.

novel pathogen overseas and that pathogen reaching Aotearoa New Zealand. This gives us a window of opportunity to learn from overseas experiences and, ideally, plan and act accordingly.

Our close physical, social, historical, political, and cultural connections with the Pacific mean that we need to work in partnership with our regional neighbours to tackle infectious diseases. The spread of infectious diseases from Aotearoa New Zealand to other Pacific nations, and vice versa, has been recorded. For example, measles spread from Aotearoa New Zealand to both Tonga and Samoa in 2019. In Tonga, a youth rugby team returned home with measles, subsequently leading to more than 600 cases.[310] In Samoa, more than 5,700 measles cases and 83 deaths were recorded in the 2019–2020 outbreak, with the outbreak occurring in a massively under-vaccinated population.[311] In a historical example, New Zealanders travelling to Samoa in 1918 introduced pandemic influenza to the country, killing one-fifth of the Samoan population (see section 2.2.1).[312]

Pacific Island nations also face infectious disease challenges that are rare in Aotearoa New Zealand. For example, several neglected tropical diseases are prevalent, including hookworm infections and dengue fever.[313] In addition, TB remains prevalent in some countries such as Kiribati and Fiji.[314] Travel can bring cases of these infections into Aotearoa New Zealand. While some imported infections have scope to spread here, many can't readily become established (e.g. dengue, which is spread by a type of mosquito that isn't currently found here). Nonetheless, infected travellers from the Pacific add to our national health burden.

Our close physical, social, historical, political, and cultural connections with the Pacific mean that **we need to work in partnership** with our regional neighbours to tackle infectious diseases.

[310] Government of Tonga. (2020). *Tonga measles outbreak 2019-20 - Situation report #18*. Retrieved from https://reliefweb.int/report/tonga/tonga-measles-outbreak-2019-20-situation-report-18

[311] Government of Samoa. (2020, 20 January). *Health Emergency Operation Centre: Update on the measles outbreak, January 20, 2020* [Press release]. Retrieved from https://reliefweb.int/report/samoa/health-emergency-operation-centre-update-measles-outbreak-january-20-2020; Craig, A.T., Heywood, A.E., & Worth, H. (2020). Measles epidemic in Samoa and other Pacific islands. *The Lancet Infectious Diseases, 20*(3), 273-275. https://doi.org/10.1016/S1473-3099(20)30053-0

[312] Ministry for Culture and Heritage. (2020, 22 April). Influenza hits Samoa. Retrieved 24 November, 2021, from https://nzhistory.govt.nz/media/photo/influenza-pandemic-hits-samoa

[313] Kline, K., McCarthy, J.S., Pearson, M., *et al.* (2013). Neglected tropical diseases of Oceania: Review of their prevalence, distribution, and opportunities for control. *PLOS Neglected Tropical Diseases, 7*(1), e1755. https://doi.org/10.1371/journal.pntd.0001755

[314] World Health Organization. (2017). *WHO country cooperation strategy 2018–2022: Pacific island countries and areas*. Retrieved from https://www.who.int/publications/i/item/WPRO-2017-DPM-027

3.4 Infectious diseases impact people significantly

The age of infectious diseases is far from behind us. This section explores the impacts of infectious diseases on human health and social and emotional wellbeing in Aotearoa New Zealand, highlights the range of economic costs that can be incurred, and shines a light on inequity in health outcomes, particularly for Māori and Pacific peoples. This section isn't intended to be comprehensive, instead taking a case study approach. Infectious diseases with specific resistance concerns are covered in part four.

3.4.1 Infection has long-term health, economic, social and emotional costs

The acute impacts of infectious disease are obvious: no one likes being sick. But the cost of disease extends beyond the days or weeks of acute infection, with flow-on effects for whānau, communities, and society. The economic costs associated with infectious diseases can be direct (e.g. healthcare expenditure) and indirect (e.g. lost productivity). Individuals may suffer due to the need to take time off work (because of their own illness, or to care for someone else), or they may miss educational or development opportunities. These financial impacts can ripple out to whānau, community and wider society.

Some infectious diseases can have long-lasting health impacts. For example, after an episode of acute rheumatic fever a patient requires prophylactic antibiotic injections every month for up to ten years to prevent repeated infection by group A *Streptococcus* and development of rheumatic heart disease. Studies investigating the lived experiences of those with rheumatic fever find substantial impacts for a person's emotional and social wellbeing, as well as causing emotional, social, and economic stress for parents, caregivers, and whānau.[315] For a detailed evidence synthesis on rheumatic fever in Aotearoa New Zealand, see the annex to this report available on the OPMCSA website.

In another example of acute illness leading to lasting health impacts, some COVID-19 survivors in Aotearoa New Zealand will likely experience post COVID-19 condition ('long COVID'), a phenomenon that has gained official recognition from the WHO.[316]

What is post-COVID-19 condition?

WHO has developed a clinical case definition of post-COVID-19 condition. This definition may change as more evidence emerges: post-COVID-19 condition is not well understood, including how long symptoms might last, what proportion or survivors are impacted, how severe those impacts are, and what the underlying mechanisms and risk factors are.

WHO's October 2021 definition of post-COVID-19 condition follows:

"Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which generally have an impact on

[315] Burgess, H. (2016). *Māori whānau experiences of rheumatic fever: Reflections of social and structural inequity.* ResearchSpace@Auckland, Auckland, New Zealand. Retrieved from https://researchspace.auckland.ac.nz/bitstream/handle/2292/30703/whole.pdf?sequence=2 ; Ryan, D. (2015). *Health care experiences of Pacific families who have children with rheumatic fever*. Wellington, NZ: Pacific Perspectives Ltd. Retrieved from https://2ad85816-c406-4fbd-96af-68d86f851586.filesusr.com/ugd/840a69_3f5dc99e07f14c5790c3d9e2fb11bcdc.pdf

[316] World Health Organization. (2021). *A clinical case definition of post COVID-19 condition by a Delphi consensus*. World Health Organization. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1

everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children."

Another example of long-term burdens resulting from infection is evident with bronchiectasis, a lung condition characterised by damaged and chronically inflamed airways – typically the result of repeated infections during childhood.[317] Bronchiectasis leads to further susceptibility to infections and reduced lung capacity throughout a person's life. In turn, this can make exercise and work difficult, and in some cases, leads to early death. This disease, which has strong links to poverty, is more prevalent in Aotearoa New Zealand than other OECD countries, and prevalence is increasing.[318] Ethnic and socio-economic disparities are stark: prevalence of bronchiectasis is six times higher among Pacific peoples and four times higher among Māori compared with New Zealand Europeans.[319] Prevalence in the most deprived quintile of people is three times higher than among the least deprived. Health inequities are discussed in more depth in section 3.4.2 below.

Case study: Healthcare-associated infections

HAIs highlight a number of the costs associated with infectious diseases in Aotearoa New Zealand. HAIs are one of the most frequent adverse events associated with healthcare,[320] causing morbidity, mortality, and wider harm to patients, whanau, and communities, as well contributing to considerable direct economic costs to DHBs and the healthcare sector.

HAIs include wound infections, SSIs, and infections associated with catheters, implants, or other medical devices. People who contract HAIs are more likely to have an extended hospital stay, an admission to an ICU, or a readmission post-discharge.[321] HAIs can result in sepsis, a life-threatening condition described below.

Many HAIs are preventable through best practice IPC measures (e.g. handwashing and septic technique), discussed in section 5.3.1. Many HAIs are made worse by the emergence of drug-resistant pathogens, some of which are commonly associated with HAIs such as *Acinetobacter baumannii* (discussed in section 2.4.2). A discussion of activities to address HAIs can be found in section 5.3.1.

[317] bpac nz. (2012). Bronchiectasis: Rates still increasing among Pacific peoples. *Best Practice Journal,* (46), 21-24. Retrieved from https://bpac.org.nz/bpj/2012/september/bronchiectasis.aspx

[318] Chang, A.B., Bell, S.C., Byrnes, C.A.*, et al.* (2010). Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand. A position statement from the Thoracic Society of Australia and New Zealand and the Australian Lung Foundation. *Medical Journal of Australia, 193*(6), 356-365. https://doi.org/https://doi.org/10.5694/j.1326-5377.2010.tb03949.x; Telfar Barnard, L., & Zhang, J. (2018). *The impact of respiratory disease in New Zealand: 2018 update*. Asthama and Respiratory Foundation NZ. Retrieved from https://www.asthmafoundation.org.nz/assets/images/NZ-Impact-Report-2018_FINAL.pdf; Twiss, J., Metcalfe, R., Edwards, E.*, et al.* (2005). New Zealand national incidence of bronchiectasis "too high" for a developed country. *Archives of Disease in Childhood, 90*(7), 737. https://doi.org/10.1136/adc.2004.066472

[319] Telfar Barnard, L., & Zhang, J. (2018). *The impact of respiratory disease in New Zealand: 2018 update*. Asthama and Respiratory Foundation NZ. Retrieved from https://www.asthmafoundation.org.nz/assets/images/NZ-Impact-Report-2018_FINAL.pdf

[320] World Health Organization. (2011). *Report on the burden of endemic health care-associated infection worldwide*. Geneva, Switzerland: Retrieved from https://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf

[321] Health Navigator New Zealand. (2020, 20 July). Preventing healthcare-associated infection. Retrieved 4 October, 2021, from https://www.healthnavigator.org.nz/health-a-z/h/healthcare-associated-infection/

Case study: Sepsis

Sepsis (also known as blood poisoning or septicaemia) is a potentially life-threatening condition that can occur when the body reacts to a severe infection or when infection occurs in an immunocompromised person.[322] Symptoms include fever and chills, fast heart rate, rapid breathing, rash, mental confusion, and/or disorientation. Septic shock is a subset of sepsis which involves a drop in blood pressure, leading to circulatory and metabolic dysfunction and a higher risk of mortality than sepsis alone. Many different infections can lead to sepsis, including pneumonia, UTIs, and wound infections.

For each hour that antibiotic administration to patients with sepsis is delayed, there is a cumulative 4% increase in the risk of mortality.

Treatment of sepsis is reliant on rapid diagnosis and immediate use of appropriate antibiotics and supporting treatment (e.g. respiratory support, regulating blood volume).[323] For each hour that antibiotic administration to patients with sepsis is delayed, there is a cumulative 4% increase in the risk of mortality.[324] However, rapid diagnosis is not straightforward, with symptoms being similar to other illnesses including influenza and gastroenteritis. In addition, barriers to accessing healthcare services may also contribute to delayed treatment, which contributes to inequitable health outcomes in Aotearoa New Zealand (explored further in section 3.4.2 below).

Impacts

While data on the incidence of sepsis is poor, some studies provide insight into the incidence of sepsis among specific population subgroups.

- **Māori are disproportionately affected.** A study looking at sepsis in a Waikato population found that Māori were over three times more likely to experience sepsis than non-Māori between 2007 and 2012.[325]
- **Avoidable sepsis occurs among pregnant women.** Of 50 cases of severe sepsis among pregnant woman admitted to an ICU or high dependency unit between 2013 and 2015, half were considered preventable by an expert clinician panel.[326]
- **Sepsis among newborn babies is becoming less prevalent.** A study undertaken in Australia and Aotearoa New Zealand found that early onset neonatal sepsis decreased by 4% each year between 2002 and 2012 and was predominantly caused by group B *Streptococcus* and *Escherichia coli.*[327] Another study, which looked at neonatal group B S*treptococcus* sepsis in Aotearoa New Zealand between 2009 and 2011, found an incidence of 0.23 per 1,000 live

[322] Huggan, P.J., Helms, T.A., Gibbons, V.*, et al.* (2021). Counting the cost of major infection and sepsis in New Zealand: An exploratory study using the National Minimum Data Set. *New Zealand Medical Journal, 134*(1528), 10-25.
[323] Polat, G., Ugan, R.A., Cadirci, E.*, et al.* (2017). Sepsis and septic shock: Current treatment strategies and new approaches. *The Eurasian Journal of Medicine, 49*(1), 53. https://doi.org/10.5152/eurasianjmed.2017.17062
[324] Seymour, C.W., Gesten, F., Prescott, H.C.*, et al.* (2017). Time to treatment and mortality during mandated emergency care for sepsis. *New England Journal of Medicine, 376*(23), 2235-2244. https://doi.org/10.1056/NEJMoa1703058
[325] Huggan, P.J., Bell, A., Waetford, J.*, et al.* (2017). Evidence of high mortality and increasing burden of sepsis in a regional sample of the New Zealand population. *Open Forum Infectious Diseases, 4*(3). https://doi.org/10.1093/ofid/ofx106
[326] Lepine, S., Lawton, B., Geller, S.*, et al.* (2018). Severe maternal morbidity due to sepsis: The burden and preventability of disease in New Zealand. *Australian and New Zealand Journal of Obstetrics and Gynaecology, 58*(6), 648-653. https://doi.org/10.1111/ajo.12787
[327] Singh, T., Barnes, E.H., & Isaacs, D. (2019). Early-onset neonatal infections in Australia and New Zealand, 2002–2012. *Archives of Disease in Childhood - Fetal and Neonatal Edition, 104*(3), F248-F252. https://doi.org/10.1136/archdischild-2017-314671

births.[328] The rate had more than halved since a similar survey 10 years prior and promotion of a prevention protocol nationally five years prior.[329]

The mortality ratio associated with sepsis is difficult to measure, in part because there are a range of different classifications of sepsis and because the underlying condition (e.g. pneumonia or cancer) may be recorded as the cause of death rather than sepsis itself.

- A 2020 systematic review and meta-analysis of results from Europe, North America, and Australia found that the average 30-day sepsis mortality was 24%, while the average 30-day mortality for the more serious septic shock was 35%.[330]
- A 2016 review paper found that, in the first year following sepsis, up to 63% of survivors were readmitted to hospital, with the most common reason for readmission being unresolved, recurrent, or new infection.[331]
- There was a decrease in mortality between 2000 to 2012 for patients in Australia and Aotearoa New Zealand critically ill with severe sepsis (with and without shock) – from 35% to 18%.[332]

Survivors of sepsis suffer long-lasting mental and physical health impacts, termed 'post-sepsis syndrome'.[333] Physical symptoms can include fatigue, breathlessness, joint and muscle pain, hair loss, and repeat infections, among others. Psychological symptoms can include panic attacks, depression, difficulty concentrating, and decreased cognitive functioning. These symptoms can persist for years, impacting quality of life[334] and resulting in lost income – which can also affect whānau and carers of sepsis survivors. In developing the National Sepsis Action Plan, the Sepsis Trust NZ found that there is little support or information for sepsis survivors to help them navigate recovery.[335]

Sepsis is costly to treat and is underappreciated in Aotearoa New Zealand's direct healthcare spending.[336]. Between 2010 and 2020, ACC estimates it has spent approximately NZ$81 million on treatment and support for New Zealanders with sepsis,[337] but the total cost is difficult to estimate given data available on the incidence of sepsis each year is poor.

[328] Darlow, B.A., Voss, L., Lennon, D.R.*, et al.* (2016). Early-onset neonatal group B *Streptococcus* sepsis following national risk-based prevention guidelines. *Australian and New Zealand Journal of Obstetrics and Gynaecology, 56*(1), 69-74. https://doi.org/10.1111/ajo.12378

[329] Ibid.

[330] Bauer, M., Gerlach, H., Vogelmann, T.*, et al.* (2020). Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019— results from a systematic review and meta-analysis. *Critical Care, 24*(1), 239. https://doi.org/10.1186/s13054-020-02950-2

[331] Shankar-Hari, M., & Rubenfeld, G.D. (2016). Understanding long-term outcomes following sepsis: Implications and challenges. *Current Infectious Disease Reports, 18*(11), 37. https://doi.org/10.1007/s11908-016-0544-7

[332] Kaukonen, K.-M., Bailey, M., Suzuki, S.*, et al.* (2014). Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *Jama, 311*(13), 1308-1316. https://doi.org/10.1001/jama.2014.2637

[333] Huang, C.Y., Daniels, R., Lembo, A.*, et al.* (2019). Life after sepsis: An international survey of survivors to understand the post-sepsis syndrome. *International Journal for Quality in Health Care, 31*(3), 191-198. https://doi.org/10.1093/intqhc/mzy137; Mostel, Z., Perl, A., Marck, M.*, et al.* (2019). Post-sepsis syndrome – an evolving entity that afflicts survivors of sepsis. *Molecular Medicine, 26*(1), 6. https://doi.org/10.1186/s10020-019-0132-z

[334] Haug, V.F., Tapking, C., Panayi, A.C.*, et al.* (2021). Long-term sequelae of critical illness in sepsis, trauma and burns: A systematic review and meta-analysis. *Journal of Trauma and Acute Care Surgery, 91*(4), 736-747. https://doi.org/10.1097/ta.0000000000003349

[335] Sepsis Trust NZ. (2021). *A national sepsis action plan for Aotearoa, New Zealand: Technical report and highlights of a national consensus meeting*. Retrieved from https://www.sepsis.org.nz/wp-content/uploads/Technical_and_Consensus_Report_P2.pdf

[336] Huggan, P.J., Helms, T.A., Gibbons, V.*, et al.* (2021). Counting the cost of major infection and sepsis in New Zealand: An exploratory study using the National Minimum Data Set. *New Zealand Medical Journal, 134*(1528), 10-25.

[337] Accident Compensation Corporation. (2020). Working together to treat and prevent sepsis. Retrieved 10 September, 2021, from https://www.acc.co.nz/newsroom/stories/working-together-to-treat-and-prevent-sepsis/

Resistance

While sepsis can be caused by viral, fungal, or bacterial infections, most cases of sepsis are due to bacterial infection, caused by organisms such as *Staphylococcus aureus*, *E. coli*, and *Pseudomonas spp*.[338] The resistance profiles of these microbes are outlined in section 4.3.1.

A multidrug-resistant strain of *Staphylococcus capitis* causes sepsis in neonatal ICUs around the world, including in Aotearoa New Zealand.[339] Genomic sequencing has implicated the neonatal ICU environment as a potential reservoir contributing to neonatal sepsis caused by *S. capitis*,[340] a major concern for the treatment of newborn babies with sepsis.

A multidrug-resistant strain of ***Staphylococcus capitis*** causes sepsis in neonatal intensive care units around the world, including in Aotearoa New Zealand.

Broad-spectrum IV antibiotics should be initiated early in sepsis, ideally within an hour of diagnosis, to improve outcomes.[341] While broad-spectrum agents drive AMR more than narrower spectrum agents, they are needed early in sepsis-related care to help ensure coverage against the range of potential causative pathogens (which will be unknown at presentation). As more information comes to hand (e.g. test results, susceptibility results), dosing should be adjusted and the antibiotics should be changed to an appropriate agent with a narrower spectrum that targets the pathogen identified. Surgery, oxygen therapy, and IV fluids may also be deployed depending on the type of infection.[342] Section 5.4 explores the role that diagnostics can play in helping Aotearoa New Zealand combat AMR and infectious diseases.

What's being done about sepsis?

Sepsis is a preventable illness. Sepsis Trust NZ is developing a National Sepsis Action Plan that has been out for public consultation but isn't yet finalised.[343] The Plan outlines five actions that aim to deliver a vision of "zero harm due to sepsis in Aotearoa New Zealand." Key among these is increasing awareness of sepsis across the health sector and among the public, empowering patients and practitioners to ask, "Could it be sepsis?".[344]

Waikato DHB developed and implemented a 'Sepsis Ready' programme in 2018. Since introduction of the programme there has been a dramatic improvement in the care provided to patients showing

[338] Dolin, H.H., Papadimos, T.J., Chen, X., *et al.* (2019). Characterization of pathogenic sepsis etiologies and patient profiles: A novel approach to triage and treatment. *Microbiology Insights, 12*, 1178636118825081. https://doi.org/10.1177/1178636118825081
[339] Thorn, L.M., Ussher, J.E., Broadbent, R.S., *et al.* (2020). Risk factors for *Staphylococcus capitis* pulsotype NRCS-A colonisation among premature neonates in the neonatal intensive care unit of a tertiary-care hospital: A retrospective case-control study. *Infection Prevention in Practice, 2*(2), 100057. https://doi.org/10.1016/j.infpip.2020.100057
[340] Carter, G.P., Ussher, J.E., Da Silva, A.G., *et al.* (2018). Genomic analysis of multiresistant *Staphylococcus capitis* associated with neonatal sepsis. *Antimicrobial Agents and Chemotherapy, 62*(11). https://doi.org/10.1128/aac.00898-18
[341] Wylie-Cheer, B., & Goodson, H. (2016). Sepsis care and treatment in New Zealand and Australia. *Journal of Emergency Medical Services, 41*(9), 60-63.
[342] bpac nz. (2018). *Sepsis: Recognition, diagnosis and early management*. Dunedin: Best Practice Advocacy Centre. Retrieved from https://bpac.org.nz/guidelines/4/docs/Sepsis.pdf
[343] Sepsis Trust NZ. (2020). *Aotearoa New Zealand National Sepsis Action Plan - Consultation Document*. Retrieved from www.sepsis.org.nz/action
[344] Sepsis Trust NZ. (2021). *A national sepsis action plan for Aotearoa, New Zealand: Technical report and highlights of a national consensus meeting*. Retrieved from https://www.sepsis.org.nz/wp-content/uploads/Technical_and_Consensus_Report_P2.pdf

symptoms of sepsis.[345] The programme has now been adapted for Taranaki DHB and launched in 2021. It includes a strong focus on equity and quality improvement.[346]

Further opportunities for improvement in the identification and treatment of sepsis might be identified by a stocktake of the protocols and data currently available and whether there are any successes that could be scaled up.

3.4.2 The human health burden is inequitable

Māori and Pacific peoples are impacted by infectious disease more than New Zealanders of other ethnicities. This is due to a complex array of factors including historical and ongoing inequities and systemic racism. Inequities also exist for people from low-income or socioeconomically deprived populations. This burden is not just felt in terms of lost health, but has ripple effects in people's lives, as discussed in section 3.4.1 above.

Evidence for the disproportionate burden infectious diseases place on Māori and Pacific peoples is abundant. For example:

- The risk of being admitted to hospital with an infectious disease is heightened for Māori, Pacific peoples, and people from socioeconomically deprived localities. Further, rates of admission for infectious disease rose faster for these groups than for others between 1989 and 2008.[347]
- Incidence of both TB and staphylococcal disease are higher among Māori and Pacific peoples when compared with New Zealanders of European descent.[348]
- Māori and Pacific infants have higher rates of both emergency department visits and hospitalisations for all viral infections compared with infants of other ethnicities.[349]
- The rate of pneumonia among adults is more than three times higher among Māori compared with non-Māori.[350]
- Hospitalisation rates are higher among Pacific children compared with other ethnicities for acute and chronic respiratory infectious diseases and serious skin infections.[351]
- Māori and Pacific peoples and children living in the most deprived areas are disproportionately likely to acquire a skin infection severe enough to require hospitalisation.[352]

[345] Waikato District Health Board. (2019, 27 June). *Waikato DHB recognised for Sepsis Ready programme* [Press release]. Retrieved from https://www.waikatodhbnewsroom.co.nz/2019/06/27/waikato-dhb-recognised-for-sepsis-ready-programme/
[346] Taranaki District Health Board. (2021, 30 June). *Sepsis programme at Taranaki DHB a New Zealand first* [Press release]. Retrieved from https://www.tdhb.org.nz/news/documents/media_release_2021_06_30.shtml
[347] Baker, M.G., Barnard, L.T., Kvalsvig, A., *et al.* (2012). Increasing incidence of serious infectious diseases and inequalities in New Zealand: A national epidemiological study. *The Lancet, 379*(9821), 1112-1119. https://doi.org/10.1016/S0140-6736(11)61780-7
[348] Crump, J.A., Murdoch, D.R., & Baker, M.G. (2001). Emerging infectious diseases in an island ecosystem: The New Zealand perspective. *Emerging Infectious Diseases, 7*(5), 767-772. https://doi.org/10.3201/eid0705.017501
[349] Prasad, N., Trenholme, A.A., Huang, Q.S., *et al.* (2020). Respiratory virus-related emergency department visits and hospitalizations among infants in New Zealand. *The Pediatric Infectious Disease Journal, 39*(8), e176-e182. https://doi.org/10.1097/inf.0000000000002681
[350] Chambers, S., Laing, R., Murdoch, D., *et al.* (2006). Māori have a much higher incidence of community-acquired pneumonia and pneumococcal pneumonia than non-Māori: findings from two New Zealand hospitals. *New Zealand Medical Journal, 119*(1234), U1978.
[351] Ryan, D., Grey, C., & Mischewski, B. (2019). *Tofa Saili: A review of evidence about health equity for Pacific Peoples in New Zealand*. Wellington, New Zealand: Pacific Perspectives Ltd. Retrieved from https://www.pacificperspectives.co.nz/publications
[352] Lim, A., Rumball-Smith, J., Jones, R., *et al.* (2017). The rise and fall of hospitalizations for skin infections in New Zealand, 2004–2014: Trends by ethnicity and socioeconomic deprivation. *Epidemiology and Infection, 145*(4), 678-684. https://doi.org/10.1017/S0950268816002685; Toi Te Ora Public Health. (2018). *Childhood admissions to hospital for serious skin infections in the Toi Te Ora Public Health area* Bay of Plenty District Health Board and Lakes District Health Board. Retrieved from https://toiteora.govt.nz/assets/Toi-Te-Ora-Public-Health/Information-For-Sector/Health-Professionals/Skin-infections/Skin_Infection_report_2018_Final.pdf

- When adjusted for age, sex, and socioeconomic deprivation, hospitalisation rates for rheumatic fever are ~24 times higher for Pacific peoples and ~12 times higher for Māori compared with European and other ethnicities.[353]
- There is higher incidence and prevalence of acute respiratory infection and resulting long-term conditions in Māori compared with non-Māori.[354]
- A hospital-based study spanning 2008 to 2018 found that Maori and Pacific children were more likely to experience paediatric septic arthritis, a type of joint infection that is relatively rare in the developed world. For Maori children, incidence was found to be similar to that in the developing world.[355]

For decades, these disparities have been reported and noted but little progress has been made to close the gaps. For Māori, these inequities are inconsistent with Te Tiriti o Waitangi.

These inequities are broadly driven by two overarching issues: the nature of the healthcare system (including access and quality of care) and the wider social determinants of health that contribute to disadvantages even before an individual engages with the health system.

It should be noted that other ethnic disparities in health outcomes exist in Aotearoa New Zealand too. For example, TB places a considerable burden on people who identify as Middle Eastern, Latin American, or African, and people who identify as Asian – TB is most prevalent among these groups.[356] People living in rural communities are less likely to be able to readily access healthcare services, discussed in more detail below.

Inequities in access and quality of care lead to inequitable outcomes

Health services are less accessible for Māori and Pacific peoples compared with non-Māori.[357] One of the foremost barriers is cost. This includes the direct costs associated with accessing health services (e.g. appointment fees) and medicines, as well as associated costs such as the costs of travelling to access services or taking time off work. A 2013 report on Pacific healthcare in Aotearoa New Zealand found that cost and transport were among the most significant barriers to access for Pacific peoples.[358]

Māori are more likely to cite cost as a barrier to accessing primary care, while Pacific children are more likely than non-Pacific children to experience unmet need for a GP due to cost.[359] With GP

[353] Bennett, J., Zhang, J., Leung, W.*, et al.* (2021). Rising ethnic inequalities in acute rheumatic fever and rheumatic heart disease, New Zealand, 2000–2018. *Emerging Infectious Diseases, 27*(1), 36. https://doi.org/10.3201/eid2701.191791

[354] Byrnes, C.A., & Trenholme, A. (2010). Respiratory infections in Tamariki (children) and Taitamariki (young people) Māori, New Zealand. *Journal of Paediatrics and Child Health, 46*(9), 521-526. https://doi.org/https://doi.org/10.1111/j.1440-1754.2010.01853.x

[355] Hunter, S., & Baker, J.F. (2021). Ten-year retrospective review of paediatric septic arthritis in a New Zealand centre. *International Orthopaedics, 45*(1), 147-154. https://doi.org/10.1007/s00264-020-04611-z

[356] Institute of Environmental Science and Research Limited (ESR). (2021). *Notifiable diseases in New Zealand: Annual report 2019*. Porirua, NZ: Ministry of Health. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/AnnualRpt/AnnualSurv/2019/2019AnnualNDReport_FINAL.pdf

[357] Health Quality & Safety Commission. (2019). *A window on the quality of Aotearoa New Zealand's health care 2019 – A view on Māori health equity*. Wellington, New Zealand: Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/publications-and-resources/publication/3721/; Ryan, D., Grey, C., & Mischewski, B. (2019). *Tofa Saili: A review of evidence about health equity for Pacific Peoples in New Zealand*. Wellington, New Zealand: Pacific Perspectives Ltd. Retrieved from https://www.pacificperspectives.co.nz/publications

[358] Southwick, M., Kenealy, T., & Ryan, D. (2012). *Primary care for pacific people: A Pacific and health systems approach*. Wellington, NZ: Pacific Perspectives. Retrieved from https://www.health.govt.nz/system/files/documents/publications/primary-care-pacific-people-pacific-health-systems-approach.pdf

[359] Health Quality & Safety Commission. (2019). *A window on the quality of Aotearoa New Zealand's health care 2019 – A view on Māori health equity*. Wellington, New Zealand: Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/publications-and-resources/publication/3721/; Ministry of Health. (2019). New Zealand Health Survey Annual Data Explorer. Retrieved 15 July, 2021, from https://minhealthnz.shinyapps.io/nz-health-survey-2018-19-annual-data-explorer

check-ups being fees free for children under 14 years, this is likely at least partially due to the cost of travel or time off work for caregivers.

Cost is also a barrier to accessing medicines. Eighteen percent of Pacific people won't fill a prescription because of cost (compared with 8% for the total population).[360] According to the New Zealand Health Survey, Pacific and Māori peoples are more than twice as likely as non-Pacific and non-Māori peoples, respectively, to not have collected a prescription due to cost.[361] Again, extension of fees free prescriptions to include all children under 14 years from late 2018 has likely helped, but costs associated with travelling to pick up a prescription may still serve as a barrier for some.

Other barriers to access include logistical barriers (e.g. the challenge of finding a way to travel to healthcare services), appointment times (e.g. available windows may be during work hours, making access for people with inflexible work schedules challenging), time costs associated with travel and waiting, poor communication or limited cultural appropriateness of messaging, and competing demands on time that reduce ability to take time to access health services (e.g. childcare).[362]

Pacific and Māori peoples are more than **twice as likely** as non-Pacific and non-Māori peoples, respectively, to not have collected a prescription due to cost.

Access to the healthcare system is not the only issue: there is also inequity in the quality of outcomes that are produced for different people through their interactions with the health system. A universal 'one-size-fits-all' approach does not adequately cater to different needs.[363]

Racism within the health system, at both systemic and personal levels, plays a role.[364] There is a well-documented link between the experience of racism and a range of negative health measures. For example, a mother's experience of healthcare-based racism is associated with increased infectious disease hospitalisations for Māori infants.[365] In a study exploring the experiences of rheumatic fever patients with the health system in Northland, Māori patients often reported feeling their concerns weren't taken seriously, contributing in some cases to delayed diagnoses.[366] Institutionalised racism in hospitals in this country has been described as "endemic."[367]

Efforts to improve healthcare quality reveal that an explicit and sustained focus on equity is necessary for lasting change. For example, immunisation inequities between Māori and non-Māori

[360] Ryan, D., Grey, C., & Mischewski, B. (2019). *Tofa Saili: A review of evidence about health equity for Pacific Peoples in New Zealand*. Wellington, New Zealand: Pacific Perspectives Ltd. Retrieved from https://www.pacificperspectives.co.nz/publications

[361] Ministry of Health. (2019). New Zealand Health Survey Annual Data Explorer. Retrieved 15 July, 2021, from https://minhealthnz.shinyapps.io/nz-health-survey-2018-19-annual-data-explorer

[362] Southwick, M., Kenealy, T., & Ryan, D. (2012). *Primary care for pacific people: A Pacific and health systems approach*. Wellington, NZ: Pacific Perspectives. Retrieved from https://www.health.govt.nz/system/files/documents/publications/primary-care-pacific-people-pacific-health-systems-approach.pdf

[363] Goodyear-Smith, F., & Ashton, T. (2019). New Zealand health system: Universalism struggles with persisting inequities. *The Lancet, 394*(10196), 432-442. https://doi.org/10.1016/s0140-6736(19)31238-3

[364] Talamaivao, N., Harris, R., Cormack, D.*, et al.* (2020). Racism and health in Aotearoa New Zealand: A systematic review of quantitative studies. *The New Zealand Medical Journal, 133*(1521), 55-55.

[365] Hobbs, M.R., Morton, S.M., Atatoa-Carr, P.*, et al.* (2017). Ethnic disparities in infectious disease hospitalisations in the first year of life in New Zealand. *Journal of Paediatrics and Child Health, 53*(3), 223-231. https://doi.org/10.1111/jpc.13377

[366] Anderson, A., Mills, C., & Eggleton, K. (2017). Whānau perceptions and experiences of acute rheumatic fever diagnosis for Māori in Northland, New Zealand. *The New Zealand Medical Journal, 130*(1465), 80-89.

[367] Anderson, A., Peat, B., Ryland, J.*, et al.* (2019). Mismatches between health service delivery and community expectations in the provision of secondary prophylaxis for rheumatic fever in New Zealand. *Australian and New Zealand Journal of Public Health, 43*(3), 294-299. https://doi.org/10.1111/1753-6405.12890

were essentially eliminated by 2014.[368] However, when focus on Māori immunisation efforts subsequently waned, immunisation coverage for Māori fell and is now 10 percentage points lower than for non-Māori.

Barriers to accessing healthcare also exist for people living rurally. Outside of the main centres, people in regional, rural, and remote settings face unique challenges in accessing healthcare. As of 2018, about one-fifth of New Zealanders lived in rural locations.[369] Further, rural towns have, overall, the lowest socioeconomic status. Māori are more likely to reside in rural areas[370] and comprise a larger proportion of the more deprived people living rurally. These populations have poor healthcare access and are underserved due to a persistent shortage in the rural medical workforce.[371] The existing workforce is ageing and relies on medical graduates from overseas.

Treating patients in rural and remote settings for infectious disease is complicated by **the lack of infectious disease expertise** outside of the main city centres.

Rural medicine requires different skillsets and approaches to medicine practice in major metropolitan areas. It may be difficult for patients who live in remote areas to return to their doctor if an illness doesn't improve. This may mean they are more likely to receive 'just-in-case' antibiotics, and that there is less ability to tailor medical advice and prescriptions as the clinical picture evolves (e.g. as laboratory results become available). Treating patients in rural and remote settings for infectious disease is complicated by the lack of infectious disease expertise outside of the main city centres.

Wider social determinants such as poverty and housing contribute

Poverty is an underlying cause of many infectious diseases in Aotearoa New Zealand. As of June 2020, more than 10% of children were living in material hardship, and Māori and Pacific children were more likely to live in households with low income or material hardship compared with New Zealand European children.[372] In Aotearoa New Zealand, poverty is associated with higher rates of paediatric infectious disease hospitalisation.[373] Poverty affects access to primary healthcare (see discussion above) and is a barrier to other determinants of health, such as access to a healthy diet and quality housing.[374] However, a recent local study found that low income alone is only weakly associated with the risk of hospitalisation in childhood – it may be too

Poverty is an underlying cause of many infectious diseases in Aotearoa New Zealand.

[368] Health Quality & Safety Commission. (2019). *A window on the quality of Aotearoa New Zealand's health care 2019 – A view on Māori health equity*. Wellington, New Zealand: Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/publications-and-resources/publication/3721/

[369] Environmental Health Intelligence New Zealand. (n.d.). Urban-rural profile. Retrieved 1 October, 2021, from https://www.ehinz.ac.nz/indicators/population-vulnerability/urbanrural-profile/

[370] Ibid.

[371] Nixon, G., & Lawrenson, R. (2019). Failing to thrive: Academic rural health in New Zealand. *Journal of Primary Health Care, 11*(1), 4-5. https://doi.org/https://doi.org/10.1071/HCv11n1_ED2

[372] Stats NZ. (2021, 22 February). *Child poverty statistics: Year ended June 2020 – corrected* [Press release]. Retrieved from https://www.stats.govt.nz/information-releases/child-poverty-statistics-year-ended-june-2020

[373] Hobbs, M.R., Morton, S.M., Atatoa-Carr, P., *et al.* (2017). Ethnic disparities in infectious disease hospitalisations in the first year of life in New Zealand. *Journal of Paediatrics and Child Health, 53*(3), 223-231. https://doi.org/10.1111/jpc.13377

[374] Department of Prime Minister and Cabinet. (2020). *Child poverty related indicators*. Wellington, NZ: Department of Prime Minister and Cabinet. Retrieved from https://dpmc.govt.nz/sites/default/files/2020-07/child-poverty-related-indicators-2020.pdf

simplistic a measure.[375] Material deprivation, which measures access to basic resources and services such as sufficient food and heating, was strongly associated with child hospitalisation.

Material deprivation, which measures access to basic resources and services such as sufficient food and heating, was strongly associated with child hospitalisation.

Cold, damp, mouldy, and crowded housing contribute to Aotearoa New Zealand's infectious disease burden. Crowding, which affects around 10% of all New Zealanders, can increase the risk of diseases such as gastroenteritis, meningococcal disease, rheumatic fever, and pneumonia.[376] More than 20% of New Zealanders live in cold houses and 30% live in damp houses, conditions that are associated with illnesses such as pneumonia and respiratory tract infections.[377] A recent study confirmed the well-established link between poor housing quality and acute respiratory infections in children.[378]

An analysis covering data from 2010-2017 found that:[379]

- Household crowding contributes to the hospitalisation of nearly 500 people every year, costing NZ$1.4 million.
- Cold homes send around 568 people to hospital every year, with hospitalisation costs of more than NZ$2.3 million.
- Dampness and mould contributed to more than 5,600 hospitalisations, costing nearly NZ$36 million.
- An estimated 161 deaths annually can be attributed to crowded, cold, damp and mouldy housing.

These figures are likely to be underestimates as some people may not be hospitalised or seek medical care. The dollar figures represent only direct costs to the healthcare sector, excluding other costs such as those associated with reduced productivity. A 2019 study estimated that if all houses were free of damp and mould, nearly 20% of

A 2019 study estimated that if all houses were free of damp and mould, nearly 20% of hospital admissions due to acute respiratory infection among children less than two years old could be prevented.

[375] Shackleton, N., Li, E., Gibb, S., *et al.* (2021). The relationship between income poverty and child hospitalisations in New Zealand: Evidence from longitudinal household panel data and Census data. *PLOS One, 16*(1), e0243920.

[376] Baker, M., McDonald, A., Zhang, J., *et al.* (2013). *Infectious diseases attributable to household crowding in New Zealand: A systematic review and burden of disease estimate*. Wellington, New Zealand: He Kainga Oranga/Housing and Health Research. Retrieved from http://www.healthyhousing.org.nz/wp-content/uploads/2010/01/HH-Crowding-ID-Burden-25-May-2013.pdf; Baker, M., McNicholas, A., Garrett, N., *et al.* (2000). Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. *Pediatric Infectious Diseases Journal, 19*(10), 983-990. https://doi.org/10.1097/00006454-200010000-00009; Grant, C.C., Emery, D., Milne, T., *et al.* (2012). Risk factors for community-acquired pneumonia in pre-school-aged children. *Journal of Paediatrics and Child Health, 48*(5), 402-412. https://doi.org/10.1111/j.1440-1754.2011.02244.x

[377] Fisk, W.J., Eliseeva, E.A., & Mendell, M.J. (2010). Association of residential dampness and mold with respiratory tract infections and bronchitis: A meta-analysis. *Environmental Health, 9*(1), 72. https://doi.org/10.1186/1476-069X-9-72; Riggs, L., Keall, M., Howden-Chapman, P., *et al.* (2021). Environmental burden of disease from unsafe and substandard housing, New Zealand, 2010–2017. *Bulletin of the World Health Organization, 99*, 259-270. https://doi.org/10.2471/BLT.20.263285

[378] Ingham, T., Keall, M., Jones, B., *et al.* (2019). Damp mouldy housing and early childhood hospital admissions for acute respiratory infection: A case control study. *Thorax, 74*(9), 849. https://doi.org/10.1136/thoraxjnl-2018-212979

[379] Riggs, L., Keall, M., Howden-Chapman, P., *et al.* (2021). Environmental burden of disease from unsafe and substandard housing, New Zealand, 2010–2017. *Bulletin of the World Health Organization, 99*, 259-270. https://doi.org/10.2471/BLT.20.263285

hospital admissions due to acute respiratory infection among children less than two years old (around 1,700 admissions every year) could be prevented.[380]

Bronchiolitis, a type of lower respiratory tract infection, is an example of a disease linked to poverty and poor-quality housing.[381] It mostly affects babies less than 12 months old. For a developed country, Aotearoa New Zealand has high (and increasing) bronchiolitis prevalence. Since 2000, rates of hospitalisation for bronchiolitis have increased by about 50%, affecting thousands of children every year.[382] Hospitalisation rates are five times higher for children from the most deprived areas compared with the least deprived neighbourhoods (see Figure 15). Rates are also 3.5-4 times higher for Māori and Pacific children compared with children of New Zealand European ethnicity.

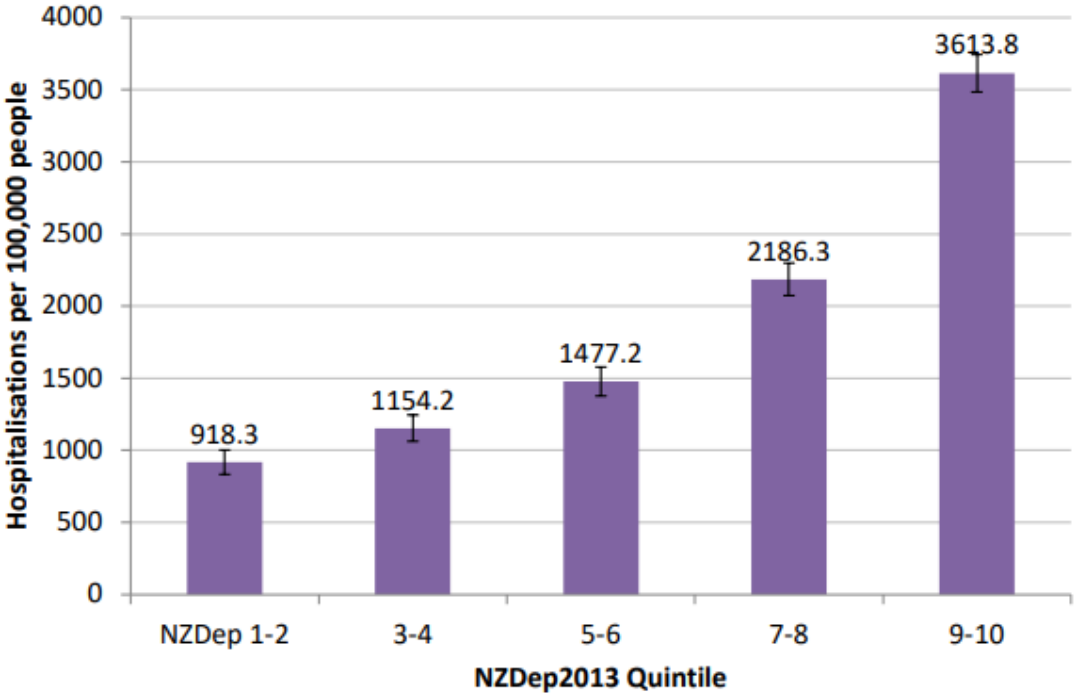

Figure 15: 2017 data showing that childhood bronchiolitis hospitalisation rates are highest among the most deprived neighbourhoods. (NB: NZDep2013 is an index of socioeconomic deprivation that combines census data relating to income, home ownership, employment, qualifications, family structure, housing, and access to transport and communications. 1 represents the least deprived and 10 represents the most deprived.)[383]

The social determinants of health not only drive inequities in the infectious diseases burden in this country: they also contribute to non-communicable diseases like asthma,[384] some of which contribute to heightened risk of contracting infectious diseases or suffering adverse outcomes (e.g. with chronic comorbidities representing significant risk factors for a fatal outcome associated with COVID-19).[385] Non-communicable diseases are beyond the scope of this report, but their significance and intersection with infectious diseases should be noted.

[380] Ingham, T., Keall, M., Jones, B.*, et al.* (2019). Damp mouldy housing and early childhood hospital admissions for acute respiratory infection: A case control study. *Thorax, 74*(9), 849. https://doi.org/10.1136/thoraxjnl-2018-212979

[381] Asher, I., & St John, S. (2016). *Child poverty and health in New Zealand*. Auckland, NZ: The Policy Observatory, Auckland University of Technology. Retrieved from https://thepolicyobservatory.aut.ac.nz/__data/assets/pdf_file/0005/75092/Asher-and-St-John-Child-Poverty-Health-in-NZ-v3.pdf

[382] Telfar Barnard, L., & Zhang, J. (2018). *The impact of respiratory disease in New Zealand: 2018 update*. Asthama and Respiratory Foundation NZ. Retrieved from https://www.asthmafoundation.org.nz/assets/images/NZ-Impact-Report-2018_FINAL.pdf

[383] Ibid.

[384] Howden-Chapman, P., Pierse, N., Nicholls, S.*, et al.* (2008). Effects of improved home heating on asthma in community dwelling children: Randomised controlled trial. *BMJ, 337*, a1411. https://doi.org/10.1136/bmj.a1411

[385] Dessie, Z.G., & Zewotir, T. (2021). Mortality-related risk factors of COVID-19: A systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infectious Diseases, 21*(1), 855. https://doi.org/10.1186/s12879-021-06536-3

Case study: Rheumatic fever

The pressing problem of lifelong impacts and inequitable burdens driven by barriers to healthcare access, issues within the healthcare system, and wider social determinants of health is clearly illustrated by rheumatic fever in Aotearoa New Zealand.

Rheumatic fever is an autoimmune disease triggered by acute group A *Streptococcus* infection. On its own, rheumatic fever is a serious condition often requiring hospitalisation. In addition, rheumatic fever can lead to inflammation and cumulative heart tissue damage, particularly as the result of repeated infections with group A *Streptococcus*. This outcome, known as rheumatic heart disease, almost exclusively afflicts Māori and Pacific peoples in Aotearoa New Zealand. Approximately 140 Māori and Pacific people die each year in Aotearoa New Zealand from rheumatic heart disease.[386] Rheumatic heart disease represents the extreme end of health inequity – and these ethnic inequities are reportedly rising.[387] Our office has produced a standalone evidence synthesis on rheumatic fever which can be found on our website.

Rheumatic fever evidence synthesis:

https://www.pmcsa.ac.nz/topics/antimicrobial-resistance-and-infectious-disease/rheumatic-fever/

[386] Bennett, J., Zhang, J., Leung, W., *et al.* (2021). Rising ethnic inequalities in acute rheumatic fever and rheumatic heart disease, New Zealand, 2000–2018. *Emerging Infectious Diseases, 27*(1), 36. https://doi.org/10.3201/eid2701.191791
[387] Ibid.

3.5 Infectious diseases impact animals and plants

Infectious diseases can harm the health and productivity of economically, socially, and culturally important plants and animals in Aotearoa New Zealand. Animal welfare is also compromised by infectious diseases. Our strong biosecurity system and geographic isolation mean that many infectious diseases can be excluded or eliminated, which has benefits for plant and animal health as well as meaning we don't have to explore the use of antimicrobials to kill or control those pathogens. However, a number of pathogens are present in Aotearoa New Zealand, some of which we are trying to eliminate and others we are trying to manage.

As with the human health section, this section on animals and plants isn't a comprehensive overview: it serves to highlight the nature of the infectious diseases landscape with relevant examples and case studies. Not all of the examples included have immediate AMR concerns, but most relate to the broader AMR landscape in that the presence of animal and plant pathogens represents a potential driver of antimicrobial use, which has scope to contribute to AMR across human, animal, plant, and environmental health (see section 2.3 for the links between antimicrobials, resistant organisms, and resistance genes across human, animal, plant, and environmental health). AMR aside, the threat posed by plant and animal pathogens is considerable.

3.5.1 Agriculturally important animals and plants are at risk

Infectious diseases can pose major risks to the welfare of animals and health of plants that are important in our agricultural industry, as well as compromising productivity. Some of these can also infect humans (see section 3.6), while others may have devastating impacts on plants or animals without any risk of directly affecting human health. Reducing and preventing infections in plants and animals is important to safeguard the agricultural industry, and also to slow the development of AMR.

Reducing and preventing infections in plants and animals is important to safeguard the agricultural industry, and also to slow the development of AMR.

Agricultural industries contribute 7% of our GDP (70% of goods exported).[388] It is important to keep our livestock and plants healthy given the importance of this sector to our economic prosperity. For example, when *M. bovis* was first identified in Aotearoa New Zealand in 2017, it was estimated that lost production and management would cost the dairy industry between NZ$606 million and NZ$1.15 billion per year. In response, the government embarked on a NZ$886 million elimination programme (see case study).[389] In 2014, MPI estimated that an outbreak of foot-and-mouth disease would cost Aotearoa New Zealand NZ$16 billion over four to five years.[390]

Table 3 below outlines some infectious diseases that are present in agriculturally important animals in Aotearoa New Zealand, as well as some diseases that have not been found here but would pose a substantial threat if introduced. Table 4 reflects the same information for agriculturally important plants. Risk profiles will continue to change over time with climate change (see section 2.5.3) and other factors such as changing farming practices. This table is not intended to be comprehensive, but

[388] Stats NZ. (n.d.). Economy. Retrieved 10 September 2021, from https://www.stats.govt.nz/topics/economy
[389] Office of the Minister for Biosecurity. (2020). *Eradicating Mycoplasma bovis – Update and next steps*. Wellington, NZ: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/41734/direct
[390] Ministry for Primary Industries. (2014). Foot-and-mouth disease. [Fact sheet]. Retrieved from https://www.mpi.govt.nz/dmsdocument/5281/direct#:~:text=It%20is%20estimated%20an%20outbreak,over%20four%20to%20five%20years.

presents information on a variety of infectious conditions, their status in Aotearoa New Zealand, and our strategy for exclusion, elimination, or management.

Pathogens that infect plants and animals can enter Aotearoa New Zealand via movement of livestock and products. For example, it is thought that Psa arrived in Aotearoa New Zealand via kiwifruit pollen imported from China. Movement within country can also spread disease – with the recent spread of *M. bovis* facilitated by movement of livestock. This means that biosecurity is an essential tool to keep diseases out of Aotearoa New Zealand and limit their spread within the country. The case study of Psa below highlights the importance of stringent measures at the border and the challenge of controlling an infectious disease once an incursion occurs.

The second case study, of *M. bovis*, reinforces the need for biosecurity but also demonstrates how we can use advanced techniques such as WGS to support efforts to control infectious disease and perhaps even achieve elimination. See section 5.4 for more details on diagnostic technologies.

… when ***M. bovis*** was first identified in Aotearoa New Zealand in 2017, it was estimated that lost production and management would cost the dairy industry between NZ$606 million and NZ$1.15 billion per year.

Table 3: Some infectious agricultural animal diseases of concern to Aotearoa New Zealand.

	Disease and pathogen	Animals affected	National status	Treatment / Strategy
Viruses	African swine fever (ASF) Caused by ASF virus	Pigs. Symptoms include fever, loss of appetite, haemorrhage, abortion, vomiting, diarrhoea.[391] Mortality ratio up to 100%.	Not found in NZ. Currently spreading through Asia[392] and into the Pacific (Papua New Guinea).[393]	Biosecurity controls at border.[394]
	Foot-and-mouth disease (FMD) Caused by FMD virus	Cloven-hooved animals. Symptoms include fever, blisters, lameness, reduced milk yield for cows, death of young animals. No food safety risk.	Not found in NZ[395] but would have severe economic impacts.[396]	Biosecurity controls in place at border (e.g. ban on importing animal products from countries with FMD unless treated to inactivate virus). Response plan is prepared in event of incursion.[397]
	Infectious bursal disease (IBD) Caused by IBD virus	Chickens. Symptoms include diarrhoea and dehydration. Can suppress immune system. Usually high morbidity and low mortality.[398] No food safety risk.	Found in poultry layer farm in Otago.[399]	Biosecurity controls to minimise spread. Exploring elimination options. Virus is successfully managed overseas.
	Bovine viral diarrhoea (BVD) Caused by BVD virus	Cattle. Symptoms include diarrhoea, immunosuppression, reduced fertility, reduced milk production.[400]	Found throughout NZ.	Managed at the farm level.
Bacteria	Clostridiosis Caused by *Clostridium* spp.	Cattle, sheep. *Clostridium* is a large genus, containing bacterial species that cause a range of	Found throughout NZ.	Vaccines against clostridial toxins available.[401]

[391] World Organisation for Animal Health (OIE). (n.d.). African swine fever. Retrieved 1 December, 2021, from https://www.oie.int/en/disease/african-swine-fever/
[392] Ibid.
[393] SPC Land Resources Division. (2020, 4 September). *Pacific countries strengthen border monitoring in response to African Swine Fever threat* [Press release]. Retrieved from https://lrd.spc.int/animal-genetics/pacific-countries-strengthen-border-monitoring-in-response-to-african-swine-fever-threat
[394] Ministry for Primary Industries. (2021). African swine fever disease prevention. Retrieved 10 September, 2021, from https://www.mpi.govt.nz/biosecurity/major-pest-and-disease-threats/african-swine-fever/
[395] Ministry for Primary Industries. (2021). About foot-and-mouth disease. Retrieved 10 September, 2021, from https://www.mpi.govt.nz/biosecurity/plans-for-responding-to-serious-disease-outbreaks/foot-and-mouth-disease/about-foot-and-mouth-disease/
[396] Forbes, R., & Halderen, A.v. (2014). *Foot-and-mouth disease economic impact assessment: What it means for New Zealand*. Wellington: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/4406-Foot-and-Mouth-Disease-Economic-Impact-Assessment-What-it-means-for-New-Zealand
[397] Ministry for Primary Industries. (2021). Response to foot-and-mouth disease. Retrieved 10 September, 2021, from https://www.mpi.govt.nz/biosecurity/plans-for-responding-to-serious-disease-outbreaks/foot-and-mouth-disease/response-to-foot-and-mouth-disease/
[398] Jackwood, D.J. (2019). Infectious bursal disease in poultry. *MSD Manual: Veterinary Manual*. Retrieved from https://www.msdvetmanual.com/poultry/infectious-bursal-disease/infectious-bursal-disease-in-poultry
[399] Ministry for Primary Industries. (2020). Infectious bursal disease virus (IBDV) prevention in Otago. Retrieved 10 September, 2021, from https://www.mpi.govt.nz/biosecurity/major-pest-and-disease-threats/infectious-bursal-disease-virus/
[400] BVD Free. (n.d.). BVD biology. Retrieved 1 December, 2021, from https://www.bvdfree.org.nz/bvd-biology
[401] Lacasta, D., Ferrer, L.M., Ramos, J.J*., et al.* (2015). Vaccination schedules in small ruminant farms. *Veterinary Microbiology, 181*(1), 34-46. https://doi.org/10.1016/j.vetmic.2015.07.018

	Disease and pathogen	Animals affected	National status	Treatment / Strategy
		pathologies. *Clostridium* bacteria can persist as resistant spores.		
	Various diseases Caused by *Mycoplasma bovis*[402]	Cattle, pigs, sheep, goats, deer. Can cause a range of serious conditions including mastitis, pneumonia, abortions. No food safety risk.	First found in NZ in 2017. Only four farms with confirmed active cases as of November 2021.	Elimination programme underway.[403] See case study below.
	Leptospirosis Caused by *Leptospira* spp.[404]	Cattle, sheep. Can cause mastitis in cows. Can cause abortion and death.	Found throughout NZ.	Vaccines available for some serotypes. Herd management techniques.
	Johne's disease Caused by *Mycobacterium avium* subspecies *paratuberculosis*	Ruminant animals. Causes wasting by preventing uptake of nutrients.	Found throughout NZ. Estimated to cost NZ$40-88 million in lost production each year.[405]	Vaccine not available for use in cattle in NZ – vaccine can confound bovine TB testing.[406] Vaccine available for sheep.[407] Control via testing, culling, herd management.
	Salmonellosis Caused by *Salmonella* spp.	Sheep, cattle, poultry.[408] Main symptom is diarrhoea. Can also cause loss of appetite, dehydration. In some cases can cause abortion and death (if severe or untreated).	Found throughout NZ.	Vaccines available. Biosecurity procedures. See case study in section 3.6.2.
	Mastitis Commonly caused by *Staphylococcus* spp. (but other causes exist, e.g. *Streptococcus uberis*)	Cattle. Inflammation of udder. Reduced milk production, pain.	Found throughout NZ.	Antibiotics for treatment and prophylaxis. Teat sealants (see section 5.3.1).
	Bovine tuberculosis Caused by *Mycobacterium bovis*	Cattle, deer. Symptoms include weakness, loss of appetite, fever, cough, diarrhoea, weight	Found in Aotearoa New Zealand. 41 herds infected as of 30 June 2021 (0.1% annual period prevalence).[410]	Surveillance and movement controls. National Pest Management Strategy (possums are infectious carriers).

[402] Ministry for Primary Industries. (2020). What is *Mycoplasma bovis*? Retrieved 9 September, 2021, from https://www.mpi.govt.nz/biosecurity/mycoplasma-bovis/what-is-mycoplasma-bovis/
[403] Ministry for Primary Industries. (n.d.). What is MPI doing about *M. bovis*? Retrieved 10 September, 2021, from https://www.mpi.govt.nz/biosecurity/mycoplasma-bovis/what-is-mpi-doing/
[404] DairyNZ. (n.d.). Leptospirosis. Retrieved 10 September, 2021, from https://www.dairynz.co.nz/animal/cow-health/leptospirosis/
[405] DairyNZ. (n.d.). Johne's Disease. Retrieved 10 September, 2021, from https://www.dairynz.co.nz/animal/cow-health/johnes-disease/
[406] Beef + Lamb New Zealand. (2016). Johne's disease – Management for New Zealand beef cattle and dairy replacements. [Fact sheet] (pp. 4). Wellington: Beef + Lamb New Zealand. Retrieved from https://beeflambnz.com/knowledge-hub/PDF/johnes-disease-cattle
[407] Beef + Lamb New Zealand. (2016). Johne's disease – Management for New Zealand sheep. [Fact sheet]. Retrieved from https://beeflambnz.com/knowledge-hub/PDF/johnes-disease-sheep.pdf
[408] DairyNZ. (n.d.). Salmonella. Retrieved 10 September, 2021, from https://www.dairynz.co.nz/animal/cow-health/salmonella/
[410] OSPRI Ltd. (2021). *Annual report 2020–2021*. Retrieved from https://www.ospri.co.nz/assets/ResourcePDFs/OSPRI-Annual-Report-2020-2021.pdf

	Disease and pathogen	Animals affected	National status	Treatment / Strategy
		loss, large lymph nodes. Bacteria can also lie dormant in host without causing disease.[409]	Costs tens of millions per year to control.	Aiming for elimination from cattle and deer herds by 2026.[411]
	Yersiniosis Caused by *Yersinia* spp.	Pigs, sheep, goats, deer, cattle.	Found in NZ.	Vaccines used (deer). Antibiotics can be administered.
	European foulbrood Caused by *Melissococcus plutonius*	Bees. Can weaken and kill colonies.	Not found in NZ.[412]	Biosecurity measures in place. Included in MPI's apiculture surveillance programme.[413]
	American foulbrood Caused by *Paenibacillus larvae larvae*	Bees. Can weaken and kill colonies. If uncontrolled, could cause considerable economic losses (honey and pollination).	Found in NZ following accidental introduction in the 1870s. Thought to have led to 70% reduction in honey production within 10 years of first detection.[414] 0.32% of hives infected in 2019/20 (down from approx. 0.5% in 2002).[415]	Infected hives and associated equipment must be destroyed. No antibiotics approved in NZ. National plan for elimination of American Foulbrood from managed colonies.[416]
Parasites	Toxoplasmosis Caused by *Toxoplasma gondii*	Sheep. Causes abortions, congenital defects.	Found throughout NZ.	Vaccine available in NZ (developed by NZ).[417]
	Coccidiosis Caused by *Eimeria* spp.	Cattle. Causes mild to severe illness.	Found throughout NZ.	Good management, including use of antiparasitic coccidiostat, and hygiene.
	Brown stomach worm *Teladorsagia circumcincta*	Cattle, sheep. Causes weight loss.	Found throughout NZ.	Use of anthelmintics ('drenching').[418]

[409] World Organisation for Animal Health (OIE). (n.d.). Bovine tuberculosis. [General Disease Information Sheet]. Retrieved from https://www.oie.int/fileadmin/Home/eng/Media_Center/docs/pdf/Disease_cards/BOVINE-TB-EN.pdf

[411] OSPRI Ltd. (n.d.). Eradicating TB through TB management areas. Retrieved from https://www.ospri.co.nz/assets/ResourcePDFs/Eradicating-TB-through-TB-Management-Areas.pdf

[412] The Management Agency National American Foulbrood Pest Management Plan. (n.d.). European foulbrood. Retrieved 1 December, 2021, from https://afb.org.nz/european-foulbrood/

[413] Ministry for Primary Industries. (n.d., 16 November 2020). Apiculture surveillance programme. Retrieved 1 December, 2021, from https://www.mpi.govt.nz/biosecurity/plans-for-responding-to-serious-disease-outbreaks/bee-biosecurity/apiculture-surveillance-programme/

[414] The Management Agency National American Foulbrood Pest Management Plan. (n.d.). History of American foulbrood in New Zealand. Retrieved 1 December, 2021, from https://afb.org.nz/history-of-american-foulbrood-in-new-zealand/

[415] The Management Agency National American Foulbrood Pest Management Plan. (2020). *Annual report 2019/2020*. Retrieved from https://afb.org.nz/wp-content/uploads/2020/12/2019-20-Annual-Report.pdf

[416] Apiculture New Zealand. (n.d.). Threats to bees. Retrieved 1 December, 2021, from https://apinz.org.nz/threats-to-bees-2/

[417] Roberts, J.O., Jones, H.F.E., & Roe, W.D. (2020). The effects of *Toxoplasma gondii* on New Zealand wildlife: Implications for conservation and management. *Pacific Conservation Biology*, -. https://doi.org/10.1071/PC20051

[418] Nisbet, A.J., McNeilly, T.N., Greer, A.W*., et al.* (2016). Protection of ewes against *Teladorsagia circumcincta* infection in the periparturient period by vaccination with recombinant antigens. *Veterinary Parasitology, 228*, 130-136. https://doi.org/10.1016/j.vetpar.2016.09.002

	Disease and pathogen	Animals affected	National status	Treatment / Strategy
	Varroa Caused by *Varroa destructor*	Bees. Mites feed on haemolymph (the "blood" of insects), facilitating the spread of viruses between bees. Can weaken and kill colonies.	First found in NZ in 2000. Causes economic losses (honey and pollination, plus cost of management).[419]	Control measures (predominantly hive surveillance and chemical miticides). Ongoing research (including investigation of biocontrols and work to breed varroa-tolerant bees).[420]
Prions	Transmissible spongiform encephalopathies (e.g. mad cow disease)	Cattle, deer, sheep, goats, etc. Neurological damage. Can infect humans through food chain.	Not found in NZ.	Surveillance programme for early detection.[421] No known treatments.

[419] Ibid.

[420] Apiculture New Zealand. (n.d.). Threats to bees. Retrieved 1 December, 2021, from https://apinz.org.nz/threats-to-bees-2/

[421] Ministry for Primary Industries. (2020). Take part in TSE surveillance. Retrieved 10 September, 2021, from https://www.mpi.govt.nz/biosecurity/how-to-find-report-and-prevent-pests-and-diseases/surveillance-programmes/take-part-in-tse-surveillance/

Table 4: Some infectious agricultural plant diseases of concern to Aotearoa New Zealand.

	Disease and pathogen	Plants affected	National status	Treatment / Strategy
Viruses	Pepino mosaic disease Caused by Pepino mosaic virus (PepMV)[422]	Mainly tomatoes, also eggplants, potatoes. Signs include stunted growth, leaf damage. Reduces production. No food safety risk.	Found in tomatoes in Tāmaki Makaurau Auckland in 2021.	Biosecurity controls and investigations.
	Plum pox[423] Caused by plum pox virus	Stone fruit. Causes leaf and fruit damage and deformation. Transmitted by aphids.	Not found in NZ. Makes fruit inedible causing substantial economic loss.	Biosecurity controls.
Bacteria	Kiwifruit vine canker Caused by *Pseudomonas syringae pv. actinidiae* (Psa)	Kiwifruit. Signs include lesions (cankers) on plants, leaf and plant wilting. Can destroy whole orchards.	Found throughout NZ. Has had substantial economic impact.	Resistant cultivars now used widely. Ongoing research and control measures.[424] See case study below.
	Fire blight Caused by *Erwinia amylovora*	Pip fruit. Signs include withering and dying of plant, cankers. Reduces production.[425]	Found in NZ.[426]	Ongoing research and management measures.[427]
Fungi	Botrytis (grey mould) Caused by *Botrytis cinerea*	Grapes, strawberries. Signs include blemishes and rot.[428]	Found throughout NZ.	Fungicidal treatments.

[422] Ministry for Primary Industries. (2021). Pepino mosaic virus (PepMV) in Auckland. Retrieved 10 September, 2021, from https://www.mpi.govt.nz/biosecurity/major-pest-and-disease-threats/pepino-mosaic-virus-pepmv-in-auckland/

[423] Plant Health and Environment Laboratory. (2019). Pathogen profile: Plum pox virus (PPV). [Newsletter] *PHELosophies* (Vol. 3): Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/39314/direct

[424] Ministry for Primary Industries. (2020). Psa – new strains (kiwifruit vine canker). Retrieved 3 September 2021, from https://www.mpi.govt.nz/biosecurity/pests-and-diseases-we-want-to-keep-out-of-new-zealand/horticultural-pests/psa-new-strains-kiwifruit-vine-canker/

[425] The Editors of Encyclopaedia Britannica. (n.d.). Fire blight. *Britannica*. Retrieved from https://www.britannica.com/science/fire-blight

[426] Horner, M.B., Hough, E.G., Hedderley, D.I.*, et al.* (2014). Comparison of fire blight resistance screening methodologies. *New Zealand Plant Protection, 67*(0), 145-150. https://doi.org/10.30843/nzpp.2014.67.5745

[427] Ministry for Primary Industries. (2018). *Approved for funding for 2018/19 – projects commencing from 1 July 2018*. Retrieved from https://www.mpi.govt.nz/dmsdocument/26554-Approved-for-SFF-Funding-for-201819-projects-commencing-from-1-July-2018

[428] Williamson, B., Tudzynski, B., Tudzynski, P.*, et al.* (2007). *Botrytis cinerea*: the cause of grey mould disease. *Molecular Plant Pathology, 8*(5), 561-580. https://doi.org/10.1111/j.1364-3703.2007.00417.x

Case study: Psa

Psa is a bacterial disease that affects kiwifruit, causing a disease known as kiwifruit vine canker. Psa can spread quickly and destroy entire orchards.[429] There is one strain of Psa (biovar 3) in Aotearoa New Zealand,[430] which affects the majority of kiwifruit orchards in the country.[431] Compared with when Psa was first detected in Aotearoa New Zealand, current kiwifruit cultivars are more tolerant to the pathogen, playing a major role in the industry's recovery.[432] Aotearoa New Zealand's experience with Psa highlights that, when exclusion fails and elimination can't be achieved, we are forced to manage introduced pathogens using a range of techniques, including antimicrobials that can contribute to AMR.

Border incursion and cost to industry

Psa was first identified in Aotearoa New Zealand in 2010 and is thought to have arrived in 2009 through kiwifruit pollen imported from China.[433] Kiwifruit growers brought a class action suit against the Crown for negligence that allowed Psa to enter the country. In 2021, the Crown settled over damages suffered from Psa for NZ$40 million after a court battle spanning seven years.[434]

Initial estimates in 2012 anticipated the damage over ten years would be NZ$500-600 million.[435] This turned out to be an underestimate: by 2014, the cost of lost exports alone might have been NZ$930 million, while the value of orchards in Aotearoa New Zealand – both infected and non-infected – dropped considerably.[436]

The challenges of controlling Psa

The kiwifruit industry responded immediately upon detection of Psa to minimise damage. Several containment strategies were trialled, including destruction of infected vines via incineration or burial in deep pits. Movement between orchards was controlled and equipment was disinfected. Actigard (an elicitor that helps reduce the symptoms of Psa) and copper-based products were used to reduce damage.[437] However, copper-based products were not long-term options – they can lead to environmental contamination and plant damage.

The antibiotics streptomycin and kasugamycin are registered for use against Psa in Aotearoa New Zealand. However, the use of antibiotics can lead to the development of resistance in Psa. Streptomycin resistance has been reported overseas and in Aotearoa New Zealand.[438] Concerns

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[429] Kim, G.H., Jung, J.S., & Koh, Y.J. (2017). Occurrence and epidemics of bacterial canker of kiwifruit in Korea. *The Plant Pathology Journal, 33*(4), 351-361. https://doi.org/10.5423/PPJ.RW.01.2017.0021

[430] Ministry for Primary Industries. (2020). Psa – new strains (kiwifruit vine canker). Retrieved 3 September 2021, from https://www.mpi.govt.nz/biosecurity/pests-and-diseases-we-want-to-keep-out-of-new-zealand/horticultural-pests/psa-new-strains-kiwifruit-vine-canker/

[431] Dwiartama, A. (2017). Resilience and transformation of the New Zealand kiwifruit industry in the face of Psa-V disease. *Journal of Rural Studies, 52*, 118-126. https://doi.org/10.1016/j.jrurstud.2017.03.002

[432] Ibid.

[433] Greer, G., & Saunders, C.M. (2012). *The costs of Psa-V to the New Zealand kiwifruit industry and the wider community* (1170-7682). Christchurch: Lincoln University.

[434] Ministry for Primary Industries. (2021, 13 February). *Crown and kiwifruit sector plaintiffs settle long-running litigation over Psa* [Press release]. Retrieved from https://www.mpi.govt.nz/news/media-releases/crown-and-kiwifruit-sector-plaintiffs-settle-long-running-litigation-over-psa/

[435] Greer, G., & Saunders, C.M. (2012). *The costs of Psa-V to the New Zealand kiwifruit industry and the wider community* (1170-7682). Christchurch: Lincoln University.

[436] Vanneste, J.L. (2017). The scientific, economic, and social impacts of the New Zealand outbreak of bacterial canker of kiwifruit (*Pseudomonas syringae pv. actinidiae*). *Annual Review of Phytopathology, 55*, 377-399. https://doi.org/10.1146/annurev-phyto-080516-035530

[437] Hoyte, S., Reglinski, T., Elmer, P.*, et al.* (2015). *Developing and using bioassays to screen for Psa resistance in New Zealand kiwifruit.* Paper presented at the International Symposium on Bacterial Canker of Kiwifruit, Leuven, Belgium.

[438] Wurms, K., Gould, E., Chee, A.A.*, et al.* (2017). Elicitor induction of defence genes and reduction of bacterial canker in kiwifruit. *New Zealand Plant Protection, 70*, 272-284. https://doi.org/10.30843/nzpp.2017.70.61

around resistance mean that streptomycin is now only used in exceptional circumstances.[439] No kasugamycin resistance has been found in Psa so far, but monitoring is ongoing.[440] The use of antibiotics in kiwifruit cultivation is banned in some European countries such as Italy and Portugal.[441]

The use of antibiotics can lead to the development of resistance in Psa.

Some varieties of golden kiwifruit are less susceptible to Psa. While still impacted by the disease, they do not suffer rapid vine death when combined with other management efforts (e.g. chemical sprays, orchard hygiene, plant management).[442] When the Psa incursion occurred, the majority of vines in Aotearoa New Zealand were one of two cultivars – a green kiwifruit ('Hayward') and a yellow kiwifruit (Hort16A). New cultivars (including G3 and Green14) are less susceptible to Psa and have replaced many vines in Aotearoa New Zealand.[443] A shift in the cultivars grown provides greater resistance against Psa, and Plant and Food Research now includes Psa tolerance among its selection traits when breeding new kiwifruit cultivars.[444] For more on solutions to Psa, see part five.

The complete genome sequence has been assembled for the strain of Psa present in the initial outbreak.[445] This can be used as a reference point for any changes in the strain over time, including to identify genes coding for AMR.

Case study: *Mycoplasma bovis*

Mycoplasma bovis[446] is a bacterium that causes serious conditions such as mastitis, pneumonia, and abortions in cattle. It negatively impacts production and can have substantial economic impacts on heavily infected farms. *M. bovis* does not infect humans. Aotearoa New Zealand was one of the last major cattle-rearing countries to experience an incursion of *M. bovis*,[447] demonstrating how our strict biosecurity practices at the border can exclude many pathogens. Current efforts to eliminate the pathogen show that one way to reduce the need for antimicrobial drugs in agriculture is to take a zero-tolerance approach to agricultural pathogens whose characteristics and prevalence make elimination a theoretical possibility. Overseas, AMR has been documented for this pathogen.[448]

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[439] Woodcock, S.D. (2016). *A review of research and development undertaken on Psa*. Tauranga: Kiwifruit Vine Health. Retrieved from http://www.kvh.org.nz/vdb/document/103504

[440] Ibid.

[441] Pereira, C., Costa, P., Pinheiro, L., *et al.* (2021). Kiwifruit bacterial canker: An integrative view focused on biocontrol strategies. *Planta, 253*(2), 49. https://doi.org/10.1007/s00425-020-03549-1

[442] Hoyte, S., Reglinski, T., Elmer, P., *et al.* (2015). *Developing and using bioassays to screen for Psa resistance in New Zealand kiwifruit.* Paper presented at the International Symposium on Bacterial Canker of Kiwifruit, Leuven, Belgium.

[443] Dwiartama, A. (2017). Resilience and transformation of the New Zealand kiwifruit industry in the face of Psa-V disease. *Journal of Rural Studies, 52*, 118-126. https://doi.org/10.1016/j.jrurstud.2017.03.002

[444] Woodcock, S.D. (2016). *A review of research and development undertaken on Psa*. Tauranga: Kiwifruit Vine Health. Retrieved from http://www.kvh.org.nz/vdb/document/103504

[445] Poulter, R., Lamont, I., Stockwell, P., *et al.* (2019). *The completely assembled genome of a strain from the New Zealand Pseudomonas syringae pv. actinidiae (PSA) outbreak.* Paper presented at the International Symposium on Bacterial Canker of Kiwifruit 1243.

[446] Ministry for Primary Industries. (2020). What is *Mycoplasma bovis*? Retrieved 9 September, 2021, from https://www.mpi.govt.nz/biosecurity/mycoplasma-bovis/what-is-mycoplasma-bovis/

[447] Dudek, K., Nicholas, R.A., Szacawa, E., *et al.* (2020). *Mycoplasma bovis* infections - Occurrence, diagnosis and control. *Pathogens, 9*(8), 640. https://doi.org/10.3390/pathogens9080640

[448] Calcutt, M.J., Lysnyansky, I., Sachse, K., *et al.* (2018). Gap analysis of *Mycoplasma bovis* disease, diagnosis and control: An aid to identify future development requirements. *Transboundary and Emerging Diseases, 65*(S1), 91-109. https://doi.org/https://doi.org/10.1111/tbed.12860

Border incursion

M. bovis was first detected here in 2017 (in a dairy herd in South Canterbury) but is thought to have been present since 2015.[449] The introduction pathway remains unknown. Imported semen, embryos, pharmaceuticals, feed supplements, and used farming equipment have all been suggested as possible transmission routes,[450] but no evidence has been found to confirm which (if any) of these is the actual pathway. While in general terms the main way *M. bovis* enters a country is through the import of live cattle,[451] Aotearoa New Zealand imports few live cattle, and surveillance of all imported bovines that were still alive and animals in contact with imported bovines did not find evidence of infection, making the live animal importation pathway highly unlikely.

WGS of 171 isolates from 115 infected properties suggests that the current outbreak came from a single international source, either as a single introduction or a small number of closely linked introductions in 2014 or 2015. These findings indicate that there were probably several simultaneous outbreaks, which implicates imported bovine semen as the source. The most closely related international isolates available that have been characterised are from Europe, but international genomic mapping of *M. bovis* is limited.[452]

Elimination programme

An elimination programme began immediately upon discovery of *M. bovis* in 2017. Movement controls were imposed on affected properties while tracing and testing were undertaken to determine the extent of spread. In May 2018 Cabinet approved a ten-year phased eradication programme in partnership with industry organisations DairyNZ and Beef + Lamb New Zealand. As of 25 November 2021, 272 infected properties have been detected, 268 of which have been depopulated and cleared of disease. 173,000 cattle have been culled as of this date, with over NZ$210 million being paid out under the compensation provisions of the Biosecurity Act 1993.[453]

Transmission between farms in Aotearoa New Zealand appears to be primarily via the movement of cattle, particularly calves. Movement of fresh milk for the feeding of calves has also contributed to spread, while other means of transmission appear to be of much less significance.[454]

Ongoing active surveillance is a key component of the eradication programme, with bulk tank milk samples being tested monthly from all in-production dairy farms. In addition, a beef surveillance programme has tested over 500,000 animals to date.[455]

As there are only four currently infected properties, all in mid-Canterbury, eradication of *M. bovis* appears feasible. However, at least four years of national surveillance will be required after the last known case has been identified will be required to provide 'proof of absence' of *M. bovis*. No other

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[449] Jordan, A.G., Sadler, R.J., Sawford, K.*, et al.* (2020). *Mycoplasma bovis* outbreak in New Zealand cattle: An assessment of transmission trends using surveillance data. *Transboundary and Emerging Diseases*, 1-15. https://doi.org/10.1111/tbed.13941

[450] Ministry for Primary Industries. (2017). *Analysis of risk pathways for the introduction of Mycoplasma bovis into New Zealand*. Wellington, NZ: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/28050-Pathways-Report-Redacted.pdf; Ministry for Primary Industries. (2021). Personal communication.

[451] Dudek, K., Nicholas, R.A., Szacawa, E.*, et al.* (2020). *Mycoplasma bovis* infections - Occurrence, diagnosis and control. *Pathogens, 9*(8), 640. https://doi.org/10.3390/pathogens9080640

[452] Browning, G., Caswell, J., Cobb, S.*, et al.* (2019). *Report of the Mycoplasma bovis technical advisory group (TAG) in response to the terms of reference (June 2019)*. Wellington: Mycoplasma bovis technical advisory group. Retrieved from https://www.mpi.govt.nz/dmsdocument/37754-report-of-the-mycoplasma-bovis-technical-advisory-group-tag-in-response-to-the-terms-of-reference-june-2019-18-october-2019; Ministry for Primary Industries. (2021). Personal communication.

[453] Ministry for Primary Industries. (n.d., 25 November 2021). Mycoplasma bovis situation report. Retrieved 1 December, 2021, from https://www.mpi.govt.nz/biosecurity/mycoplasma-bovis/situation-report/

[454] Jordan, A.G., Sadler, R.J., Sawford, K.*, et al.* (2020). *Mycoplasma bovis* outbreak in New Zealand cattle: An assessment of transmission trends using surveillance data. *Transboundary and Emerging Diseases*, 1-15. https://doi.org/10.1111/tbed.13941

[455] *Mycoplasma bovis* Info hub for affected farmers. (2020, 11 February). National beef surveillance. Retrieved 1 December, 2021, from https://www.mbovis.govt.nz/mycoplasma-bovis-info-hub/national-surveillance/national-beef-surveillance/

country has attempted to eradicate *M. bovis*, so the methodology of the eradication programme has been adapted from other disease control programmes and developed from first principles.

As with human diseases, the growing use of WGS in agriculture provides opportunities to better survey, track, understand, and control infectious diseases. As discussed above, WGS provides clues as to how *M. bovis* breached our borders, while it has been deployed for tracking *M. bovis* transmission in combination with epidemiological data, similar to how we use WGS to track and trace COVID-19 cases.[456] WGS is discussed in more depth in section 5.4.3.

3.5.2 Native flora and fauna are also at risk

Aotearoa New Zealand's biological heritage is unique, having evolved in isolation for millions of years. This isolation also means that our flora and fauna have evolved in the absence of many infectious diseases that are present elsewhere. Diseases that arrive on our shores, both naturally and as the result of human activities, are therefore of particular concern for our flora and fauna.

Many species affected are taonga to Māori, and their decline has implications for cultural practices and identity.[457] The infectious diseases that threaten our native flora and fauna underscore the importance of biosecurity to first prevent diseases reaching Aotearoa New Zealand, and then to control their spread if they do end up here. In addition, some infectious diseases occurring in native animals can also infect other animals and humans (e.g. as seen in a *Salmonella enterica* outbreak in 2000),[458] highlighting the connectivity between human and animal health.

Native animals

Table 5 outlines some of the infectious diseases that can infect native fauna in Aotearoa New Zealand, drawn from a 2019 review article published in the New Zealand Veterinary Journal.[459]

What about native bats?

Aotearoa New Zealand has two native bat species, but it is unknown whether they carry viruses dangerous to humans. Overseas, bats are important reservoirs for zoonotic diseases, including novel infectious diseases – for example, the closest known relative to the SARS-CoV-2 virus is a bat coronavirus, and the two other human coronaviruses that emerged this century (SARS and MERS) are also thought to have bat origins.[460] In Australia, bats and flying foxes are reservoirs of Hendra virus and the rabies-like lyssavirus.

A non-pathogenic coronavirus has been isolated from bat faeces on Whenua Hou Codfish Island in Aotearoa New Zealand,[461] but it has been suggested that Aotearoa New Zealand's bat populations are too small and fragmented to support the diversity of viruses observed in bat species overseas.[462]

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[456] French, N. (2021). Personal communication.
[457] Lambert, S., Waipara, N., Black, A.*, et al.* (2018). Indigenous biosecurity: Māori responses to kauri dieback and myrtle rust in Aotearoa New Zealand. In Urquhart, Marzano and Potter (Eds.), *The Human Dimensions of Forest and Tree Health: Global Perspectives* (pp. 109-137). Cham: Springer International Publishing.
[458] Alley, M.R., & Gartrell, B.D. (2019). Wildlife diseases in New Zealand: Recent findings and future challenges. *New Zealand Veterinary Journal, 67*(1), 1-11. https://doi.org/10.1080/00480169.2018.1520656
[459] Ibid.
[460] Hu, B., Guo, H., Zhou, P.*, et al.* (2021). Characteristics of SARS-CoV-2 and COVID-19. *Nature Reviews Microbiology, 19*(3), 141-154. https://doi.org/10.1038/s41579-020-00459-7; Zhou, P., Yang, X.-L., Wang, X.-G.*, et al.* (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature, 579*(7798), 270-273. https://doi.org/10.1038/s41586-020-2012-7
[461] Hall, R., Wang, J., Peacey, M.*, et al.* (2014). New alphacoronavirus in *Mystacina tuberculata* bats, New Zealand. *Emerging Infectious Diseases, 20*(4), 697. https://doi.org/10.3201/eid2004.131441
[462] Alley, M.R., & Gartrell, B.D. (2019). Wildlife diseases in New Zealand: Recent findings and future challenges. *New Zealand Veterinary Journal, 67*(1), 1-11. https://doi.org/10.1080/00480169.2018.1520656

Table 5: Some infectious diseases relevant to native fauna in Aotearoa New Zealand.[463]

	Disease and pathogen	Animals affected	Zoonotic?	Comments
Viruses	Avian influenza Caused by various influenza viruses	Birds, especially waterfowl (e.g. ducks, migratory shorebirds) and poultry (e.g. chickens).	Yes	Routine surveillance of mallard ducks. Only low-pathogenic strains isolated so far. However, if a highly pathogenic strain of avian influenza were to enter Aotearoa New Zealand, reservoirs and transmission pathways are present to facilitate spread.
	Newcastle disease Caused by avian paramyxovirus	Birds, especially waterfowl and poultry.	Rarely infects humans; mostly non-symptomatic.	An outbreak has never been detected in Aotearoa New Zealand. MPI undertakes routine surveillance in wild duck populations, occasionally finding evidence of a non-pathogenic strain of the virus that doesn't cause Newcastle disease.
	Avipox Caused by avipoxvirus	Birds including pipits, silvereyes, black robins, North Island robins, oystercatchers, weka, shore plovers, saddlebacks, kereru, kiwi.	No	Seen with increasing frequency in wide range of native species over the last two decades.
	Psittacine beak and feather disease (PBFD) Caused by beak and feather disease virus (BFDV)	Parrots.	No	Has been identified in wild and captive exotic parrot species (e.g. eastern rosellas). Native parrot species appear less susceptible.
	Pacheco's disease Caused by Psittacid alphaherpesvirus-1	Parrots.	No	Two outbreaks in captive exotic parrots in 1977 and 1997. No further confirmed cases in captive or wild parrots since. A threat to our endemic parrots if it became established in NZ.
	Polyomavirus disease Caused by avian polyomavirus	Parrots.	No	Endemic in budgie flocks in Aotearoa New Zealand. A threat to our native and endemic species.
Bacteria	Salmonellosis Caused by *Salmonella* spp.	Birds including hihi, saddlebacks, kākā, kākāriki, black-backed gulls, takahe. Reptiles (commensal, rarely pathogenic).	Yes	An outbreak in Aotearoa New Zealand in 2000 spread between wild birds, livestock and humans.
	Tuberculosis Caused by *Mycobacterium avium*	Birds.	Yes, but only causes disease in people with weakened immune systems.	Found in wild harriers and in some captive native bird species that have come into contact with infected poultry, game birds or domesticated pigs.
	Tuberculosis Caused by *Mycobacterium pinnipedii*	Fur seals, NZ sea lions, Hector's dolphins.	Yes	Can also infect cattle that graze coastal pastures.
	Erysipelas Caused by *Erysipelothrix rhusiopathiae*	Birds including takahē, kiwi, kakī, kākāpō	Yes	Has caused sudden deaths in native birds.

[463] Ibid.

	Disease and pathogen	Animals affected	Zoonotic?	Comments
	Yersiniosis Caused by *Yersinia* spp. (e.g. *Y. pseudotuberculosis*)	Birds including kererū, kākā.	Yes	Can also infect a variety of livestock.
	Chlamydiosis Caused by *Chlamydia psittaci*	Birds.	Yes, causes psittacosis or 'parrot fever' in humans	An outbreak in Tāmaki Makaurau Auckland in 2009 in a population of wild spotted doves resulted in human infections.
	Various infections Caused by *Klebsiella pneumoniae*	NZ sea lions.	Yes	An important cause of mortality among NZ sea lions on Motu Maha the Auckland Islands. Also an opportunistic pathogen in humans.
	Campylobacteriosis Caused by *Campylobacter* spp.	Birds including poultry, takahe, kiwi.[464] Tuatara.	Yes	Most infections in wildlife are subclinical.
Fungi	Aspergillosis Caused by *Aspergillosis* spp. (e.g. *A. fumigatus*)	Hihi, kea, tūī, penguins, kiwi, kākāriki, shore plovers.	Yes	One of the most common diseases of birds in NZ and throughout the world. Opportunistic pathogen that usually infects immunosuppressed or stressed birds.
	Chytridiomycosis Caused by *Batrachochytrium dendrobatidis*	Frogs.	No	Endemic frog species appear to have some innate or acquired immunity to chytrid fungus, which is devastating frog populations elsewhere in the world. However, thought to have caused the decline of one population of Archey's frogs
	Dermatitis Caused by *Paranannizziopsis australasiensis*	Reptiles including tuatara.	No	An emerging pathogen that has been detected in two captive tuatara populations. Appears to be self-limiting.
Protozoans	Avian malaria Caused by *Plasmodium* spp.	Birds including mohua, saddlebacks, penguins, hihi, kiwi.	No	Introduced blackbirds are thought to be the source of infection for some of our endemic species.
	Leucocytozoonosis Caused by *Leucocytozoon* spp.	Yellow-eyed penguins.	No	Has caused deaths in juvenile yellow-eyed penguins on Stewart Island. High prevalence on Stewart Island and subantarctic islands.
	Coccidiosis Caused by *Eimeria* spp.	Birds including North Island robins, saddelbacks, tūī, kiwi, hihi, poultry.	No	Usually don't proliferate at high enough numbers to cause harm in wild populations but can be a serious infection for captive-bred chicks.
	Toxoplasmosis Caused by *Toxoplasma gondii*	Hector's and Māui dolphins, NZ sea lions. Birds including kiwi, parrots, ducks.	Yes	Cats carry this parasite and thus cat faeces can readily contaminate the environment, infecting wildlife (also causes disease in humans and is particularly high risk for developing babies, who can become infected in the womb).
Helminths	*Enteritis* Caused by *Uncinaria* spp.	NZ sea lions.	No	Can cause death in pups.

[464] On, S.L.W., Brett, B., Horan, S.*, et al.* (2019). Isolation and genotyping of *Campylobacter* species from kiwi (*Apteryx* spp.) in captivity: Implications for transmission to and from humans. *New Zealand Veterinary Journal, 67*(3), 134-137. https://doi.org/10.1080/00480169.2019.1580167

Native plants

Infectious diseases can also impact our native plants. For example, kauri dieback is caused by a fungus-like pathogen, *Phytophthora agathidicida*.[465] *P. agathidicida* infects the roots of kauri trees, causing root rot and damage to tissues that transport water and nutrients, leaving the tree to starve to death. *P. agathidicida* is found in soil and can be spread by footwear, vehicles, and animals such as feral pigs. We don't know where *P. agathidicida* originated from.

Having proactive surveillance to identify pathogens threatening taonga species and protocols to act on emerging risks is key to **protecting our biological and cultural heritage**.

Kauri dieback was first discovered in Aotearoa New Zealand on Aotea Great Barrier Island in 1972 but was not detected on the mainland until 2006.[466] By this time, kauri dieback had already spread to many kauri stands on the mainland. There are at least six *Phytophthora* species that can infect kauri in Aotearoa New Zealand, but only *P. agathidicida* has reached epidemic proportions.[467] Having proactive surveillance to identify pathogens threatening taonga species and protocols to act on emerging risks is key to protecting our biological and cultural heritage. Kauri dieback is discussed further in sections 5.3.1 and 5.4.3.

Another example of an infectious disease impacting our native plants is the myrtle rust fungus, explored in the case study below.

Case study: Myrtle rust

Myrtle rust is an invasive airborne fungal disease that affects plants in the myrtle (*Myrtaceae*) family, including mānuka, pōhutukawa, rātā, ramarama (native), eucalyptus, and feijoa (exotic). It is caused by *Austropuccinia psidii,* a fungus which has several different strains.[468] Myrtle rust affects new plant growth, making seedlings especially vulnerable. Severe or recurrent infections can kill infected plants.

The strain present here is known as the 'pandemic' strain and has been found across most parts of the country.

Myrtle rust was first detected on Aotearoa New Zealand's mainland in May 2017. The strain present here is known as the 'pandemic' strain and has been found across most parts of the country.[469] Some response measures had already been developed before the fungus was detected on the mainland, including DNA tests. However, with our current tools and level of knowledge, elimination or effective management of myrtle rust is not possible. Economic impacts of myrtle rust to mānuka

[465] Keep Kauri Standing. (n.d.). Understanding the disease. Retrieved 12 October, 2021, from https://www.kauriprotection.co.nz/science-and-research/understanding-the-disease/
[466] Bradshaw, R.E., Bellgard, S.E., Black, A.*, et al.* (2020). *Phytophthora agathidicida*: Research progress, cultural perspectives and knowledge gaps in the control and management of kauri dieback in New Zealand. *Plant Pathology, 69*(1), 3-16. https://doi.org/10.1111/ppa.13104
[467] Beever, R.E., Waipara, N.W., Ramsfield, T.D.*, et al.* (2007). *Kauri (Agathis australis) Under Threat From Phytophthora?* Paper presented at the Fourth Meeting of the International Union of Forest Research Organizations (IUFRO) Working Party S07.02.09, Monterey, California.
[468] Velarde, S.J., Grant, A., Bellingham, P.J.*, et al.* (2019). *MPI 18607 Project Report: Evaluating impacts of and responses to myrtle rust in New Zealand*. Wellington: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/37506-evaluating-impacts-of-and-responses-to-myrtle-rust-in-new-zealand-report
[469] Ibid.

and kānuka have been estimated to be NZ$157.7 million over 20 years, while plant deaths have implications for carbon sequestration. The cultural impacts of losing taonga species are immeasurable.[470]

MPI funded more than twenty research projects worth NZ$3.7 million between 2017-2019. This research is summarised in Table 6. It is not well understood how myrtle rust will behave in our largely temperate climate and how it will impact ecosystems. Nationwide data is no longer being collected on its spread, intensification, and impacts, with very limited resource available to carry out robust, long-term, national surveillance and monitoring. The societal implications of myrtle rust in Aotearoa New Zealand, including those for Māori communities, have so far only been partially explored. Research into myrtle rust is now funded by the Ministry of Business, Innovation and Employment (MBIE) through the Endeavour Fund.[471]

… with our current tools and level of knowledge, elimination or effective management of myrtle rust is not possible.

Botanic gardens are working to maintain ex situ collections of at-risk species and are also working with mana whenua who manage their own collections (as well as being kaitiaki of the taonga in their natural environment). This is probably the most important link with AMR as the glasshouse collections rely on regular applications of fungicide to keep these specimens free from myrtle rust. There are risks in their continued use – not only of resistance developing but also that over time the use of fungicides diminishes the populations of beneficial microbes present in the plants. Fungicide use to manage the impact of myrtle rust is also being undertaken by the nursery industry. HortPlus and Plant & Food Research have developed guidance on fungicide use and management protocols for the sector.[472]

The Biological Heritage National Science Challenge holds regular online sessions with interested organisations and individuals to share information and ideas. In addition, an interagency group (consisting of MBIE, the Department of Conservation, Biosecurity NZ, and Te Uru Rākau) meets regularly to oversee a number of improvements and small funded initiatives to improve communication and provide some opportunity for operational research into fungicide treatments.[473]

Table 6: Myrtle rust research in Aotearoa New Zealand.

Research	Summary
Strategy	The Myrtle Rust Science Plan[474] identifies these areas requiring investment: exploring tools for surveillance, monitoring and understanding the impact of disease; research focusing on the epidemiology of myrtle rust, how this affects ecosystems and how to encourage resilience to myrtle rust; developing a te ao Māori and mātauranga Māori framework and strong co-design and co-implementation practices; understanding the social links between people and ecosystems, and the associated socioeconomic factors; and implementation of effective species conservation, disease control and management.

[470] Ibid.
[471] Manaaki Whenua – Landcare Research. (n.d.). Beyond myrtle rust. Retrieved 1 December, 2021, from https://www.landcareresearch.co.nz/discover-our-research/biosecurity/ecosystem-resilience/beyond-myrtle-rust/
[472] New Zealand Plant Producers Incorporated. (2021, 4 February). *Myrtle rust online tool* [Press release]. Retrieved from https://nzppi.co.nz/Myrtle-Rust-online-tool/19791-c4692668-a081-44e0-8aa3-05dfa52ef54a-s119794/
[473] Ministry for Primary Industries. (2021). Personal communication.
[474] Biosecurity New Zealand and Department of Conservation. (2020). Myrtle rust science plan. Retrieved 7 September, 2021, from https://www.myrtlerust.org.nz/science-and-research/myrtle-rust-science-plan/

Research	Summary
Surveillance and monitoring	Sightings of myrtle rust are now primarily led by citizen science and reported through iNaturalist. There is also a monitoring form to assist community-led monitoring and new hosts and new areas may also be identified through the MPI-led High Risk Site Surveillance programme.[475] Recent innovations include remote monitoring (unmanned aerial vehicles),[476] modelling of myrtle species distributions,[477] improved long-term community monitoring methods and the identification of 'indicator' species for surveillance.[478]
Evaluating impacts	There is a framework to understand the environmental, economic, and social-cultural responses to and impacts of myrtle rust.[479]
Control tools	Controls that have been used overseas have been reviewed.[480] There have also been trials of fungicides[481] and work to identify how they could be implemented here.[482] MPI investing in further research for the 2021/22 financial year.[483]
Te ao Māori	A greater understanding of te ao Māori implications of myrtle rust has been developed.[484] This knowledge aims to support more effective investments, and improved use of mātauranga, specific Māori knowledge, and kaupapa Māori approaches in management regimes.
Understanding myrtle rust	An improved knowledge base of myrtle rust has been developed which includes research on the myrtle rust genome and genetic resistance, host plant susceptibility, climate or microbial impacts for myrtle rust and susceptibility of natives to the South African strain of myrtle rust.[485]
Seed banking and breeding	There has been exploration of how resistance in myrtle species might be enhanced.[486] Seed collection began in 2017 to safeguard native myrtle species and act as an insurance policy against regional or national extinctions.[487] Work is ongoing to assess the viability of the oldest collection of stored seed.
Building engagement	Overviews of how to build engagement and social licence have been explored.[488] This work included the development of tools for assessment, understanding motivated networks, a survey of impacts of myrtle rust and responses to the incursion in Taranaki.
Ongoing research programmes	Aspects of the MPI-funded research have been picked up by ongoing research programs 'Beyond Myrtle Rust' and 'Ngā Rākau Taketake –– Saving our Iconic Trees'. These programmes will involve universities, Crown Research Institutes, Government departments and communities.

[475] Ministry for Primary Industries. (2021). Surveillance programmes for pests and diseases. Retrieved 10 September, 2021, from https://www.mpi.govt.nz/biosecurity/how-to-find-report-and-prevent-pests-and-diseases/surveillance-programmes/

[476] Pearse, G., Soewarto, J., Watt, M.*, et al.* (2019). *Developing improved methods for mapping Metrosideros species in New Zealand*. Wellington: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/37269-developing-improved-methods-for-mapping-metrosideros-species-in-new-zealand-report

[477] McCarthy, J.K., Richardson, S.J., Cooper, J.A.*, et al.* (2019). *Species distribution models of the native New Zealand Myrtaceae*. Wellington: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/37272-species-distribution-models-of-the-native-new-zealand-myrtaceae-report

[478] Ganley, B., Soewarto, J., Sutherland, R.*, et al.* (2019). *Improved myrtle rust surveillance*. Wellington, NZ: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/37263-improved-myrtle-rust-surveillance-report

[479] Velarde, S.J., Grant, A., Bellingham, P.J.*, et al.* (2019). *MPI 18607 Project Report: Evaluating impacts of and responses to myrtle rust in New Zealand*. Wellington: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/37506-evaluating-impacts-of-and-responses-to-myrtle-rust-in-new-zealand-report

[480] Chng, S., Soewarto, J., Adusei-Fosu, K.*, et al.* (2019). *MPI 18607 Project Report: Potential disease control tools most likely to be effective against Austropuccinia psidii*. Wellington: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/37284-potential-disease-control-tools-most-likely-to-be-effective-against-austropuccinia-psidii-report

[481] Adusei-Fosu, K., & Rolando, C.A. (2019). *MPI 18607 Project Report: Pilot trials for control of myrtle rust using fungicides*. Wellington: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/37275-pilot-trials-for-control-of-myrtle-rust-using-fungicides-report

[482] Adusei-Fosu, K., & Rolando, C.A. (2019). *MPI 18607 Project Report: Chemical control – review of control methods and fungicides*. Wellington: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/37278-chemical-control-review-of-control-methods-and-fungicides-report

[483] Ministry for Primary Industries. (2021). Personal communication.

[484] Marsh, A., Wood, W., Ropata, H.*, et al.* (2019). *Myrtle rust — Te ao Māori theme 2*. Wellington: Ministry for Primary Industries. Retrieved from https://www.myrtlerust.org.nz/assets/Uploads/Myrtle-rust-Te-Ao-Maori.pdf

[485] Ministry for Primary Industries. (n.d.). MPI-funded research reports. Retrieved 10 September, 2021, from https://www.myrtlerust.org.nz/science-and-research/mpi-research-reports/

[486] Freeman, J., Bus, V., Klapste, J.*, et al.* (2019). *MPI 18607 Project Report: Scoping a resistance breeding programme: Strategy pathways for implementation*. Wellington: Ministry for Primary Industries. Retrieved from https://www.myrtlerust.org.nz/assets/Uploads/Scoping-a-resistance-breeding-programme-Strategy-pathways-for-implementa..-.pdf

[487] Department of Conservation. (n.d.). Seed collection: Looking to our future. Retrieved 10 September, 2021, from https://www.doc.govt.nz/nature/pests-and-threats/diseases/myrtle-rust/our-safeguard-seed-banking/

[488] Grant, A., Stronge, D., Allen, W.*, et al.* (2019). *MPI 18607 Project Report: Building engagement and social licence: Research overview and recommendations*. Wellington: Ministry for Primary Industries. Retrieved from https://www.myrtlerust.org.nz/assets/Uploads/Building-engagement-and-social-license-Research-overview-and-recommendat..-.pdf

3.6 Infectious disease at the human-animal-environment interface

The connections between infectious diseases in the human, animal, plant, and environmental sectors mean that it is important to take a holistic, cross-sector approach. This section considers pathogens at the human-animal-environment interface, with a particular focus on foodborne, waterborne, and zoonotic diseases given some of these diseases are particularly prevalent in Aotearoa New Zealand.

3.6.1 Prevalence of foodborne, waterborne and zoonotic diseases

The annual prevalence of notified foodborne diseases (or *potentially* foodborne diseases – see note on terminology below) per 100,000 people in Aotearoa New Zealand was relatively stable between 2008 and 2019 (Figure 16). The substantial drop between 2007 and 2008 largely resulted from concerted efforts to reduce the prevalence of campylobacteriosis (see case study), which accounts for roughly half of all foodborne disease notifications in the country (Figure 16).

The actual prevalence of foodborne diseases is higher than the prevalence of notified foodborne diseases each year: not all people with foodborne illnesses present to healthcare facilities and get tested. In 2010, it was estimated that for every notified case of an acute gastrointestinal illness, there are more than an additional 200 cases in the community that are not notified.[489] The notified cases therefore represent only the tip of the iceberg. However, the trends in notified cases help to indicate disease trajectory over time.

In 2010, it was estimated that for every notified case of an acute gastrointestinal illness, there are more than **an additional 200 cases** in the community that are not notified.

Foodborne diseases – A note on terminology

There are many pathogens that can spread to humans through food (e.g. consuming contaminated or undercooked food), water (e.g. drinking contaminated water, recreational activities in water), and through contact with animals (e.g. on farms or in meat processing, contact with pets, contact with wildlife). In addition, once pathogens move from the environment or an animal into humans, they can be further spread by person-to-person contact. With many pathogens able to be transmitted by multiple pathways, it isn't always possible to ascertain how a person became infected.

In this section of the report, the term 'foodborne' should be taken to mean 'potentially foodborne' unless specified. ESR has provided estimates for the proportion of cases of a range of potentially foodborne illnesses that are thought to actually be acquired through food as opposed to from other sources. This information is included in Table 7.[490]

[489] Lake, R., Adlam, S., Perera, S., *et al.* (2010). The disease pyramid for acute gastrointestinal illness in New Zealand. *Epidemiology and Infection, 138*(10), 1468-1471. https://doi.org/10.1017/S0950268810000397

[490] Horn, B., Pattis, I., Armstrong, B., *et al.* (2021). *Annual report concerning foodborne diseases in New Zealand 2020*. Christchurch, NZ: Institute for Environmental Science Research Ltd. Retrieved from https://www.mpi.govt.nz/dmsdocument/47986-Annual-report-concerning-Foodborne-Diseases-in-New-Zealand-2020-Report

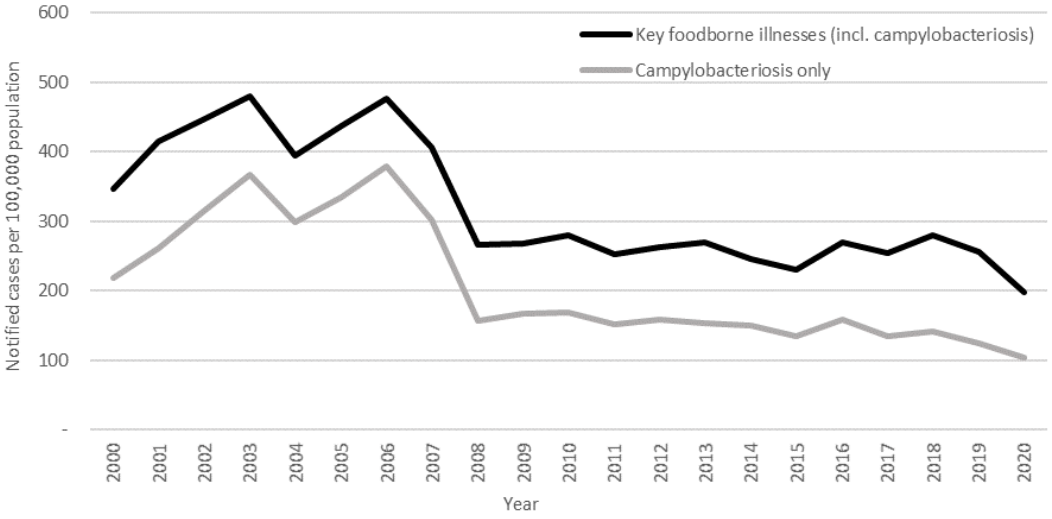

Figure 16: Notified cases of key foodborne illnesses per 100,000 population in Aotearoa New Zealand from 2000-2020. Diseases included are campylobacteriosis, cryptosporidiosis, giardiasis, hepatitis A, listeriosis, salmonellosis, STEC, shigellosis, and yersiniosis. Campylobacteriosis is also shown separately. Data from ESR and MPI.

Why are we using 2019 data?

Foodborne disease data for 2020 is available,[491] but for most of this section we use data up to 2019.[492] This is because COVID-19 had a range of impacts on both foodborne disease incidence and notifications, which are difficult to disentangle and may not reflect meaningful data trends.

Between 2019 and 2020, notified cases of for all main foodborne diseases were lower than in the previous three years (see Figure 16), except for yersiniosis and listeriosis. A reduction in foodborne illnesses has also been reported in Australia,[493] Spain,[494] and Germany.[495] While at least some of this reduction may reflect a genuine decrease driven by public health measures implemented to stop the spread of COVID-19,[496] the overall picture is more complicated.

With lab attention and resources diverted to COVID-19 diagnostics and New Zealanders making fewer visits to health facilities for non-COVID-19 reasons, disease detection may have dropped in 2020. A range of factors could have also impacted actual disease incidence, including travel restrictions, physical distancing leading to less socialising and shared food, more home cooking rather than eating out, and greater emphasis on hygiene.[497]

For further details on the impacts COVID-19 has had on other infectious diseases and AMR, see section 2.5.2.

[491] Ibid.
[492] Pattis, I., Horn, B., Armstrong, B., *et al.* (2020). *Annual report concerning foodborne diseases in New Zealand 2019*. Christchurch, NZ: Institute of Environmental Science & Research Ltd.
[493] Bright, A., Glynn-Robinson, A.-J., Kane, S., *et al.* (2020). The effect of COVID-19 public health measures on nationally notifiable diseases in Australia: Preliminary analysis. *Communicable Diseases Intelligence, 44*, 1-16. https://doi.org/10.33321/cdi.2020.44.85
[494] de Miguel Buckley, R., Trigo, E., de la Calle-Prieto, F., *et al.* (2020). Social distancing to combat COVID-19 led to a marked decrease in food-borne infections and sexually transmitted diseases in Spain. *Journal of Travel Medicine, 27*(8), 134. https://doi.org/10.1093/jtm/taaa134
[495] Ullrich, A., Schranz, M., Rexroth, U., *et al.* (2021). Impact of the COVID-19 pandemic and associated non-pharmaceutical interventions on other notifiable infectious diseases in Germany: An analysis of national surveillance data during week 1–2016–week 32–2020. *The Lancet Regional Health-Europe*, 100103. https://doi.org/10.1016/j.lanepe.2021.100103
[496] Knox, M.A., Garcia-R, J.C., Ogbuigwe, P., *et al.* (2021). Absence of *Cryptosporidium hominis* and dominance of zoonotic *Cryptosporidium* species in patients after COVID-19 restrictions in Auckland, New Zealand. *Parasitology*, 1-5. https://doi.org/10.1017/S0031182021000974
[497] Horn, B., Pattis, I., Armstrong, B., *et al.* (2021). *Annual report concerning foodborne diseases in New Zealand 2020*. Christchurch, NZ: Institute for Environmental Science Research Ltd. Retrieved from https://www.mpi.govt.nz/dmsdocument/47986-Annual-report-concerning-Foodborne-Diseases-in-New-Zealand-2020-Report

As well as being responsible for around half of all foodborne disease notifications in Aotearoa New Zealand, campylobacteriosis is also the leading cause of hospitalisation for any foodborne illness, followed by salmonellosis (see Figure 17).

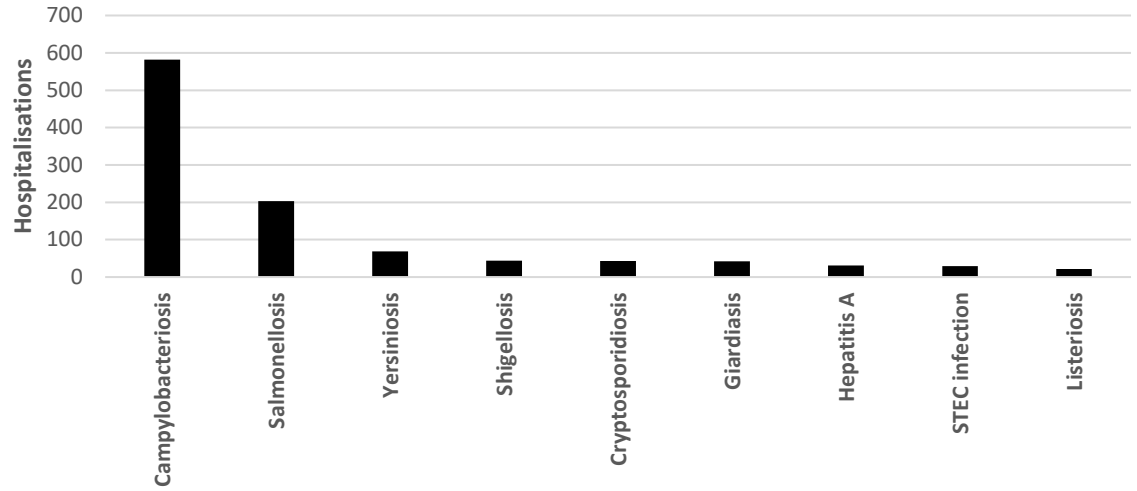

Figure 17: Hospitalisations for key foodborne diseases (principal diagnosis) in Aotearoa New Zealand 2019.

3.6.2 Selected zoonotic, foodborne and waterborne infectious diseases of concern

Despite overall prevalence of foodborne disease holding relatively constant between 2008 and 2019, there is considerable diversity in the trajectory of different diseases that is masked by this general trend. In this section, individual foodborne diseases are explored in detail, including three case studies looking at STEC, salmonellosis, and campylobacteriosis.

A selection of infectious diseases at the human-animal-environment interface is outlined in Table 7. Key trends include:[498]

- **Decreasing incidence of campylobacteriosis acquired from food.** By estimating the incidence of domestically acquired foodborne campylobacteriosis (which includes excluding the major 2016 Havelock North waterborne outbreak of 2016 discussed in the case study below, as well as campylobacteriosis acquired from other sources, including overseas), ESR has calculated that by 2020 campylobacteriosis incidence had fallen by more than 10% from the 2012-2014 baseline, in line with the MPI performance target (see Figure 16 above).
- **Higher prevalence of shigellosis and yersiniosis** compared with 2013 (see Figure 18).
- **The sharp STEC increase is thought to be driven by increased ascertainment.** While STEC prevalence appears to be sharply increasing, this is likely due to increased ascertainment resulting from a change in diagnostic methodology starting in 2015 and may not reflect an actual increase in STEC prevalence. Research projects are currently underway to determine with greater clarity the impacts of changed methodology on reported STEC cases. See the case study below for more details.
- **Cryptosporidiosis prevalence has fluctuated a lot**, with prevalence currently falling following a 2018 peak, but still above 2014 levels.

[498] Pattis, I., Horn, B., Armstrong, B., *et al.* (2020). *Annual report concerning foodborne diseases in New Zealand 2019*. Christchurch, NZ: Institute of Environmental Science & Research Ltd.

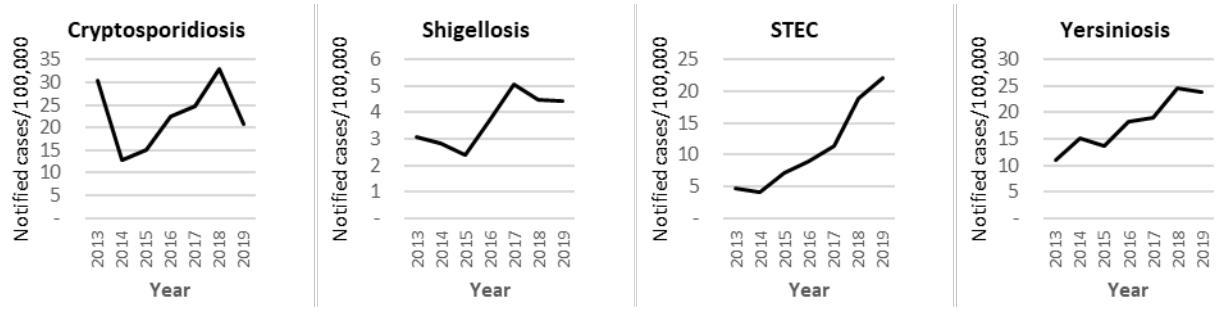

Figure 18: Notified cases of selected foodborne illnesses per 100,000 population in Aotearoa New Zealand from 2013-2019. (NB: The apparently sharp increase in STEC prevalence is thought to be due to a change to the diagnostic methodology rather than reflective of an actual increase, see the case study on STEC below.)

Table 7: Selected foodborne, waterborne, and zoonotic infectious diseases of concern in Aotearoa New Zealand.[499]

	Disease and pathogen	**Summary** NB: prevalence is based on notified case numbers in 2019.
Bacteria	Campylobacteriosis Caused by *Campylobacter* spp.	**Infects:** Humans and animals. **How it spreads:** Food products, contaminated drinking water, direct animal contact, contact with a contaminated environment, person-to-person (faecal-oral). **Estimated percentage of infections from food (NZ):** 75%. **Prevalence:** Approx. 125 cases per 100,000 population. **Trend: D**ecrease since 2007, stable in last five years (6,218 cases in 2015, 6,202 cases in 2019). NB: this does not include the 2016 Havelock North outbreak (see case study below). **Vaccine:** Sheep.
	Salmonellosis[500] Caused by *Salmonella enterica* subsp. *enterica*	**Infects:** Humans and animals. **How it spreads:** Food products, contaminated drinking water, direct animal contact, contact with a contaminated environment. **Estimated percentage of infections from food (NZ):** 62% (non-typhoidal). **Prevalence:** Approx. 24 cases per 100,000 population. **Trend:** Stable (1,051 cases in 2015, 1,188 cases in 2019). **Vaccine:** Sheep, cattle, poultry.
	Yersiniosis[501] caused by *Yersinia* spp. (predominately *Y. enterocolitica* and *Y. pseudotuberculosis)*	**Infects:** Humans and animals. **How it spreads:** Food products, including but not limited to pig products. Main sources of pathogen and modes of transmission not well understood. Research exploring potential food sources in NZ is underway.[502] **Estimated percentage of infections from food (NZ):** 75%. **Prevalence:** Approx. 24 cases per 100,000 population. High compared with other developed countries.[503] **Trends:** Increasing (634 cases in 2015, 1,186 cases in 2019). In 2014, an outbreak (220 laboratory-confirmed cases) of yersiniosis caused by *Y. pseudotuberculosis* occurred.[504]

[499] Institute of Environmental Science and Research Limited (ESR). (2021). Annual notifiable disease tables. Retrieved 1 September, 2021, from https://surv.esr.cri.nz/surveillance/annual_diseasetables.php; Horn, B., Pattis, I., Armstrong, B., *et al.* (2021). *Annual report concerning foodborne diseases in New Zealand 2020*. Christchurch, NZ: Institute for Environmental Science Research Ltd. Retrieved from https://www.mpi.govt.nz/dmsdocument/47986-Annual-report-concerning-Foodborne-Diseases-in-New-Zealand-2020-Report

[500] Chousalkar, K., Gast, R., Martelli, F., *et al.* (2018). Review of egg-related salmonellosis and reduction strategies in United States, Australia, United Kingdom and New Zealand. *Critical Reviews in Microbiology, 44*(3), 290-303. https://doi.org/10.1080/1040841x.2017.1368998

[501] Rivas, L., Strydom, H., Paine, S., *et al.* (2021). Yersiniosis in New Zealand. *Pathogens, 10*(2). https://doi.org/10.3390/pathogens10020191

[502] Institute of Environmental Science and Research Limited (ESR). (2021). Detection of pathogenic *Yersinia* in foods. Retrieved 1 September, 2021, from https://www.esr.cri.nz/home/about-esr/our-science-in-action/detection-of-pathogenic-yersinia-in-foods/

[503] Rivas, L., Strydom, H., Paine, S., *et al.* (2021). Yersiniosis in New Zealand. *Pathogens, 10*(2). https://doi.org/10.3390/pathogens10020191

[504] Williamson, D.A., Baines, S.L., Carter, G.P., *et al.* (2016). Genomic insights into a sustained national outbreak of *Yersinia pseudotuberculosis*. *Genome Biology and Evolution, 8*(12), 3806-3814. https://doi.org/10.1093/gbe/evw285

	Disease and pathogen	Summary NB: prevalence is based on notified case numbers in 2019.
		Vaccine: Deer.
	STEC Caused by Shiga toxin-producing *Escherichia coli* (also known as Verotoxin-producing *E. coli*)	**Infects:** Humans and animals. **How it spreads:** Contact with animals or farms, contaminated food or water. Drinking raw milk has been linked to outbreaks in NZ. Cattle, sheep, goats, and deer are primary reservoirs. **Estimated percentage of infections from food (NZ):** 40%**.** **Prevalence:** Approx. 22 cases per 100,000 population. **Trends:** Apparent increase since 2015 attributed to changed diagnostic methodology rather than true increase (330 cases in 2015, 1,101 cases in 2019). **Vaccine:** No STEC-specific vaccine in NZ, but general *E. coli* vaccines registered for use in cattle and sheep.
	Listeriosis Caused by *Listeria monocytogenes*	**Infects:** Humans and animals. **How it spreads:** Widely found in soil, water, plants and animal faecal matter. Commonly transmitted by eating contaminated food. **Estimated percentage of infections from food (NZ):** 88%. **Prevalence:** Approx. 0.6 cases per 100,000 population. **Trends:** Stable (26 cases in 2015, 31 cases in 2019). **Vaccine:** No.
	Leptospirosis[505] Caused by *Leptospira* spp.	**Infects:** Humans and animals. **How it spreads:** From a range of animals to humans, through exposure to urine or excrement or via contaminated soil or water. People working in the livestock industry are the most commonly infected. **Estimated percentage of infections from food (NZ):** Not foodborne. **Prevalence:** Approx. 2 cases per 100,000 population. High compared with other countries.[506] A study in 2020 estimated the cost of leptospirosis each year in NZ to be approx. NZ$18 million.[507] **Trends:** Increasing (63 cases in 2015, 96 cases in 2019). **Vaccine:** Cattle, sheep, deer, dogs. While 99% of dairy farms have a vaccination programme for leptospirosis, there are much lower vaccination coverage for dry stock (farming for meat, wool in sheep, etc.).[508] However, dry stock farming contributes as many leptospirosis cases as dairy farming.[509]
	Shigellosis[510] Caused by *Shigella* spp.	**Infects:** Humans. **How it spreads:** Faecal-oral transmission, often through food or water. Person-to-person. More than half of NZ's cases are acquired overseas. **Estimated percentage of infections from food (NZ):** No estimate (WHO estimate 7-36%). **Prevalence:** Approx. 4 cases per 100,000 population. **Trends:** Increasing (111 cases in 2015, 222 cases in 2019). **Vaccine:** No.

[505] Benschop, J., Nisa, S., & Spencer, S.E.F. (2021). Still 'dairy farm fever'? A Bayesian model for leptospirosis notification data in New Zealand. *Journal of The Royal Society Interface, 18*(175), 20200964. https://doi.org/10.1098/rsif.2020.0964; Bolwell, C.F., Rogers, C.W., Benschop, J.*, et al.* (2020). Seroprevalence of *Leptospira* in racehorses and broodmares in New Zealand. *Animals, 10*(11), 1952. https://doi.org/10.3390/ani10111952; El-Tras, W.F., Bruce, M., Holt, H.R.*, et al.* (2018). Update on the status of leptospirosis in New Zealand. *Acta Tropica, 188*, 161-167. https://doi.org/10.1016/j.actatropica.2018.08.021

[506] El-Tras, W.F., Bruce, M., Holt, H.R.*, et al.* (2018). Update on the status of leptospirosis in New Zealand. *Acta Tropica, 188*, 161-167. https://doi.org/10.1016/j.actatropica.2018.08.021

[507] Sanhueza, J.M., Baker, M.G., Benschop, J.*, et al.* (2020). Estimation of the burden of leptospirosis in New Zealand. *Zoonoses and Public Health, 67*(2), 167-176. https://doi.org/10.1111/zph.12668

[508] Benschop, J., Nisa, S., & Spencer, S.E.F. (2021). Still 'dairy farm fever'? A Bayesian model for leptospirosis notification data in New Zealand. *Journal of The Royal Society Interface, 18*(175), 20200964. https://doi.org/10.1098/rsif.2020.0964

[509] Ibid.

[510] Ministry of Health. (2018). Shigellosis. Retrieved 1 September, 2021, from https://www.health.govt.nz/our-work/diseases-and-conditions/communicable-disease-control-manual/shigellosis

	Disease and pathogen	Summary NB: prevalence is based on notified case numbers in 2019.
		Resistance: Antibiotic resistance in shigellosis cases is a growing concern.[511] A study in 2018 found that resistance to the currently recommended first-line antibiotics were relatively high (56.7% trimethoprim + sulfamethoxazole, 22.8% fluoroquinolone (ciprofloxacin or norfloxacin).[512] Resistant strains were as likely to be acquired locally as they were from an overseas source. The paper reported that ESR plans to monitor resistance trends more regularly (using three-yearly surveys).[513]
Viruses	Hepatitis A Caused by hepatitis A virus	**Infects:** Humans. **How it spreads:** Person-to-person (faecal-oral transmission), often through food or water. Sexual contact. **Estimated percentage of infections from food (NZ):** No estimate (WHO estimate 29-42%). **Prevalence:** Approx. 1 case per 100,000 population. **Trends:** Stable (47 cases in 2015, 58 cases in 2019). **Vaccine:** Human.
Parasites	Giardiasis Caused by *Giardia lamblia*	**Infects:** Humans and animals (domestic and farm). **How it spreads:** Contaminated soil, food, or water (faecal-oral transmission). Commonly through contaminated drinking water or recreational water (swimming pools, lakes etc.). **Estimated percentage of infections from food (NZ):** No estimate (WHO estimate 11-14%). **Prevalence:** Approx. 35 cases per 100,000 population. **Trends:** Stable (1,510 cases in 2015, 1,749 cases in 2019). **Vaccine:** Not available in NZ. Overseas – cats and dogs.[514]
	Cryptosporidiosis Caused by *Cryptosporidium parvum* and *C. hominis*	**Infects:** Humans and animals (domestic and farm). **How it spreads:** Person-to-person, animals, or through food. Commonly through contaminated drinking water or recreational water (swimming pools, lakes etc.). **Estimated percentage of infections from food (NZ):** No estimate (WHO estimate 8-16%). **Prevalence:** Approx. 21 cases per 100,000 population. High compared with other developed countries.[515] **Trends:** Increase over last five years (696 cases in 2015, 1,035 cases in 2019). **Vaccine:** No.

[511] Heffernan, H., Woodhouse, R., Hewison, C.*, et al.* (2018). Antimicrobial resistance among *Shigella* in New Zealand. *New Zealand Medical Journal, 131*(1477), 56-62.
[512] Ibid.
[513] Ibid.
[514] Serradell, M.C., Saura, A., Rupil, L.L.*, et al.* (2016). Vaccination of domestic animals with a novel oral vaccine prevents Giardia infections, alleviates signs of giardiasis and reduces transmission to humans. *npj Vaccines, 1*(1), 16018. https://doi.org/10.1038/npjvaccines.2016.18
[515] Garcia-R, J.C., Pita, A.B., Velathanthiri, N.*, et al.* (2020). Species and genotypes causing human cryptosporidiosis in New Zealand. *Parasitology Research, 119*, 2317-2326. https://doi.org/10.1007/s00436-020-06729-w; Snel, S.J., Baker, M.G., Kamalesh, V.*, et al.* (2009). A tale of two parasites: The comparative epidemiology of cryptosporidiosis and giardiasis. *Epidemiology and Infection, 137*(11), 1641-1650. https://doi.org/10.1017/S0950268809002465

Case study: Shiga toxin-producing *E. coli* (STEC)

STEC (previously known as verotoxin producing *E. coli* or VTEC) is an illness that causes acute onset diarrhoea and in serious cases can progress to haemolytic uraemic syndrome (which in some cases can lead to kidney impairment and even kidney failure)[516] or thrombotic thrombocytopenic purpura (a blood clotting disorder). STEC is most often notified in those under four years old and those over 70 years old.[517] There was one death and 52 hospitalisations associated with cases of STEC in Aotearoa New Zealand 2019.[518]

The prevalence of notified STEC cases has increased steeply since 2014 from 187 cases per year to 1,101 cases in 2019. However, this is likely due to increased ascertainment resulting from a change in diagnostic methodology rather than a reflection of an actual increase in STEC prevalence. Labs in Aotearoa New Zealand have been replacing culture-based methods for diagnosing enteric pathogens with culture-independent diagnostic tests using polymerase chain reaction (PCR) tests. In addition, those that haven't shifted to PCR have expanded the range of STEC serotypes that their tests can detect. This highlights that, by improving our diagnostic tools, we can get a better idea of disease prevalence in Aotearoa New Zealand, although also demonstrates that caution is required when comparing data over time where diagnostic techniques and screening protocols aren't constant. In addition to changing diagnostic techniques, all confirmed clinical samples of STEC now also undergo WGS so that serotype can be reliably identified.[519] See section 5.4 for more details on diagnostic techniques.

STEC prevalence in Aotearoa New Zealand (22 cases per 100,000) is high compared with other developed countries – it is 10 times higher than the average notified cases in Europe in 2019 (2.2 cases per 100,000).[520] Ireland reported 16.3 cases per 100,000 population in 2019. However, as with comparing disease prevalence across time where methodologies aren't constant, comparisons between countries should also be approached with caution.

A study in Aotearoa New Zealand used WGS to investigate transmission of strains, and found there were **multiple transmission pathways** between cows, calves, the environment, feed, and water sources.

A relationship between STEC and rural settings is well understood, with the main reservoir being cattle.[521] A study in Aotearoa New Zealand found contact with animal manure, presence of cattle, and contact with recreational waters to be the most significant risk factors for human infection, rather than consumption of food products.[522] Through expert consultation, ESR estimates that 40%

[516] Thomas, D.E., & Elliott, E.J. (2013). Interventions for preventing diarrhea-associated hemolytic uremic syndrome: Systematic review. *BMC Public Health, 13*(1), 799. https://doi.org/10.1186/1471-2458-13-799

[517] Ministry for Primary Industries. (2021). *E. coli* (STEC) infection: Symptoms and advice. Retrieved 10 September, 2021, from https://www.mpi.govt.nz/food-safety-home/food-poisoning-symptoms-causes/e-coli-stec-infection-symptoms-and-advice/

[518] Pattis, I., Horn, B., Armstrong, B., *et al.* (2020). *Annual report concerning foodborne diseases in New Zealand 2019*. Christchurch, NZ: Institute of Environmental Science & Research Ltd.

[519] Institute of Environmental Science and Research Limited (ESR). (2020). VTEC/STEC isolates 2020. Retrieved 1 December, 2021, from https://surv.esr.cri.nz/enteric_reference/vtec_isolates.php?we_objectID=5148

[520] European Centre for Disease Prevention and Control. (2021). *Shiga toxin-producing Escherichia coli (STEC) infection*. Stockholm: ECDC. Retrieved from https://www.ecdc.europa.eu/sites/default/files/documents/AER-STEC-2019.pdf

[521] Ingle, D.J., da Silva, A.G., Valcanis, M., *et al.* (2019). Emergence and divergence of major lineages of Shiga-toxin-producing *Escherichia coli* in Australia. *Microbial genomics, 5*(5). https://doi.org/10.1099/mgen.0.000268

[522] Jaros, P., Cookson, A.L., Campbell, D.M., *et al.* (2013). A prospective case-control and molecular epidemiological study of human cases of Shiga toxin-producing Escherichia coli in New Zealand. *BMC infectious diseases, 13*, 450. https://doi.org/10.1186/1471-2334-13-450

of STEC cases are food-related.[523] Raw meat, unpasteurised milk, dairy products, and raw produce are common food sources of STEC infections.[524] One outbreak of three cases was recorded in 2019 that was possibly associated with raw milk.[525]

A study of young calves on dairy farms found widespread presence of STEC, which occurred at a higher prevalence than in adult cattle.[526] Calves slaughtered for meat may therefore present a greater potential food safety risk.

A study in Aotearoa New Zealand used WGS to investigate transmission of strains, and found there were multiple transmission pathways between cows, calves, the environment, feed, and water sources.[527] The study found that controlling transmission on farm would be difficult – not least because STEC is asymptomatic in cattle and is a normal part of their microbiota – but conditions of transport, slaughter, and dressing can profoundly impact the level of cross-contamination of the carcass and potential for foodborne transmission to humans.[528] Vaccines and dietary supplements can decrease STEC shedding[529] but there are economic and practical constraints to uptake.

Case study: Salmonellosis

Salmonellosis is caused by *Salmonella enterica* subsp. *enterica* bacteria. Salmonellosis affects both humans and animals (including poultry, cattle, and sheep). In humans, symptoms can include abdominal pains, diarrhoea, fever, nausea, and vomiting. At the extreme end, sepsis is possible. In Aotearoa New Zealand there were approximately 24 cases per 100,000 population in 2019 (1,188 cases), with prevalence holding fairly stable over the last five years.

Figure 19: Brown Shaver hen. Most commercial layer hens are Hyaline Brown or Brown Shaver varieties.

An estimated 62% of non-typhoidal Salmonellosis cases in Aotearoa New Zealand are food-associated. Foodborne transmission routes are particularly important in outbreaks (as opposed to sporadic cases).[530] *Salmonella* is often associated with food products of animal origin, including eggs and chicken. However, non-poultry food sources are also often implicated. For example, in 2019 there were 15 outbreaks with food reported as a possible mode of transmission in Aotearoa New Zealand. One of these outbreaks was strongly linked to alfalfa sprouts and another was strongly linked to flavoured water (the others couldn't be strongly linked to a specific food source). Mahinga kai, including shellfish, tuna (eels), seaweed and watercress, can be

[523] Horn, B., Pattis, I., Armstrong, B., *et al.* (2021). *Annual report concerning foodborne diseases in New Zealand 2020*. Christchurch, NZ: Institute for Environmental Science Research Ltd. Retrieved from https://www.mpi.govt.nz/dmsdocument/47986-Annual-report-concerning-Foodborne-Diseases-in-New-Zealand-2020-Report

[524] Ministry for Primary Industries. (2021). *E. coli* (STEC) infection: Symptoms and advice. Retrieved 10 September, 2021, from https://www.mpi.govt.nz/food-safety-home/food-poisoning-symptoms-causes/e-coli-stec-infection-symptoms-and-advice/

[525] Pattis, I., Horn, B., Armstrong, B., *et al.* (2020). *Annual report concerning foodborne diseases in New Zealand 2019*. Christchurch, NZ: Institute of Environmental Science & Research Ltd.

[526] Browne, A.S., Midwinter, A.C., Withers, H., *et al.* (2018). Molecular epidemiology of Shiga toxin-producing *Escherichia coli* (STEC) on New Zealand dairy farms: Application of a culture-independent assay and whole-genome sequencing. *Applied and Environmental Microbiology, 84*(14), e00481-00418. https://doi.org/10.1128/AEM.00481-18

[527] Browne, A.S., Midwinter, A.C., Withers, H., *et al.* (2021). Evaluating transmission dynamics of Shiga toxin-producing *E. coli* (STEC) in New Zealand cattle from farm to slaughter using PCR/MALDI-TOF and genome sequencing. *Applied and Environmental Microbiology*.

[528] Ibid.

[529] Schmidt, N., Barth, S.A., Frahm, J., *et al.* (2018). Decreased STEC shedding by cattle following passive and active vaccination based on recombinant *Escherichia coli* Shiga toxoids. *Veterinary Research, 49*(1), 28. https://doi.org/10.1186/s13567-018-0523-0

[530] King, N., Lake, R., & Campbell, D. (2011). Source attribution of nontyphoid salmonellosis in New Zealand using outbreak surveillance data. *Journal of Food Protection, 74*(3), 438-445. https://doi.org/10.4315/0362-028x.Jfp-10-323

infected with *Salmonella*.[531] This may be a concern where food is gathered from waterways in rural areas.[532] Non-food sources include contact with infected animals or contaminated water or environments.

There are a variety of different strains of *Salmonella*, and ESR regularly reports on the strains isolated from samples from humans[533] and animals.[534] The major strains are most likely transmitted via direct contact or environmental contact with domestic animals and wildlife[535] – this includes *Salmonella* Typhimurium and *Salmonella* Brandenburg, and the more recently emerging *Salmonella* Bovismorbificans and *Salmonella* Give. This year *Salmonella* Enteritidis caused a food outbreak and possibly some sporadic cases associated with poultry meat and eggs.[536] Phasing out of conventional caged systems for eggs by 31 December 2022 may reduce salmonellosis; there is baseline data from which any impact on prevalence can be gauged.[537]

Historically there have been specific targets to reduce salmonellosis, but they were removed in 2015 and salmonellosis monitoring and review is now covered by under the core business of New Zealand Food Safety. The targets were lifted because it was assessed that there was little evidence of any significant ongoing foodborne illness associated with salmonellosis that would warrant specific targets.[538]

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[532] Donnison, A., Ross, C., & Dixon, L. (2009). Faecal microbial contamination of watercress (*Nasturtium officinale*) gathered by a Māori protocol in New Zealand streams. *New Zealand Journal of Marine and Freshwater Research, 43*(4), 901-910. https://doi.org/10.1080/00288330909510048

[533] Institute of Environmental Science and Research Limited (ESR). (n.d.). Human *Salmonella* isolates. Retrieved 10 November, 2021, from https://surv.esr.cri.nz/enteric_reference/human_salmonella.php

[534] Institute of Environmental Science and Research Limited (ESR). (2021, August). Non-human *Salmonella* isolates. Retrieved 1 December, 2021, from https://surv.esr.cri.nz/enteric_reference/nonhuman_salmonella.php?we_objectID=5181

[535] Alley, M.R., Connolly, J.H., Fenwick, S.G.*, et al.* (2002). An epidemic of salmonellosis caused by *Salmonella* Typhimurium DT160 in wild birds and humans in New Zealand. *New Zealand Veterinary Journal, 50*(5), 170-176. https://doi.org/10.1080/00480169.2002.36306; Baker, M.G., Thornley, C.N., Lopez, L.D.*, et al.* (2007). A recurring salmonellosis epidemic in New Zealand linked to contact with sheep. *Epidemiology and Infection, 135*(1), 76-83. https://doi.org/10.1017/S0950268806006534; Bloomfield, S., Benschop, J., Biggs, P.*, et al.* (2017). Genomic analysis of *Salmonella enterica* serovar Typhimurium DT160 associated with a 14-year outbreak, New Zealand, 1998–2012. *Emerging Infectious Diseases, 23*(6), 906. https://doi.org/10.3201/eid2306.161934

[536] Ministry for Primary Industries. (2021, 17 June). *New Zealand Food Safety places precautionary controls on North Island egg producer* [Press release]. Retrieved from https://www.mpi.govt.nz/news/media-releases/new-zealand-food-safety-places-precautionary-controls-on-north-island-egg-producer-after-detection-of-salmonella-enteritidis/; Regional Public Health. (2021, 17 June). *Salmonella detected at egg producer: food safety messages* [Press release]. Retrieved from https://www.rph.org.nz/health-professionals/public-health-alerts/2021-06-17-salmonella-enteritidis-food-safety-messages.pdf

[537] Kingsbury, J.M., Thom, K., Erskine, H.*, et al.* (2019). Prevalence and genetic analysis of *Salmonella enterica* from a cross-sectional survey of the new zealand egg production environment. *Journal of Food Protection, 82*(12), 2201-2214. https://doi.org/10.4315/0362-028X.JFP-19-159

[538] Pattis, I., Horn, B., Armstrong, B.*, et al.* (2020). *Annual report concerning foodborne diseases in New Zealand 2019*. Christchurch, NZ: Institute of Environmental Science & Research Ltd.

Case study: Spotlight on *Campylobacter*

Campylobacter spp. are a group of bacteria that infect the intestine, causing campylobacteriosis.[539] *Campylobacter* is the most common cause of foodborne illness in Aotearoa New Zealand, with symptoms including muscle and abdominal pain, nausea, headaches and fever, and diarrhoea. As with other foodborne illnesses, most people will recover but those with weaker immune systems (such as the elderly, sick, young children, babies and pregnant women) are at higher risk of experiencing serious chronic illness or death.

Between 2009 and 2018, a mean average of 6,898 cases were notified per year. Accounting for under-detection (i.e. one UK study finding that for every notified case there are 9.3 community cases) this equates to over 64,000 cases a year. For the same period, the mean average annual number of people hospitalised with campylobacteriosis was 652.[540]

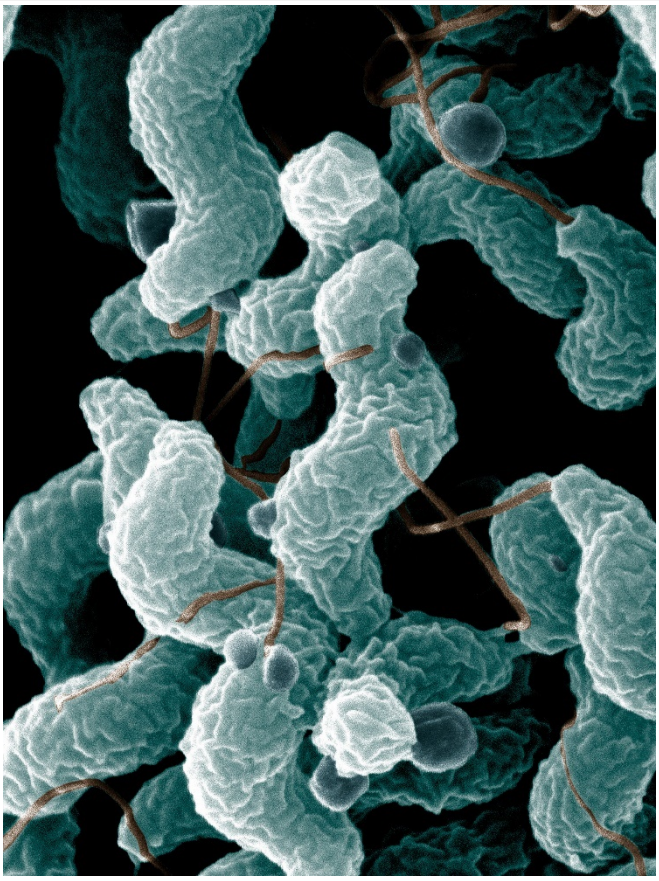

Figure 20: Scanning electron microscope image of *Campylobacter jejuni.*

Of particular concern is the connection between campylobacteriosis and the onset of Guillain-Barré syndrome – a disease that affects the nervous system and can result in temporary paralysis of the limbs, face, and respiratory system, lasting for weeks (see section below).

Campylobacter is the most common cause of foodborne illness in Aotearoa New Zealand.

The economic cost of campylobacteriosis is substantial. In 2006-2007 it was estimated to cost NZ$134 million,[541] while another cost of illness analysis put the figure at NZ$99 million (comprising NZ$6.2 million direct costs and NZ$93 million indirect costs).[542] Although the incidence of

[539] Ministry for Primary Industries. (2020). Managing the foodborne risk of *Campylobacter*. Retrieved 15 July, 2021, from https://www.mpi.govt.nz/science/food-safety-and-suitability-research/managing-the-risk-of-campylobacter/
[540] Baker, M.G., Grout, L., & Wilson, N. (2021). Update on the *Campylobacter* epidemic from chicken meat in New Zealand: The urgent need for an upgraded regulatory response. *Epidemiology and Infection, 149*, 1-10. https://doi.org/10.1017/s095026882000299x
[541] Lake, R.J., Cressey, P.J., Campbell, D.M*., et al.* (2010). Risk ranking for foodborne microbial hazards in New Zealand: burden of disease estimates. *Risk Analysis: an International Journal, 30*(5), 743-752.
[542] Duncan, G.E. (2014). Determining the health benefits of poultry industry compliance measures: The case of campylobacteriosis regulation in New Zealand. *New Zealand Medical Journal, 127*(1391), 22-37.

campylobacteriosis has decreased since these analyses, the cost remains high, with a recent estimate of NZ$56 million per year between 2009 and 2018.[543]

Sources and risk factors for infection

While campylobacteriosis is often a foodborne illness (with an estimated 75% of cases in Aotearoa New Zealand being acquired from food[544]), there are also other sources of infection – most famously demonstrated through the 2016 outbreak in Havelock North, which saw up to an estimated 8,320 people infected by contaminated drinking water (see section below).

Key pathways to contracting campylobacteriosis include:[545]

- Eating or preparing poultry meat or contaminated products (especially undercooked poultry). This is the main pathway: an estimated 84% of food-related campylobacteriosis cases are attributed to poultry.
- Direct contact with farm animals, including living and working on a farm.
- Drinking raw milk.
- Drinking contaminated water (including rainwater or roof tank water, reticulated water supplies from unchlorinated groundwater and surface water systems).[546]

There are a variety of other potential transmission routes and risk factors, but these are much rarer than the above. These include, for example, water-based recreation (e.g. swimming in contaminated water), contact with another person who has campylobacteriosis, and having pet chickens.[547]

An estimated 84% of food-related campylobacteriosis cases are attributed to poultry.

Surveillance and strains

In Aotearoa New Zealand, the majority (90%) of campylobacteriosis cases are caused by two different bacterial species: *C. jejuni* and *C. coli*. There are also several other species that have been associated with human gastrointestinal infections: *C. concisus*, *C. upsaliensis,* and *C. lari*.

Campylobacteriosis is a notifiable disease and has been since 1980.[548] This means that probable or confirmed cases of campylobacteriosis must be reported. Where there may be an outbreak, or a patient is in a high-risk occupation (i.e. where they could transmit the disease to others, such as in food service or in healthcare), investigation is also undertaken. Investigation includes obtaining food and water consumption history, animal contact, occupation, and testing samples where patients are

[543] Baker, M.G., Grout, L., & Wilson, N. (2021). Update on the *Campylobacter* epidemic from chicken meat in New Zealand: The urgent need for an upgraded regulatory response. *Epidemiology and Infection, 149*, 1-10. https://doi.org/10.1017/s095026882000299x
[544] Horn, B., Pattis, I., Armstrong, B.*, et al.* (2021). *Annual report concerning foodborne diseases in New Zealand 2020*. Christchurch, NZ: Institute for Environmental Science Research Ltd. Retrieved from https://www.mpi.govt.nz/dmsdocument/47986-Annual-report-concerning-Foodborne-Diseases-in-New-Zealand-2020-Report
[545] Lake, R., Ashmore, E., Cressey, P.*, et al.* (2020). *Source assigned campylobacteriosis in New Zealand study*. Wellington, NZ: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/39896-Source-Assigned-Campylobacteriosis-in-New-Zealand-Study-SACNZS-Report; Lake, R.J., Campbell, D.M., Hathaway, S.C.*, et al.* (2021). Source attributed case-control study of campylobacteriosis in New Zealand. *International Journal of Infectious Diseases, 103*, 268-277. https://doi.org/10.1016/j.ijid.2020.11.167; Varrone, L., Glass, K., Stafford, R.J.*, et al.* (2020). A meta-analysis of case-control studies examining sporadic campylobacteriosis in Australia and New Zealand from 1990 to 2016. *Australian and New Zealand Journal of Public Health, 44*(4), 313-319.
[546] Gilpin, B.J., Walker, T., Paine, S.*, et al.* (2020). A large scale waterborne campylobacteriosis outbreak, Havelock North, New Zealand. *Journal of Infection, 81*(3), 390-395. https://doi.org/10.1016/j.jinf.2020.06.065
[547] Kuhn, K.G., Hvass, A.K., Christiansen, A.H.*, et al.* (2021). Sexual contact as risk factor for campylobacter infection, Denmark. *Emerging Infectious Diseases, 27*(4), 1133-1140. https://doi.org/10.3201/eid2704.202337
[548] Baker, M.G., Sneyd, E., & Wilson, N.A. (2007). Is the major increase in notified campylobacteriosis in New Zealand real? *Epidemiology and Infection, 135*(1), 163-170. https://doi.org/10.1017/S0950268806006583; Ministry of Health. (2021). Notifiable diseases. Retrieved 23 July, 2021, from https://www.health.govt.nz/our-work/diseases-and-conditions/notifiable-diseases

symptomatic.[549] However, many people who experience campylobacteriosis will clear the infection without having visited a health professional, so will not be captured in notified cases.

In 2005, MPI initiated a campylobacteriosis sentinel surveillance site.[550] This site has provided information on the epidemiology of *Campylobacter* in Aotearoa New Zealand, including source attribution studies that have identified poultry as the primary source of disease in urban areas.[551] Evidence from this surveillance also suggested that ruminants are a more important source of human illness in rural areas.[552] Research continues to highlight poultry as a key source of infection, while identifying other sources by examining source attribution and spatial distribution.[553] There is also surveillance of the incidence of *Campylobacter* through the National Microbiological Database. This measures levels of *Campylobacter* in processed chicken.

Figure 21: Cobb chicken pictured in a commercial shed in Aotearoa New Zealand. Cobb and Ross are the breeds commercially farmed for meat in Aotearoa New Zealand.

Prevalence of campylobacteriosis over time

Historically, the prevalence of campylobacteriosis in Aotearoa New Zealand was much higher than it is now. Prevalence peaked in 2006, and in August that year MPI published its first *Campylobacter Risk Management Strategy*.[554] Voluntary biosecurity interventions by the poultry industry and changes to slaughter and processing, together with the implementation the MPI strategy, led to an approximately 50% reduction in incidence of campylobacteriosis during 2006-2008.[555] Interventions were both at the regulatory and industry level, including an introduction of mandatory targets for *Campylobacter* contamination levels on poultry carcasses after processing.[556]

[549] Ministry of Health. (2017). Campylobacteriosis. Retrieved 23 July, 2021, from https://www.health.govt.nz/our-work/diseases-and-conditions/communicable-disease-control-manual/campylobacteriosis

[550] Bolwell, C., Gilpin, B., Campbell, D., *et al.* (2015). Evaluation of the representativeness of a sentinel surveillance site for campylobacteriosis. *Epidemiology & Infection, 143*(9), 1990-2002. https://doi.org/10.1017/S0950268814003173

[551] Mullner, P., Spencer, S.E.F., Wilson, D.J., *et al.* (2009). Assigning the source of human campylobacteriosis in New Zealand: A comparative genetic and epidemiological approach. *Infection, Genetics and Evolution, 9*(6), 1311-1319. https://doi.org/10.1016/j.meegid.2009.09.003

[552] Liao, S.-J., Marshall, J., Hazelton, M.L., *et al.* (2019). Extending statistical models for source attribution of zoonotic diseases: A study of campylobacteriosis. *Journal of the Royal Society Interface, 16*(150), 20180534. https://doi.org/10.1098/rsif.2018.0534

[553] Spencer, S., Marshall, J., Pirie, R., *et al.* (2012). The spatial and temporal determinants of campylobacteriosis notifications in New Zealand, 2001–2007. *Epidemiology and Infection, 140*(9), 1663-1677. https://doi.org/10.1017/S0950268811002159; Spencer, S.E., Marshall, J., Pirie, R., *et al.* (2011). The detection of spatially localised outbreaks in campylobacteriosis notification data. *Spatial and spatio-temporal epidemiology, 2*(3), 173-183. https://doi.org/10.1016/j.sste.2011.07.008

[554] Ministry for Primary Industries. (2017). *Campylobacter Risk Management Strategy*. Wellington, NZ: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/22375/direct

[555] Sears, A., Baker, M.G., Wilson, N., *et al.* (2011). Marked campylobacteriosis decline after interventions aimed at poultry, New Zealand. *Emerging Infectious Diseases, 17*(6), 1007. https://doi.org/10.3201/eid1706.101272

[556] Ibid.

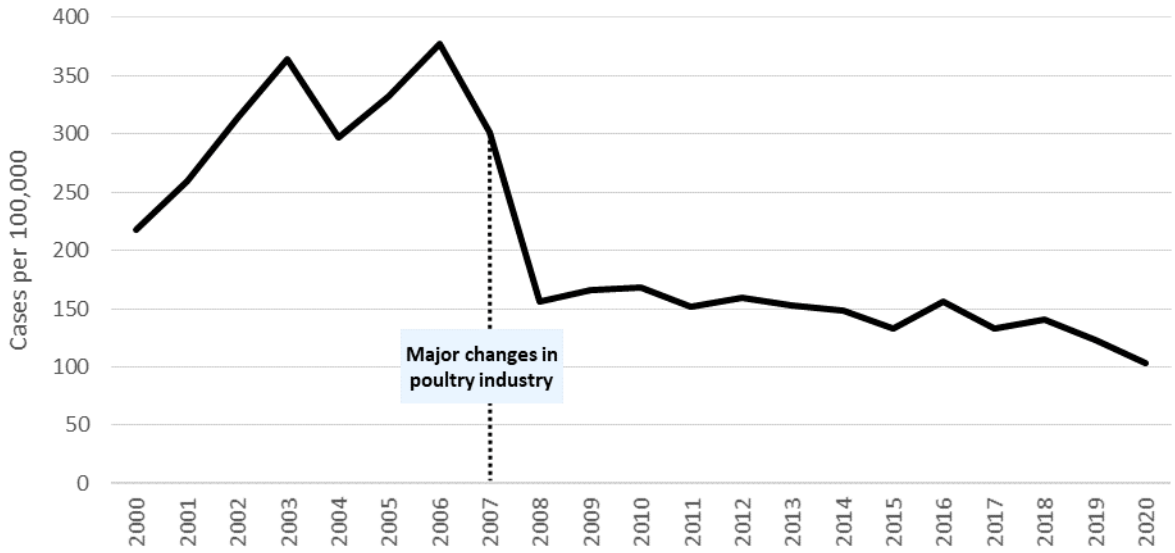

Figure 22: Notified cases of campylobacteriosis per 100,000 in Aotearoa New Zealand from 2000-2020. Public Health Surveillance Data from ESR and the Ministry of Health. Denominator data from Stats NZ mid-year population estimates.

The prevalence of campylobacteriosis (excluding major, non-foodborne outbreaks) has continued to trend down over the last ten years, though at a much slower pace (Figure 22), despite increasing poultry consumption per capita. Prevalence in Aotearoa New Zealand is still high when compared with many other developed countries (Figure 24).

The prevalence of campylobacteriosis (excluding major, non-foodborne outbreaks) has **continued to trend down** over the last ten years, though at a much slower pace.

Prevalence in Aotearoa New Zealand is **still high** when compared with many other developed countries.

Further action in the poultry industry is underway

There are many routes of infection of poultry with *Campylobacter* throughout the production process, which can lead to campylobacteriosis in humans (see Table 8).

Table 8: Examples of sources of *Campylobacter* infection throughout the production stages of poultry meat in Aotearoa New Zealand.

Production stage	Examples of sources of *Campylobacter* infection	Significance
Breeding	*Campylobacter* may be present in breeder flock and eggs may be contaminated during development or through environmental contamination during or after hatching. Transport from breeders to farms also presents risks of infection spread – through transport methods, machinery and personnel.	Risk for direct infection with farm workers. Risk amplifies downstream.
On-farm	Infection on-farm may come from *Campylobacter* already present in the farm environment or could be introduced from new chicks. Once present *Campylobacter* will quickly spread throughout the flock (due to close proximity of birds, litter, shared water and food sources etc.). Other routes of infection are also possible.	Risk for infection to spread throughout flock and wider farm environment. Risk for direct infection with farm workers. Risk amplifies downstream.
Processing	Poultry may already be infected with *Campylobacter* or be exposed to *Campylobacter* already present in the processing environment. Some processing methods may reduce *Campylobacter* risk (e.g. heating, freezing).	Infection may not be eliminated or may spread.
Consumer	The resulting poultry meat may be contaminated with *Campylobacter*. While *Campylobacter* is killed by heat, undercooked chicken or contamination of other foods with chicken juices provides opportunity for human infection.	Risk of infection in consumer.

Further reduction of allowable *Campylobacter* levels on fresh poultry could lead to further reduction in campylobacteriosis levels.[557] There is currently no vaccine available for *Campylobacter* in poultry, though research continues in this area.[558] Having achieved the MPI campylobacteriosis target of a 10% reduction in prevalence of domestically acquired foodborne campylobacteriosis cases by 2020 from a 2012-2014 baseline, a new target has been set for 2024, aiming for a 20% reduction from a 2017-

Figure 23: Commercial chicken shed in Aotearoa New Zealand within hours of a new cycle of chicks being introduced to the shed.

[557] Baker, M.G., Grout, L., & Wilson, N. (2021). Update on the *Campylobacter* epidemic from chicken meat in New Zealand: The urgent need for an upgraded regulatory response. *Epidemiology and Infection, 149*, 1-10. https://doi.org/10.1017/s095026882000299x

[558] Meunier, M., Guyard-Nicodème, M., Vigouroux, E., *et al.* (2017). Promising new vaccine candidates against *Campylobacter* in broilers. *PLOS One, 12*(11), e0188472. https://doi.org/10.1371/journal.pone.0188472

2019 baseline.[559] The 2020-2021 *Campylobacter Action Plan*[560] outlines how the government, industry and others will continue to work together to reduce the foodborne burden of campylobacteriosis. This includes immediate action to:

- enhance consumer engagement,
- review guidance for on-farm controls, and
- review the National Microbiological Database programme[561] regulatory performance target for meat.

There is further research underway aimed at supporting campylobacteriosis reduction (see Table 9), with the Poultry Industry Association of New Zealand (PIANZ) working alongside MPI to reduce *Campylobacter* levels in poultry. Two major projects have been commissioned through the New Zealand Food Safety Science and Research Centre[562] with the project team including industry, ESR, Massey University and scientists from the Centre.

Table 9: Key research projects on *Campylobacter* in poultry in Aotearoa New Zealand.

Production stage	Research questions and goals
Control on-farm	This study, initiated in 2019, aimed to **better understand on-farm, pre-processing sources for *Campylobacter* contamination in broiler flocks**. The study used a new metabarcoding method (Patrick Biggs, Massey) and also isolates for WGS, in an attempt to link different samples and reveal sources of contamination. Conventional methods of testing can miss *Campylobacter* in samples. The study followed a broiler flock on one farm, taking samples and testing for *Campylobacter* from potential vectors or reservoirs from the previous flock, and hatching, until the final group of chickens were transported off the farm for processing. Of 738 samples tested, 26% (~189) were positive for *Campylobacter*. WGS was undertaken for 199 *C. jejuni* isolates. Preliminary findings suggest that carry-over contamination from the previous flock and ingress via catchers and equipment are important reservoirs and vectors for *Campylobacter* contamination, highlighting potential targets for future mitigation strategies. This matches the literature which shows that worker movement into sheds is the most important vector for *Campylobacter* ingress. There is also increased risk of *Campylobacter* when there are neighbouring broiler farms (but less risk for other nearby livestock). No evidence that wildlife, breeder flock, feed, drinking water or litter is a source of infection.
Control in processing	The goal of this study was to **evaluate and assess the efficacy of current broiler poultry processing steps and interventions in controlling *Campylobacter* numbers**. There are many stages of processing e.g. scalding, plucking, evisceration, rinsing. The project involves a longitudinal study at the processing premises of the three major poultry processors in Aotearoa New Zealand with the goal of identifying steps in the processing chain for further interventions to reduce *Campylobacter* prevalence. The research developed an improved detection method for finding bacteria in poultry rinsate (i.e. the liquid after the carcass has been disinfected). This new method is ten times more sensitive (can detect 20 colony-forming units (CFU) compared with previous sensitivity of 200 CFU). When compared with the previous National Microbiological Database method, the new method detected *Campylobacter* in 2.8 times more samples. Current primary processing steps result in six-fold reduction in *Campylobacter* numbers and there is no detection on 76% of samples at end of primary processing. The research will use WGS to assess the effect of antimicrobial processing steps on the types of *Campylobacter* present on the product.

[559] Horn, B., Pattis, I., Armstrong, B*., et al.* (2021). *Annual report concerning foodborne diseases in New Zealand 2020*. Christchurch, NZ: Institute for Environmental Science Research Ltd. Retrieved from https://www.mpi.govt.nz/dmsdocument/47986-Annual-report-concerning-Foodborne-Diseases-in-New-Zealand-2020-Report

[560] New Zealand Food Safety. (2020). *Campylobacter Action Plan 2020–2021*. Wellington: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/42766-Campylobacter-Action-Plan-2020-21

[561] Ministry for Primary Industries. (2021). National Microbiological Database programme for meat. Retrieved 23 July, 2021, from https://www.mpi.govt.nz/food-business/food-monitoring-surveillance/national-microbiological-database-programme-meat/

[562] The NZFSSRC coordinates food safety research and aims to enhance New Zealand's reputation as a source of safe food. It brings together the expertise and resources of three Crown Research Institutes, three Universities and Cawthron Institute in a partnership between government and industry.

Campylobacter in Aotearoa New Zealand compared to overseas jurisdictions

While the prevalence of campylobacteriosis in Aotearoa New Zealand is similar to in Australia, it is substantially higher than many comparable countries (see Figure 24). Prevalence is twice as high as in the EU and more than five times that of Canada and the US. However, comparisons between countries should be interpreted with caution given each country has different approaches to disease notification, diagnosis, and reporting.

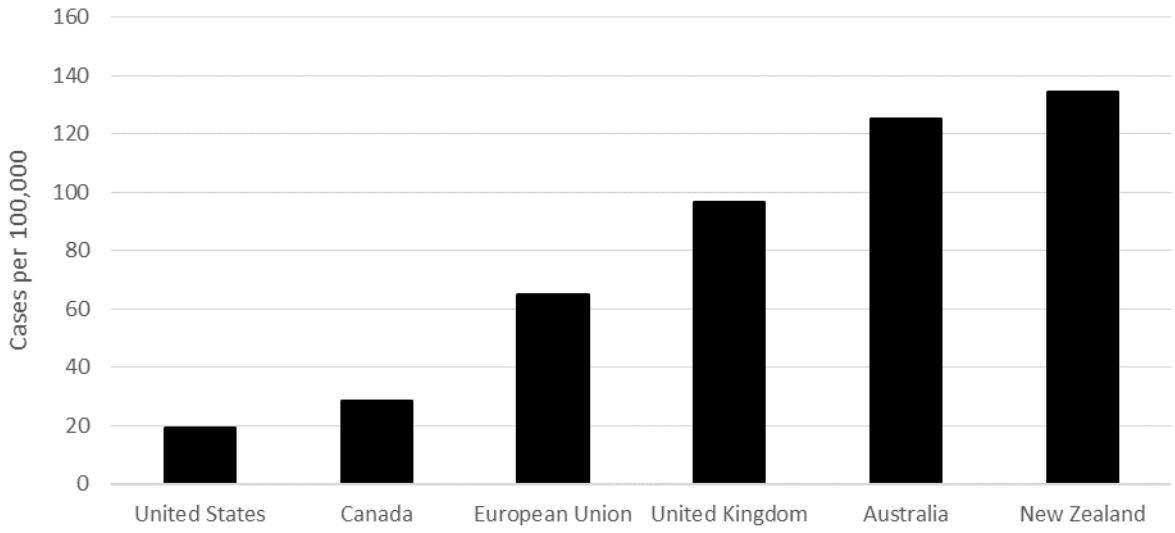

Figure 24: Notified cases of campylobacteriosis per 100,000 in 2017 in the United States (Data: Foodborne Diseases Active Surveillance Network), Canada (Data: Notifiable Diseases Online), European Union (European Food Safety Authority Zoonosis reporting), United Kingdom (Public Health England Zoonoses reporting), Australia (OZFoodNet), and Aotearoa New Zealand.

While the domestic efforts described in the section above are a helpful step in tackling our *Campylobacter* problem, there is scope to look to other jurisdictions with much lower incidence of campylobacteriosis (e.g. the US, Canada and EU) and learn from their experiences.

More experimental research in this area considers the use of novel technologies and strategies such as cold plasma, ultraviolet light, high-intensity light pulses, pulsed electric fields, antimicrobials, and modified atmosphere packaging in processing stages.[563] However, the use of these technologies are not yet operational in commercial processing plants. The use of antimicrobials in these processes would also require careful consideration of potential for AMR.

Resistance data and treatment of campylobacteriosis

AMR in *Campylobacter* spp. in human cases has rapidly increased in Aotearoa New Zealand (see section 4.3.1). While campylobacteriosis does not usually require antibiotics, they may be prescribed in cases where the infection is particularly invasive, severe, or persistent, or for immunocompromised

AMR in ***Campylobacter*** spp. in human cases has **rapidly increased** in Aotearoa New Zealand.

[563] Soro, A.B., Whyte, P., Bolton, D.J., *et al.* (2020). Strategies and novel technologies to control *Campylobacter* in the poultry chain: A review. *Comprehensive Reviews in Food Science and Food Safety, 19*(4), 1353-1377.

patients.[564] Antibiotics used to treat campylobacteriosis in humans include macrolides (e.g. erythromycin, azithromycin) and fluoroquinolones (e.g. ciprofloxacin).[565] The increasing resistance of *Campylobacter* to fluoroquinolones in humans means that resistance to other potential antibiotic treatments, primarily macrolides, is of major concern. *Campylobacter* resistance to macrolides such as erythromycin is currently low in Aotearoa New Zealand, at 0-2% in human patients over the years 2000-2013.[566]

Resistant *Campylobacter* has also been detected in animals, where antibiotics are used to protect animal health. To guide the use of antimicrobials in the animal industry, a survey looking at AMR in agricultural animals was conducted between 2009 and 2010. At that time, AMR in *Campylobacter* isolates collected from young calves and poultry was limited. Among *C. jejuni* isolates (which made up 94.5% of *Campylobacter* isolates in the study), 2.7% of isolates from poultry were resistant to ciprofloxacin/nalidixic acid and streptomycin resistance was detected in 8.2% of calf isolates and 1% of poultry isolates.[567]

Resistant ***Campylobacter*** has also been detected in animals, where antibiotics are used to protect animal health.

Resistance in animals has implications for human health, given that *Campylobacter* is zoonotic. In 2014, drug-resistant *C. jejuni* sequence type 6964 (ST-6964) emerged in poultry in three different North Island poultry companies. The lineage was resistant to tetracycline and fluoroquinolones.[568] In 2015, testing found this sequence type in human patients in both the North and South Islands.[569] The isolates of *Campylobacter* tested in patients found that 15.5% of the isolates were resistant to ciprofloxacin (a fluoroquinolone), 14.5% to tetracycline, and 13.5% were resistant to both.[570] In Tāmaki Makuarau Auckland, the occurrence of the drug resistant strain was highest, with around one third of cases involving the drug resistant strain ST-6964.[571]

Resistance may also be present in *Campylobacter* found in other animals in Aotearoa New Zealand. For example, there is evidence in other countries of drug-resistant isolates of *C. jejuni* in beef cattle that are transmissible to humans.[572] There is also presence of AMR in *Campylobacter* isolates in sheep.[573]

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[564] Williamson, D., Dyet, K., & Heffernan, H. (2015). *Antimicrobial resistance in human isolates of Campylobacter jejuni, 2015*. Porirua, NZ: ESR.
[565] Whitehouse, C.A., Zhao, S., & Tate, H. (2018). Antimicrobial resistance in *Campylobacter* species: Mechanisms and genomic epidemiology. In Sariaslani and Gadd (Eds.), *Advances in Applied Microbiology* (Vol. 103, pp. 1-47): Academic Press.
[566] Williamson, D., Dyet, K., & Heffernan, H. (2015). *Antimicrobial resistance in human isolates of Campylobacter jejuni, 2015*. Porirua, NZ: ESR.
[567] Heffernan, H., Wong, T.L., Lindsay, J., *et al.* (2011). *A baseline survey of antimicrobial resistance in bacteria from selected New Zealand foods, 2009-2010*. Wellington, NZ: Ministry of Agriculture and Fisheries.
[568] French, N., Zhang, J., Carter, G., *et al.* (2019). Genomic analysis of fluoroquinolone- and tetracycline-resistant *Campylobacter jejuni* sequence type 6964 in humans and poultry, New Zealand, 2014–2016. *Emerging Infectious Diseases, 25*(12), 2226. https://doi.org/10.3201/eid2512.190267
[569] Williamson, D., Dyet, K., & Heffernan, H. (2015). *Antimicrobial resistance in human isolates of Campylobacter jejuni, 2015*. Porirua, NZ: ESR.
[570] Ibid.
[571] Ibid.
[572] Cha, W., Mosci, R.E., Wengert, S.L., *et al.* (2017). Comparing the genetic diversity and antimicrobial resistance profiles of Campylobacter jejuni recovered from cattle and humans. *Frontiers in Microbiology, 8*, 818. https://doi.org/10.3389/fmicb.2017.00818; Lawrence, K., Wakeford, L., Toombs-Ruane, L., *et al.* (2019). Bacterial isolates, antimicrobial susceptibility and multidrug resistance in cultures from samples collected from beef and pre-production dairy cattle in New Zealand (2003–2016). *New Zealand Veterinary Journal, 67*(4), 180-187. https://doi.org/10.1080/00480169.2019.1605943
[573] Rivas, L., Dupont, P.-Y., Gilpin, B., *et al.* (2021). Prevalence and genotyping of *Campylobacter jejuni* and *Campylobacter coli* from ovine carcasses in New Zealand. *Journal of Food Protection, 84*(1), 14-22. https://doi.org/10.4315/jfp-20-220

AMR in *Campylobacter* is also a concern in other countries.[574] In particular, increasing resistance to fluoroquinolone antibiotics in human patients has led to restrictions in fluoroquinolone use in poultry in many countries. In Aotearoa New Zealand, fluoroquinolones are still used in companion and farm animals.[575]

Campylobacteriosis link with Guillain-Barré syndrome

Campylobacter is the key trigger of the autoimmune disorder Guillain-Barré syndrome, though the precise mechanism is not understood and there are also other triggers.[576] Infection with *C. jejuni* in particular has been associated with Guillain-Barré syndrome.[577]

Guillain-Barré syndrome symptoms include muscle weakness and paralysis of the limbs, face, or respiratory system. While most people recover from the disorder, around 20-30% may have some permanent weakness and around 5% of cases are fatal.[578] Similar to COVID-19 and rheumatic heart disease, the burden of disease outlasts the acute phase of infection.

In Aotearoa New Zealand, prevalence of Guillain-Barré syndrome declined following the introduction of campylobacteriosis controls in 2006-2007.

In Aotearoa New Zealand, prevalence of Guillain-Barré syndrome declined following the introduction of campylobacteriosis controls in 2006-2007.[579] Since 2008, prevalence of both campylobacteriosis and Guillain-Barré syndrome have slightly trended down (Figure 25).

[574] Bolinger, H., & Kathariou, S. (2017). The current state of macrolide resistance in *Campylobacter* spp.: Trends and impacts of resistance mechanisms. *Applied and environmental microbiology, 83*(12), e00416-00417. https://doi.org/10.1128/AEM.00416-17

[575] The Agricultural Compounds and Veterinary Medicines Team (New Zealand Food Safety). (2020). Antibiotic sales analysis 2018. Wellington, New Zealand: Ministry for Primary Industries; Agricultural Compounds and Veterinary Medicines Team. [in press] 2019 Antibiotic agricultural compound sales analysis; The Agricultural Compounds and Veterinary Medicines Team (New Zealand Food Safety). (2020). Antibiotic sales analysis 2018. Wellington, New Zealand: Ministry for Primary Industries; Lane, R., & Briggs, S. (2014). Campylobacteriosis in New Zealand: Room for further improvement. New Zealand Medical Journal, 127(1391), 6-9.

[576] Wachira, V.K., Peixoto, H.M., & de Oliveira, M.R.F. (2019). Systematic review of factors associated with the development of Guillain–Barré syndrome 2007–2017: what has changed? *Tropical Medicine & International Health, 24*(2), 132-142. https://doi.org/10.1111/tmi.13181

[577] Whitehouse, C.A., Zhao, S., & Tate, H. (2018). Antimicrobial resistance in *Campylobacter* species: Mechanisms and genomic epidemiology. In Sariaslani and Gadd (Eds.), *Advances in Applied Microbiology* (Vol. 103, pp. 1-47): Academic Press.

[578] Shahrizaila, N., Lehmann, H.C., & Kuwabara, S. (2021). Guillain-Barré syndrome. *The Lancet, 397*(10280), 1214-1228. https://doi.org/10.1016/S0140-6736(21)00517-1

[579] Baker, M.G., Kvalsvig, A., Zhang, J.*, et al.* (2012). Declining Guillain-Barré syndrome after campylobacteriosis control, New Zealand, 1988–2010. *Emerging Infectious Diseases, 18*(2), 226. https://doi.org/10.3201/eid1802.111126

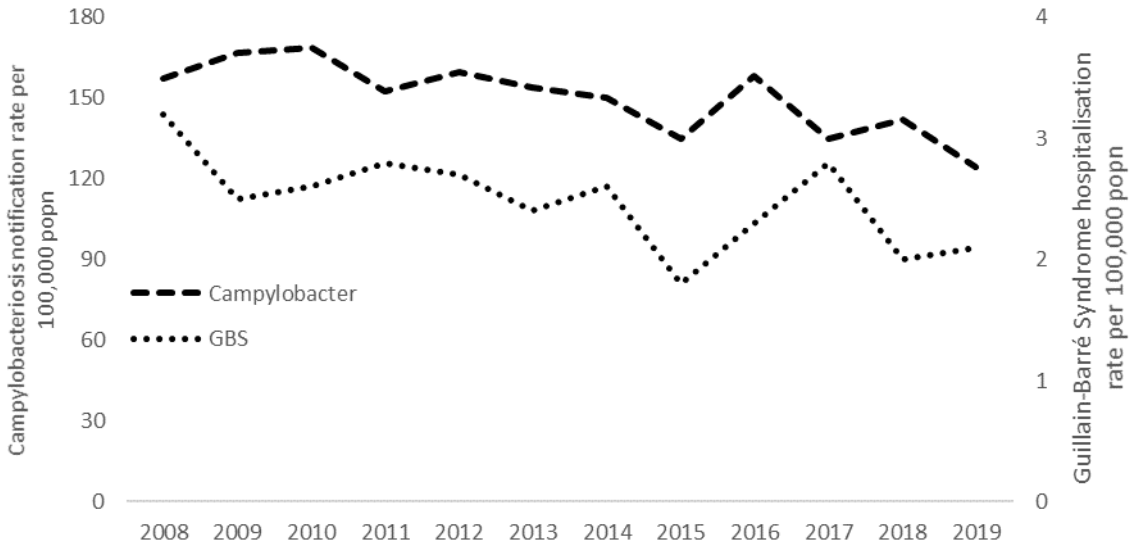


Figure 25: Cases per 100,000 population in Aotearoa New Zealand of campylobacteriosis notification and Guillain-Barré syndrome hospitalisations between 2008-2019.

A waterborne outbreak

While poultry meat is the major driver of campylobacteriosis, there have been highly publicised major outbreaks linked to other sources, most notably the 2016 large-scale waterborne campylobacteriosis outbreak in Karanema Havelock North.[580]

On the morning of Friday 12 August 2016, the Hawke's Bay District Health Board was notified that the Karanema Havelock North water supply was likely to be contaminated. *E. coli* was detected in a water sample, accompanied by an increase in campylobacteriosis notifications. Meanwhile, a pharmacist reported unusually high numbers of requests for anti-diarrhoeal medication.[581] The untreated water supply was not only contaminated with *E. coli*, but also with *C. jejuni*. The DHB issued a 'boil water' notice and commenced chlorination of the water supply. Over a few days, thousands of people in Karanema Havelock North fell ill with gastroenteritis, and a further 1,000 people outside the town also became ill.

In total, 953 cases were notified, but up to **an estimated 8,320 people** could have contracted campylobacteriosis in the outbreak.

In total, 953 cases were notified (Figure 26), but up to an estimated 8,320 people could have contracted campylobacteriosis in the outbreak.[582] Four people died and three people developed

[580] Gilpin, B.J., Walker, T., Paine, S., *et al.* (2020). A large scale waterborne campylobacteriosis outbreak, Havelock North, New Zealand. *Journal of Infection, 81*(3), 390-395. https://doi.org/10.1016/j.jinf.2020.06.065
[581] Vicary, D., Salman, S., Jones, N., *et al.* (2020). Hawke's Bay pharmacists' activities during a *Campylobacter* contamination of public water supply in Havelock North during 2016. *Journal of Primary Health Care, 12*(2), 122-128.
[582] Gilpin, B.J., Walker, T., Paine, S., *et al.* (2020). A large scale waterborne campylobacteriosis outbreak, Havelock North, New Zealand. *Journal of Infection, 81*(3), 390-395. https://doi.org/10.1016/j.jinf.2020.06.065

Guillain-Barré syndrome.[583] This outbreak – the largest ever recorded for *Campylobacter* – comprised approximately 13% of all notified campylobacteriosis cases in Aotearoa New Zealand in 2016 and was a driver in making 2016 the year with the highest number of notified cases since 2007.[584]

WGS played an important role in identifying the source and determining the size of the outbreak. Genotyping revealed a conclusive link between drinking water, sheep faeces on paddocks adjacent to a shallow aquifer, and isolates from confirmed human cases.[585] These linked genotypes provided strong evidence for the source of the outbreak: heavy rainfall had swept sheep faeces, containing *C. jejuni*, into a nearby shallow untreated aquifer, which in turn supplied contaminated drinking water to people in the town of Karanema Havelock North. WGS also allowed geographically and temporally separated isolates to be linked to the outbreak (alongside robust, standardised epidemiology). WGS also revealed that very little person-to-person transmission occurred, as there was only one genomically linked case detected after the outbreak resolved.

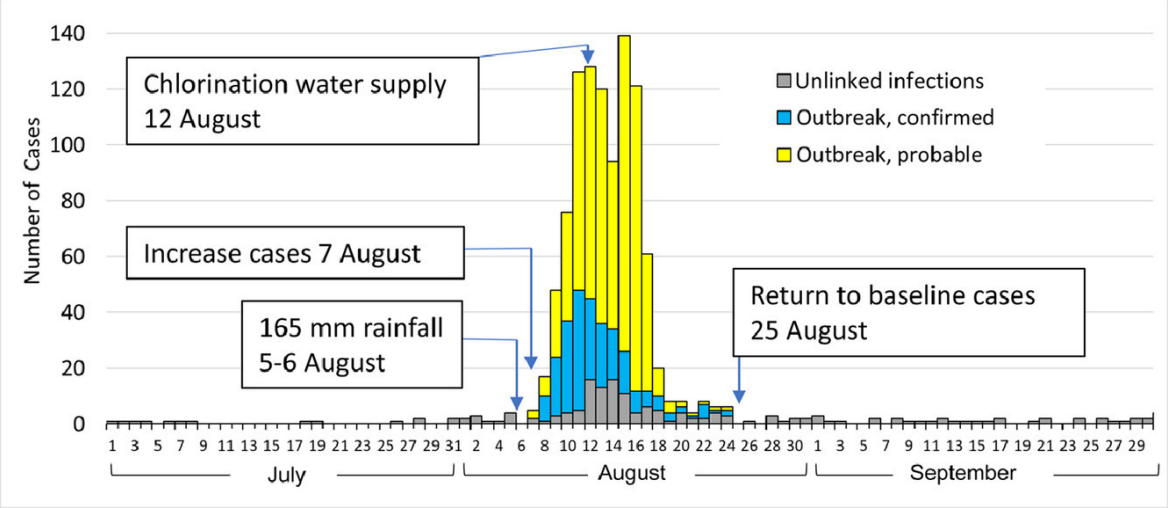


Figure 26: Campylobacteriosis cases in the Hawke's Bay from July to September 2016 graphed according to onset of symptoms.[586]

This outbreak highlights the value and utility of WGS in early detection and determination of the source and scale of outbreaks. It also underscores the importance of continuing to isolate and genotype pathogens in addition to culture-independent diagnostic testing.

The total economic costs associated with this outbreak were estimated to be in excess of NZ$21 million.[587] While the disease burden from waterborne sources is estimated to be low compared with other sources,[588] appropriate management of waterways and treatment of drinking water are some of the many ways that incidence of campylobacteriosis in humans can be reduced. Intensification of farming is likely to increase risks to water supplies from farms and while sheep and other animals

[583] Pattis, I., Lopez, L., Cressey, P., *et al.* (2017). *Foodborne disease in New Zealand 2016*. Christchurch, NZ: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/19700-Annual-report-concerning-foodborne-disease-in-New-Zealand-2016
[584] Institute of Environmental Science and Research Limited (ESR). (2020). Public health surveillance: Surveillance reports. Retrieved 13 August, 2021, from https://surv.esr.cri.nz/surveillance/surveillance.php
[585] Gilpin, B.J., Walker, T., Paine, S., *et al.* (2020). A large scale waterborne campylobacteriosis outbreak, Havelock North, New Zealand. *Journal of Infection, 81*(3), 390-395. https://doi.org/10.1016/j.jinf.2020.06.065
[586] Ibid.
[587] Moore, D., Drew, R., Davies, P., *et al.* (2017). *The economic costs of the Havelock North August 2016 waterborn disease outbreak*. Ministry of Health. Retrieved from https://www.moh.govt.nz/NoteBook/nbbooks.nsf/0/3232817F4C13AE6CCC25820E0072CCBC/$file/havelock_north_outbreak_costing_final_report_-_august_2017.pdf
[588] Lake, R.J., Campbell, D.M., Hathaway, S.C., *et al.* (2021). Source attributed case-control study of campylobacteriosis in New Zealand. *International Journal of Infectious Diseases, 103*, 268-277. https://doi.org/10.1016/j.ijid.2020.11.167

can be vaccinated against *Campylobacter*, this is of variable efficacy, and other pathogens can also cause similar issues (e.g. *E. coli*, *Cryptosporidium*).[589]

Indeed, basic public health measures around securing safe water sources are key to prevention in this case. The Havelock North Drinking Water Inquiry recommended establishing a drinking water regulator alongside mandated universal treatment for all water supplies with an appropriate residual disinfectant (e.g. chlorine).[590]

[589] Menzies, P.I. (2012). Vaccination programs for reproductive disorders of small ruminants. *Animal Reproduction Science, 130*(3), 162-172. https://doi.org/10.1016/j.anireprosci.2012.01.010

[590] Government Inquiry into Havelock North Drinking Water. (2017). *Report of the Havelock North drinking water inquiry: Stage 2*. Retrieved from https://www.dia.govt.nz/diawebsite.nsf/Files/Report-Havelock-North-Water-Inquiry-Stage-2/$file/Report-Havelock-North-Water-Inquiry-Stage-2.pdf

3.7 Summary

The Aotearoa New Zealand infectious disease context is unique – we are a relatively small island nation in the Pacific, with a highly mobile population and strong biosecurity. As a country, we have had some successes eliminating certain infectious diseases (see section 3.3.2) but nonetheless, they remain a prominent feature of the health riskscape.

There are a range of infectious diseases that affect our people, animals and plants and part three has explored a selection of these through a series of case studies.

Sepsis and HAIs demonstrate how infectious disease can have long-term health, economic and social impacts on people. These impacts are not felt equally by all parts of society, with inequitable infectious disease burden – for Māori and Pacific peoples in particular – a key issue to address. This will mean addressing inequities in access and quality of care, as well as focusing on wider social determinants of health.

Infectious disease also affects agriculturally important animals and plants, such as the *Mycoplasma bovis* outbreak impacting cattle and the Psa incursion resulting in disastrous consequences for the kiwifruit industry.

Our natural and cultural heritage is also at risk, with pathogens such as kauri dieback and myrtle rust infecting taonga species.

Some infectious diseases are transmitted across the human-animal-environment interface. We provide a brief overview of zoonotic, foodborne, and waterborne infectious diseases, with brief case studies on STEC and *Salmonella*, and a close look at *Campylobacter* to illustrate the connections between human, animal, and environmental health.

These case studies and accompanying discussion highlight existing and emerging threats, clearly illustrating the key message of part three: we cannot ignore infectious disease.

This overarching message is certainly hammered home by the infectious disease currently occupying our collective global attention: COVID-19. The emergence of COVID-19 underscores the importance of a globally coordinated response to these threats; no one is safe until we are all safe. This means that in addition to tackling infectious disease threats on-the-ground in Aotearoa New Zealand, it will be important to connect to international efforts.

Among the variety of infectious diseases threatening the wellbeing of our people, animals and plants, some display the worrying trend of AMR. In the next part, we take a closer look at the evidence for AMR in people, animals, plants and the wider environment.

4 Part four: Drug-resistant infections in Aotearoa New Zealand

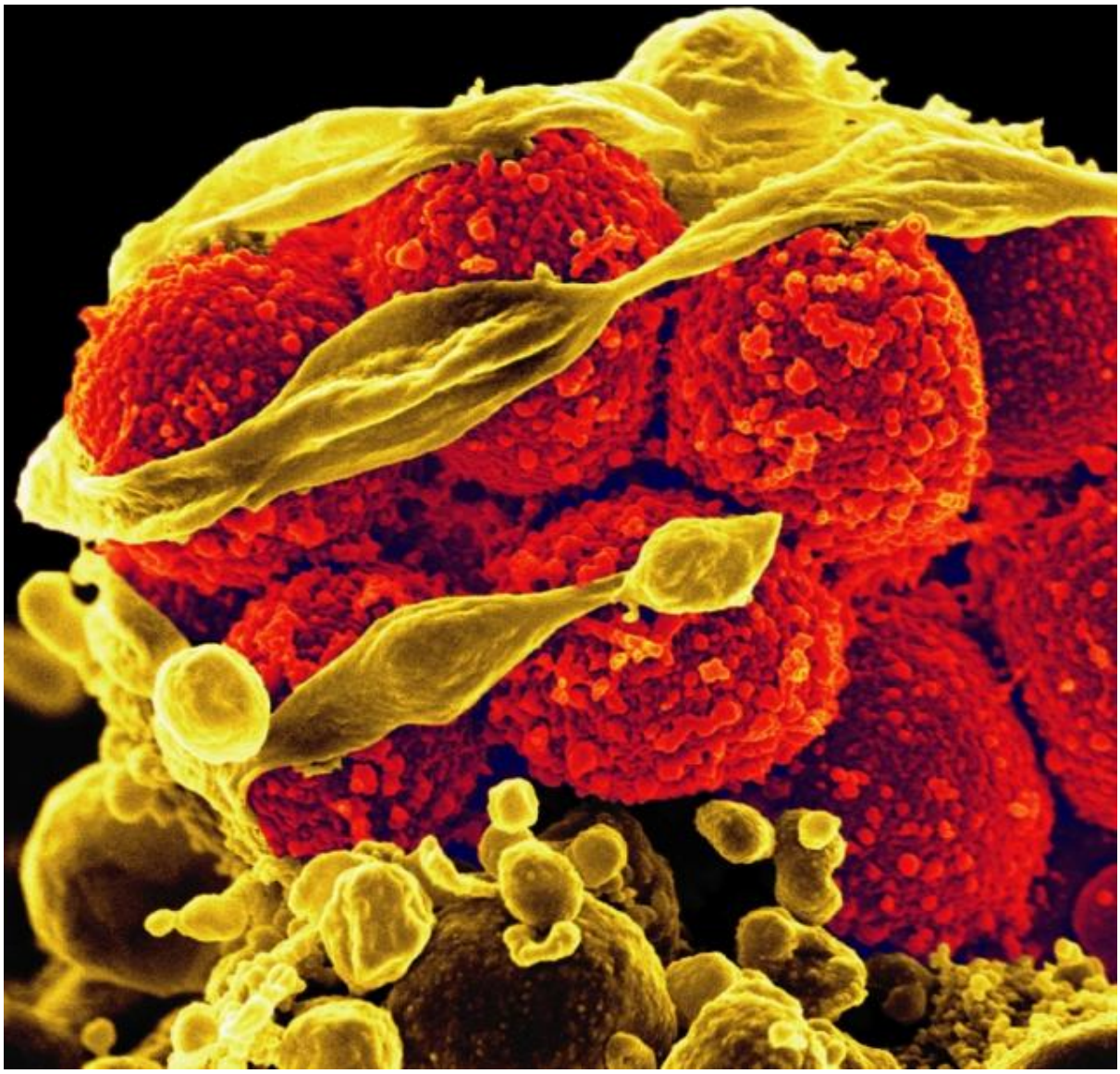


Figure 27: Scanning electron microscope image showing methicillin-resistant *Staphylococcus aureus* (MRSA, in red) escaping from a human immune cell (yellow). Image credit: NIAID/Flickr (CC BY 2.0).

4.1 Overview

AMR is a present and pressing challenge that already affects human, animal, and plant health in Aotearoa New Zealand. Available evidence suggests the prevalence of some resistant microbes is rising. Part four describes AMR and antimicrobial use in Aotearoa New Zealand. While humans, animals, plants, and the environment are explored in separate sections, the connections between these spheres, as described in section 2.3.3, should be noted – a holistic approach drawing on both One Health and kotahitanga (see section 2.3.4).

Part four begins by detailing what is known about AMR in Aotearoa New Zealand. While useful information about the proportion of infections caused by AMR pathogens can be derived from available data, there are a lot of knowledge gaps. These gaps, which are particularly substantial for plants and the environment, but also considerable for animals and humans, are noted where relevant.

This is followed by an overview of the level of antimicrobial use across human, animal, and plant health, and what is known about the presence of antimicrobials in the environment. As outlined in section 2.3.2, use of antimicrobials is a key driver of the development of AMR, so it is important to evaluate our current use patterns. As with AMR data, there are considerable knowledge gaps. Gaps relate to both the quantity and the quality of antimicrobial use.

We then provide four case studies to illustrate the impacts of drug-resistant pathogens that impact human health in Aotearoa New Zealand. The case studies we cover follow:

- MRSA, a gram-positive bacterium that causes a range of infections including of the skin and blood (section 4.5).
- A range of gram-negative bacteria that cause drug-resistant UTIs (section 4.6)
- *Mycobacterium tuberculosis*, which causes TB (section 4.7).
- *Neisseria gonorrhoeae,* a bacterium that causes the STI gonorrhoea (section 4.8).

We finish with a summary of part four, which includes brief commentary on current activities to mitigate AMR, leading into part five where solutions to the challenges posed by AMR and infectious diseases are explored in detail.

4.2 Key messages

- At the moment, drug-resistant pathogens are less prevalent in Aotearoa New Zealand compared with most countries. However, AMR already presents challenges to human, animal, and plant health, and available evidence suggests the prevalence of some resistant pathogens is rising.

- AMR surveillance in humans is often sporadic, and surveillance isn't routinely conducted in animals, plants, or the environment. Collection and reporting of data on the quantity and quality of antimicrobial use could be strengthened substantially. We need systematic, integrated, and regular surveillance of antimicrobial-resistant organisms, AMR genes, and antimicrobial use to inform and evaluate action across the human, animal, plant, and environmental spheres.

- The drivers of AMR are present in Aotearoa New Zealand. We need to act now to preserve our low AMR levels as best as possible and build resilience.

- Aotearoa New Zealand has very high consumption of antimicrobials in human health compared with other developed countries. This high use is in part driven by inappropriate use of antimicrobials – for example, the use of antibiotics in patients with viral infections. However, some New Zealanders, such as Māori and Pacific peoples, are under prescribed antimicrobials. Any attempts to decrease our use of antimicrobial drugs should ensure that those decreases occur in the right places (i.e. where antimicrobial drugs are being used inappropriately), not among people who could benefit from greater access.

- Our use of antimicrobials in agriculturally important animals is low compared with other countries, but AMS practices in animal health could still be improved, including through increased uptake of non-antimicrobial solutions to prevent disease in farming. While antimicrobial use in companion animals accounts for a small portion of total antimicrobial use in Aotearoa New Zealand, we need better data to better understand relative use in this sector.

- We don't have a comprehensive picture of antimicrobial use and AMR in plants, nor do we have good data on the presence of resistant organisms, resistant genes, and antimicrobial contaminants in the environment. What's more, we don't have a good understanding of how AMR and antimicrobial use in plants and the environment links to human and animal health – more research is needed.

- In addition to AMR that develops in Aotearoa New Zealand, MDROs from overseas regularly enter Aotearoa New Zealand from overseas, threatening our low levels of drug resistance.

4.3 Antimicrobial resistance: Are there drug-resistant infections in Aotearoa New Zealand?

As outlined in section 2.4.2, the threat of AMR is escalating worldwide. Although resistant pathogens may not yet be as prevalent in Aotearoa New Zealand as they are in many places overseas, available evidence suggests the prevalence of some resistant pathogens is rising. We need to act now.

Tracking the presence and transmission of antimicrobial-resistant microbes (or the genes that confer resistance) is critical to understanding the threat they pose, monitoring trends over time, and reducing harm caused to people, animals, and plants. In this section, building on section 2.4.2 which describes the international context, we summarise the local evidence for antimicrobial-resistant organisms in humans, animals, plants, and the wider environment. In many cases, data is dated or incomplete. Data gaps are noted where relevant. Solutions relating to improving detection are explored in section 5.4.

4.3.1 Evidence of antimicrobial resistance in human pathogens in Aotearoa New Zealand

Antimicrobial-resistant pathogens account for an increasing number or proportion of infections across six pathogens or pathogen groups in Aotearoa New Zealand, based on screening, surveillance, and routine susceptibility testing results reported by ESR. Particularly concerning is the growing number of isolates with acquired carbapenemases, with these pathogens able to resist the effects of nearly all known antibiotics (see section 2.4.2 and below for details).

For six other pathogens reported on by ESR, the number or proportion of infections caused by antimicrobial-resistant pathogens is relatively stable. This includes group A *Streptococcus*, where AMR is not a major concern at present. However, any changes in resistance prevalence should be watched for closely given the significance this would have for patients relying on prophylactic antibiotics to prevent rheumatic fever and escalation to rheumatic heart disease (see the rheumatic fever evidence synthesis on the OPMCSA website).

This section begins with a brief case vignette describing the real-world impact of AMR on a New Zealander. This is followed by a brief description of how ESR gathers information about AMR in humans in Aotearoa New Zealand. We then describe AMR trends in Aotearoa New Zealand based on available information gathered by ESR (and where applicable, peer-reviewed literature). For each pathogen, where relevant, an indication is provided as to whether the pathogen is deemed by WHO as being of high priority for the development of new antimicrobials, and whether it is classified as an ESKAPE pathogen (see section 2.4.2). This section then explores data blind spots and barriers to developing a more comprehensive AMR dataset for human health in Aotearoa New Zealand and concludes with the findings of a modelling study that aims to predict possible changes in AMR levels out to 2030. Case studies on AMR pathogens and their impacts on human health are covered in detailed case studies in sections 4.5, 4.6, 4.7 and 4.8.

Case vignette: An Aotearoa New Zealand woman with cystic fibrosis

Mrs R is a 34-year-old woman with severe cystic fibrosis, who received bilateral lung transplants in 2020. About a week after surgery, she had an episode of pneumonia caused by two bacteria (*E. coli* and *Stenotrophomonas maltophilia*) that were resistant to most commonly used antibiotics. The healthcare team identified antibiotics effective against the infecting bacteria and treatment with them did lead to resolution of her pneumonia.

In 2021, about one year following her lung transplantation, she had recurrence of airway infection due to the same bacteria as before, plus a third bacterium (*P. aeruginosa*). The *E. coli* had become

resistant to all commonly used antibiotics except for meropenem, and the *P. aeruginosa* was resistant to all potentially useful antibiotics except colistin. She was treated with colistin for one month with some benefit.

Because of persistent damage to her transplanted lungs, it is almost impossible for her immune responses plus antibiotic treatment to eliminate the bacteria that have caused these recent lung infections. There are very few antibiotics that can be used to treat future infection with these bacteria. Therefore, further episodes of lung infection with the same bacteria as before pose a severe threat to her health.

Story told with patient's permission.

How is data gathered in Aotearoa New Zealand?

Laboratories throughout the country gather data on AMR in pathogens that infect humans in Aotearoa New Zealand. ESR works to understand national patterns in AMR for a particular pathogen or resistance mechanism, collaborating with healthcare facilities and clinical labs to achieve this.[591] There are a number of ways ESR assesses AMR at the national level:

- ESR receives data on antimicrobial susceptibility from hospital and community diagnostic labs and compiles that data to build a national picture. Hospital and community labs gather susceptibility data in the course of their work, through patient screening and routine susceptibility testing.
  - MDRO screening occurs when patients engaging with healthcare facilities are automatically tested for resistant microbes based on activities or associations that are assessed to put them at greater risk of carrying drug-resistant microbes. Chief among these screening criteria is hospitalisation overseas. But other screening criteria exist too, such as travel to AMR 'hotspot' countries without hospitalisation, or a recent invasive medical procedure. Canterbury DHB's MDRO screening flowchart is included in Figure 29 to demonstrate how hospitals work out who to test.
  - Routine susceptibility testing occurs when, in the course of providing healthcare to patients, the antimicrobial susceptibility of the pathogens causing the patient's infection is tested so that appropriate antimicrobial drugs can be prescribed. This testing occurs for clinically significant organisms where antimicrobial breakpoints are available.
- ESR undertakes susceptibility testing on bacterial pathogens referred to it for epidemiological typing. Currently the susceptibility of invasive isolates of *Streptococcus pneumoniae* and *Neisseria meningitidis* is routinely monitored and the enteric *Salmonella* spp. and *Shigella* spp. are tested every 3-4 years.
- ESR conducts point prevalence surveys, requesting hospital and community labs to refer all samples of a particular pathogen to them so that they can conduct antimicrobial susceptibility testing (AST) and report the proportion of isolates that are resistant to specific antimicrobials (e.g. in 2017 labs were asked to refer all clinical MRSA isolated during a one-month period to ESR for AST and strain characterisation). This data can be annualised.
- ESR continuously monitors AMR in some pathogens or for particular resistance mechanisms of concern, requesting hospital and community diagnostic labs to centrally report and refer all detected instances of a particular resistant pathogen or mechanism (e.g. all detected carbapenemase-producing Enterobacterales, CPEs, are referred to ESR).

[591] Institute of Environmental Science & Research Limited. (2021). Personal communication.

How does antimicrobial susceptibility testing work?

AST is used to determine which antimicrobials are likely to be able to inhibit the growth of a particular pathogen. Traditional culture-based techniques are the mainstay of AST in Aotearoa New Zealand. Once a sample has been collected from a patient, the pathogen is isolated and grown ('cultured') in the presence of antimicrobials. If the pathogen is able to grow, this indicates it is resistant to the antimicrobials that are present. This process typically takes 24 hours.

AST is used both to understand Aotearoa New Zealand's AMR risk profile and inform patient treatments by indicating which antimicrobials are most likely to be effective against the given pathogen. Before receiving AST results, a clinician will often begin a patient's treatment based on local guidelines, particularly where treatment is time-sensitive (e.g. sepsis, see section 3.4). However, once they receive AST results, they can tailor the antimicrobial treatment to the susceptibility profile of the pathogen(s) causing the patient's infection. Increasing the speed of AST can therefore help reduce use of broad-spectrum antimicrobials or antimicrobials that aren't likely to be effective for a given patient – see section 5.4 for more details.

The New Zealand National Antimicrobial Susceptibility Testing Committee, formed in 2017, is part of the New Zealand Microbiology Network.[592] It provides expert advice to diagnostic laboratories across Aotearoa New Zealand, including developing advisory guidelines for reporting antimicrobial susceptibility[593] and recommending minimum lab requirements for the detection of CPEs.[594] It also publishes antibiograms provided by DHBs and labs on its website as they become available.[595] The Committee sends out 'mystery' microbes to labs that they work to identify, honing their detection skills for drug-resistant organisms.

Generally, emerging drug resistance mechanisms are first detected overseas and reported at international conferences and in the scientific literature. When isolates are detected in Aotearoa New Zealand, data is disseminated via the New Zealand Microbiology Network – so people know what to test and look out for – and via the scientific literature.[596] Once numbers start to increase, ESR considers regular reporting.

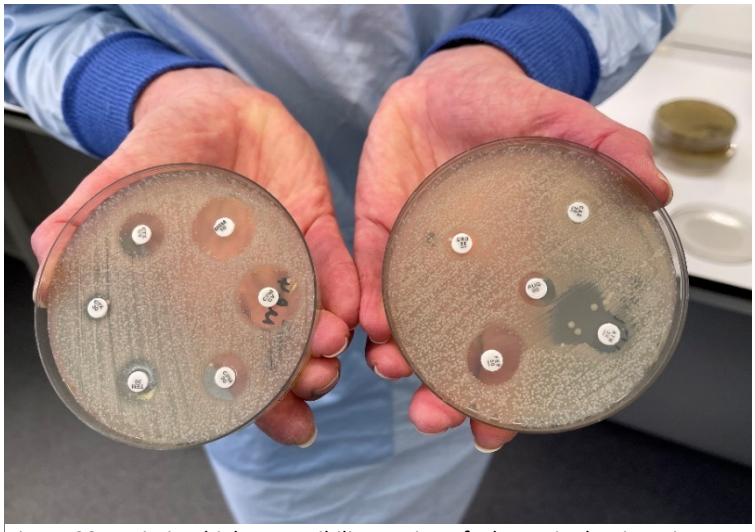


Figure 28: Antimicrobial susceptibility testing of a bacteria that is resistant to multiple antibiotics. Each white disk contains a different antibiotic. When there is clear space around the disk, it means the antibiotic is preventing growth of the bacteria. Note: gloves are not routinely worn for AST work in diagnostic labs.

[592] The New Zealand Microbiology Network. (n.d.). NZ NAC. Retrieved 17 November, 2021, from https://www.nzmn.org.nz/nz-nac/
[593] New Zealand National Antimicrobial Susceptibility Testing Committee, & The Royal College of Pathologists of Australasia. (2020). *Guideline for reporting of antimicrobials for New Zealand microbiology laboratories*. Retrieved from https://www.nzmn.org.nz/assets/NZMN/NZ-version-selective-reporting-July2021.pdf
[594] New Zealand National Antimicrobial Susceptibility Testing Committee. (2021). *Minimum laboratory requirements for the detection of carbapenemase-producing Enterobacterales from clinical samples and screening specimens*. Retrieved from https://www.nzmn.org.nz/assets/NZMN/minimum-laboratory-requirements-for-CPE-detection-March-2021.pdf
[595] The New Zealand Microbiology Network. (n.d.). Antibiograms. Retrieved 17 November, 2021, from https://www.nzmn.org.nz/antibiograms/
[596] Dyet, K. (2021). Personal communication.

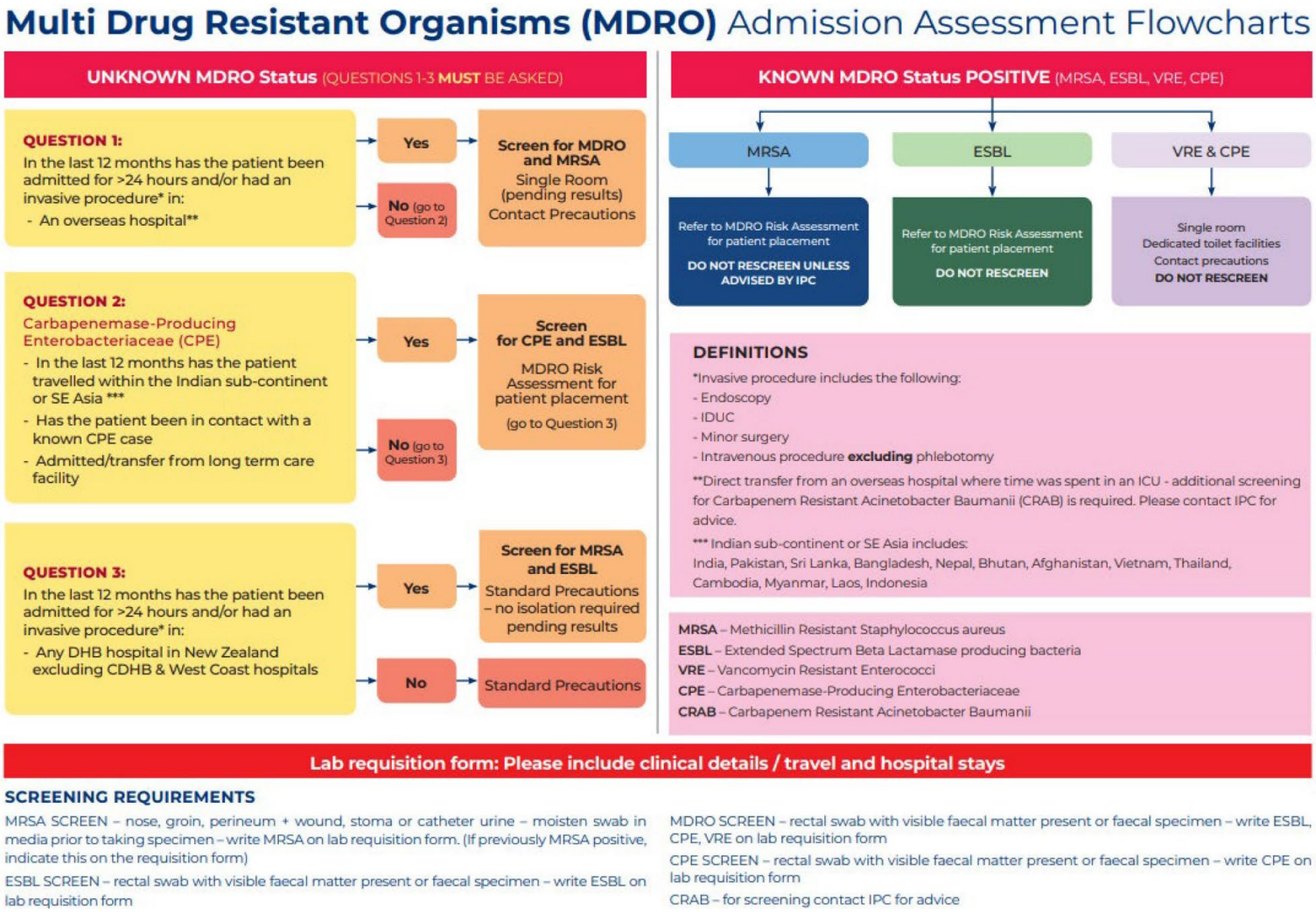


Figure 29: Canterbury DHB's MDRO screening flowchart, 2019. Image credit: Canterbury DHB.

Evidence for AMR in human pathogens in Aotearoa New Zealand

The sections below outline the most recent data for organisms monitored at the national level by ESR, as well as data from peer-reviewed publications. Individual diagnostic labs often also have in-house or regional surveillance and AMR reporting, but this data is not always readily accessible.

In addition to those listed below, penicillin non-susceptible *Streptococcus pyogenes*, organisms with critical emerging resistance mechanisms, and MDROs associated with outbreaks are targeted for enhanced surveillance, but data is not always published by ESR. In the case of penicillin non-susceptible *S. pyogenes*, this is because referring laboratories are yet to detect it.

There are other resistant organisms or mechanisms of concern that aren't monitored systematically by ESR but for which regional data is available (e.g. *Mycoplasma genitalium*[597]). Of particular concern is carbapenem-resistant *Acinetobacter baumannii*, identified by WHO as critically requiring the development of new antimicrobials (see section 2.4.2). Extensively drug-resistant *A. baumannii* is a cause of hospital-acquired infection in many locations worldwide – including neighbouring Pacific islands and territories. An outbreak of infection due to a multidrug-resistant strain of *A. baumannii* occurred in an intensive care burns unit at Middlemore Hospital in 1998-99, although this strain was susceptible to carbapenems.[598] A relatively small number of carbapenem-resistant *A. baumannii* isolates (<50) have been identified in Aotearoa New Zealand in the last decade, with most cases having a history of hospitalisation overseas.[599] This organism isn't currently reported on by ESR, however, detection has increased since 2015 in association with the transnational spread of a single *A. baumannii* strain in the Pacific.[600] *A. baumannii* is discussed further in section 2.4.2.

Enterobacterales and *Pseudomonas aeruginosa* with acquired carbapenemases

Can cause: UTI, intra-abdominal infection, surgical site infection (SSI), bloodstream infection, healthcare-associated pneumonia, sepsis.
AMR trajectory: increasing.
Most recent national data: 2021.
See also section 2.4.2.

Carbapenemases are enzymes that are able to break down a wide range of β-lactam antibiotics, including carbapenem antibiotics (which are broad spectrum). They can be found in Enterobacterales (i.e. CPEs), *Pseudomonas* spp., and other species. They may be collectively referred to as carbapenemase-producing organisms (CPOs). CPOs can be resistant to nearly all known antibiotics, so WHO regards development of new treatments for this group of pathogens as 'critical.'

Enterobacterales (e.g. *Escherichia coli* and *Klebsiella pneumoniae*) are an order of bacteria that commonly inhabit the gut without causing any problems. But if they invade body sites where they do not naturally occur (e.g. bladder, kidneys, bile ducts in the liver, bloodstream) they can cause infection.

P. aeruginosa is an opportunistically pathogenic gram-negative bacteria that is associated with HAIs, particularly in patients fitted with invasive devices or patients with open wounds from surgery or

[597] Anderson, T., Coughlan, E., Werno, A., *et al.* (2017). *Mycoplasma genitalium* macrolide and fluoroquinolone resistance detection and clinical implications in a selected cohort in New Zealand. *Journal of Clinical Microbiology, 55*(11), 3242-3248. https://doi.org/10.1128/JCM.01087-17
[598] Roberts, S.A., Findlay, R., & Lang, S.D.R. (2001). Investigation of an outbreak of multi-drug resistant *Acinetobacter baumannii* in anintensive care burns unit. *Journal of Hospital Infection, 48*(3), 228-232. https://doi.org/10.1053/jhin.2001.0985
[599] Blakiston, M. (2021). Personal communication.
[600] Ibid.

burns. *P. aeruginosa* is found in soil and water, but also spreads via surfaces, hands, and equipment in healthcare settings.

Colistin is a drug of last resort for infections caused by CPOs, but can be toxic to humans, particularly impacting the kidneys and nervous system (including the brain). It is not very effective and expensive – both in terms of dollar cost, and in cost to the patient, who will likely have a longer hospital stay and worse outcome. Resistance to colistin among CPOs has been observed, including in Aotearoa New Zealand.

CPOs can be **resistant to nearly all known antibiotics**… This stark lack of treatment options, coupled with wide international spread over the last decade, make CPOs **one of the foremost AMR threats** facing Aotearoa New Zealand.

This stark lack of treatment options, coupled with wide international spread over the last decade, make CPOs one of the foremost AMR threats facing Aotearoa New Zealand. CPOs are targeted for enhanced surveillance, with labs requested to send all isolates to ESR. The graph below pertains only to CPEs (ESR has not yet reported on *Pseudomonas* spp. – this is a data gap that needs filling).

The first CPE was detected in Aotearoa New Zealand in 2009.[601] Since then, the number of isolates detected has increased substantially. While travel overseas (especially hospitalisation abroad) is a major risk factor for getting infected with a CPE, transmission of CPEs in healthcare and long-term care facilities and in the community has been detected since 2015.[602] Figure 30 shows the rise in CPE detections since 2009, with a dip in 2020 attributed to decreased international arrivals and New Zealanders returning from travel due to the COVID-19 pandemic. In 2021, ESR has reported 41 isolates of CPOs (to 31 October 2021).[603] Of note, locally acquired cases have become increasingly common since 2015.[604]

… evidence suggests that **screening may need to be extended** to anyone who has been overseas to places with high community prevalence of CPEs, and their household contacts.

Patients admitted to hospital in Aotearoa New Zealand are screened for CPEs if they have been in hospital overseas (e.g. see Figure 29 above). However, evidence suggests that screening may need to be extended to anyone who has been overseas to places with high community prevalence of CPEs, and their household contacts. In December 2015, a patient was admitted to hospital in Tāmaki Makaurau Auckland. The patient had not travelled overseas, and so was not screened for CPE. Nearly two weeks later, screening of faeces identified carbapenemase-producing *E. coli*, which the patient likely acquired from household contacts who had travelled, without

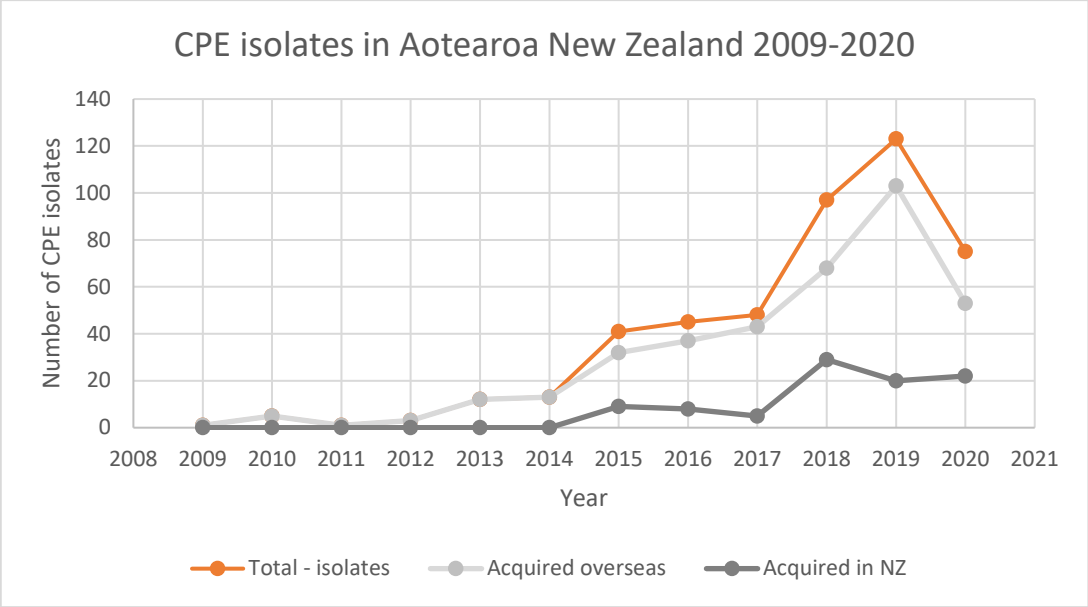
[601] Institute of Environmental Science and Research Limited (ESR). (2014). *Enterobacteriaceae with acquired carbapenemases, 2009-2014*. ESR. Retrieved from https://surv.esr.cri.nz/antimicrobial/AccqEnterobacteriaceae.php

[602] Institute of Environmental Science and Research Limited (ESR). (2015). *Enterobacteriaceae with acquired carbapenemases, 2015*. ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/ACE/2015Carbap.pdf; Howard, J.C., Creighton, J., Heffernan, H., *et al.* (2016). Evidence of transmission of an NDM-5-producing *Klebsiella pneumoniae* in a healthcare facility in New Zealand. *Journal of Antimicrobial Chemotherapy*, dkw498. https://doi.org/10.1093/jac/dkw498

[603] Institute of Environmental Science and Research Limited (ESR). (n.d.). Acquired carbapenemases in Enterobacterales and *Pseudomonas aeruginosa*. Retrieved 2 September, 2021, from https://surv.esr.cri.nz/antimicrobial/AccqEnterobacteriaceae.php

[604] Institute of Environmental Science and Research Limited (ESR). (2020). *Enterobacterales with acquired carbapenemases, 2020*. ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/ACE/2020Carbap.pdf

healthcare contact, to the Indian subcontinent several months earlier.[605] There is also evidence from both Aotearoa New Zealand and Europe that travellers returning from places such as the Indian subcontinent and Southeast Asia are carrying CPEs, despite not having contact with healthcare in



these places.[606]

Figure 30: CPE isolates, 2009-2020. The decrease in 2020 is likely due to decreased international travel in the wake of the COVID-19 pandemic. Data from ESR.

It is likely that CPEs are under-detected in Aotearoa New Zealand, with screening focused on people returning from overseas travel rather than considering possible community transmission,[607] and with some CPEs being difficult to detect using AST.[608] CPEs are not notifiable in Aotearoa New Zealand and there is no other formal national notification process in place. Members of the NZMN will let the network know about outbreaks, but this is voluntary and ad hoc.

Action to limit the spread and mitigate the impacts of CPEs is needed urgently. There have been multiple CPE outbreaks in hospitals[609] and an outbreak related to a food outlet in the Te Whanganui-a-Tara Wellington region.[610] The Australasian Society of Infectious Diseases warns that without prevention measures, CPEs are likely to spread in aged care facilities.[611]

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[605] Blakiston, M., Roberts, S.A., Freeman, J.T., *et al.* (2017). Household transmission of NDM-producing *E. coli* in New Zealand. *The New Zealand Medical Journal, 130*(1452), 63-65.
[606] Blakiston, M., Heffernan, H., Roberts, S., *et al.* (2017). The clear and present danger of carbapenemase-producing Enterobacteriaceae (CPE) in New Zealand: time for a national response plan. *The New Zealand Medical Journal, 130*(1454), 72.
[607] Barratt, R., Brown, L., & O'Callaghan, M. (2017). A challenging outbreak of New Delhi metallo-β-lactamase-5 producing *Klebsiella pneumoniae* in a New Zealand Tertiary Hospital: A case report. *Infection, Disease & Health, 22*(3), 144-149. https://doi.org/10.1016/j.idh.2017.05.001
[608] Howard, J.C., Anderson, T., Creighton, J., *et al.* (2018). Geographical and temporal clustering of OXA-48-producing *Escherichia coli* ST410 causing community-onset urinary tract infection in Christchurch, New Zealand. *Journal of Antimicrobial Chemotherapy, 73*(10), 2900-2901. https://doi.org/10.1093/jac/dky269
[609] Howard, J.C., Creighton, J., Heffernan, H., *et al.* (2016). Evidence of transmission of an NDM-5-producing *Klebsiella pneumoniae* in a healthcare facility in New Zealand. *Journal of Antimicrobial Chemotherapy*, dkw498. https://doi.org/10.1093/jac/dkw498; Barratt, R., Brown, L., & O'Callaghan, M. (2017). A challenging outbreak of New Delhi metallo-β-lactamase-5 producing *Klebsiella pneumoniae* in a New Zealand Tertiary Hospital: A case report. *Infection, Disease & Health, 22*(3), 144-149. https://doi.org/10.1016/j.idh.2017.05.001; Institute of Environmental Science and Research Limited (ESR). (2015). *Enterobacteriaceae with acquired carbapenemases, 2015*. ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/ACE/2015Carbap.pdf
[610] Institute of Environmental Science and Research Limited (ESR). (2020). *Enterobacterales with acquired carbapenemases, 2020*. ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/ACE/2020Carbap.pdf
[611] Australasian Society for Infectious Diseases. (2018). *Minimum specifications for New Zealand's national response plan for Carbapenemase Producing Enterobacteriaceae (CPE)*. Retrieved from https://www.asid.net.au/documents/item/1492

The *New Zealand AMR Action Plan* lists two activities relevant to CPEs, both of which were slated to be undertaken in 2018.[612] The activities related to developing national response plans for the prevention and control of gram-negative MDRO spread (including CPEs), as well as developing an enhanced surveillance programme for those pathogens that encompasses screening, laboratory identification, surveillance, and alerts.

There is currently no national response plan for the prevention and control of CPEs or other gram-negative MDROs, despite the *New Zealand AMR Action Plan* calling for a plan to be developed.[613] A publication from 2017 and a position statement from ASID outline recommendations for a national response to CPEs in Aotearoa New Zealand.[614] The Australasian Society of Infectious Diseases further suggests that setting up a response to CPE would provide a useful framework for managing future AMR threats.

Campylobacter jejuni

Can cause: campylobacteriosis, an infection of the intestines that causes diarrhoea.
AMR trajectory: increasing.
Most recent national data: 2015.
See also section 3.6.2.

WHO priority organism: HIGH

Until 2014, prevalence of fluoroquinolone resistance in *C. jejuni* across Aotearoa New Zealand was low: between 2002 and 2013, prevalence among tested isolates hovered between 1% and 3.6%.[615] In November 2014, ESR was alerted to a possible cluster of fluoroquinolone-resistant campylobacteriosis cases in Tāmaki Makaurau Auckland. A subsequent analysis of 297 isolates from across Aotearoa New Zealand found that 15.5% were resistant to ciprofloxacin (the most commonly prescribed fluoroquinolone) and 14.5% were resistant to tetracycline.[616] The majority of ciprofloxacin-resistant isolates were also resistant to tetracycline. Most resistant isolates were from Tāmaki Makaurau Auckland, Te Whanganui-a-Tara Wellington, and Te Tai Tokerau Northland.

On the basis of this rapid rise in resistance, the analysis called for "ongoing periodic surveillance of AMR in *Campylobacter*."[617] However, nationwide AMR data for *C. jejuni* has not been reported since 2015, [618] which ESR reports was due to monitoring of *Staphylococcus aureus* (see below) being prioritised above *C. jejuni*.[619]

… nationwide AMR data for ***C. jejuni*** has not been reported since 2015.

[612] Ministry of Health and Ministry for Primary Industries. (2017). *New Zealand Antimicrobial Resistance Action Plan*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/publication/new-zealand-antimicrobial-resistance-action-plan
[613] Ibid.
[614] Australasian Society for Infectious Diseases. (2018). *Minimum specifications for New Zealand's national response plan for Carbapenemase Producing Enterobacteriaceae (CPE)*. Retrieved from https://www.asid.net.au/documents/item/1492; Blakiston, M., Heffernan, H., Roberts, S., *et al.* (2017). The clear and present danger of carbapenemase-producing Enterobacteriaceae (CPE) in New Zealand: time for a national response plan. *The New Zealand Medical Journal, 130*(1454), 72.
[615] Williamson, D., Dyet, K., & Heffernan, H. (2015). *Antimicrobial resistance in human isolates of Campylobacter jejuni, 2015*. Porirua, NZ: ESR.
[616] Ibid.
[617] Ibid.
[618] Institute of Environmental Science and Research Limited (ESR). (n.d.). General antimicrobial susceptibility data collected from hospital and community laboratories. Retrieved 2 September, 2021, from https://surv.esr.cri.nz/antimicrobial/general_antimicrobial_susceptibility.php
[619] Institute of Environmental Science & Research Limited. (2021). Personal communication.

ESBL-producing Enterobacterales

ESKAPE pathogen

Can cause: UTI, intra-abdominal infection, surgical site infection (SSI), bloodstream infection, healthcare-associated pneumonia, sepsis.
AMR trajectory: increasing (from 1996 to 2013), now potentially decreasing but unclear.
Most recent national data: 2016 (2019 survey conducted but results not yet published).
See also section 2.4.2.

Some Enterobacterales acquire the ability to produce ESBLs, enzymes capable of breaking down β-lactam antibiotics (the most commonly used antibiotic class). While ESBL-producing Enterobacterales remain susceptible to carbapenems, they cause a greater number of infections in Aotearoa New Zealand than CPEs at present, so are a major concern.

Figure 31 shows the number of ESBL-producing Enterobacterales isolated in Aotearoa from 1996 to 2016. Until 2005, all laboratories were requested to refer all ESBL-producing isolates to ESR. In 1996, there were 35 confirmed isolates of ESBL-producing Enterobacterales referred to ESR. By 2002, this had increased to 230,[620] and an estimated 737 isolates in 2005.[621] ESR switched methodology from 2005, conducting month-long prevalence surveys and annualising data for comparison with previous years instead of collecting all ESBL-producing isolates throughout the year. With this new methodology a steady increase in the number of ESBL isolates continued to be observed until 2013.[622] Since 2014, only two point-prevalence surveys have been conducted (one in 2016 and one in 2019, with results for the latter yet to be published). Data from 2014 and 2016 indicate a downward trend, but the 2019 data is needed to confirm the trend.

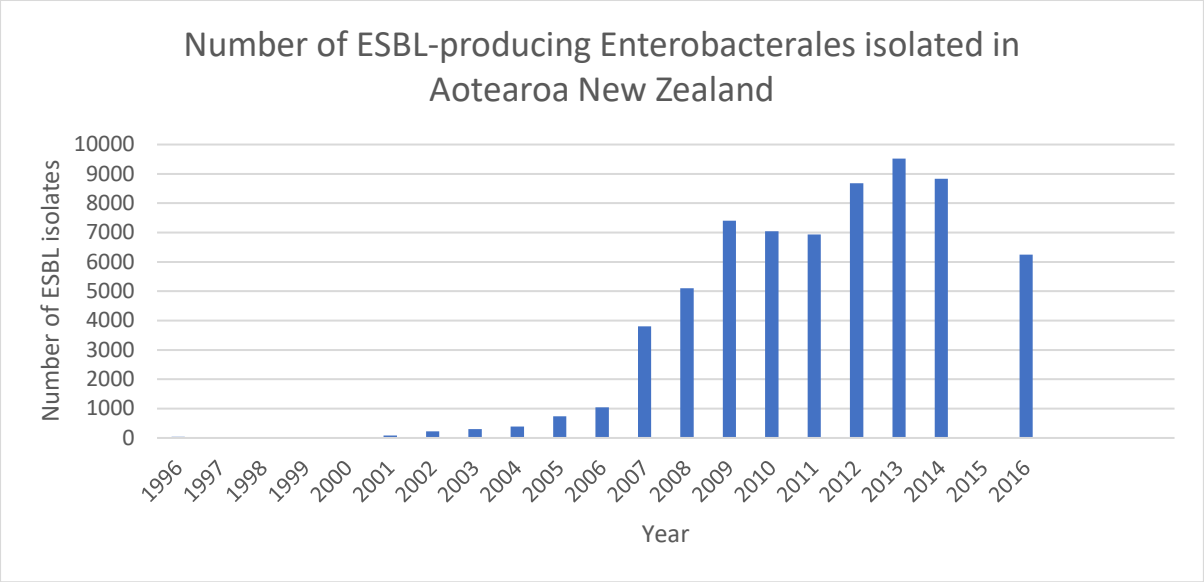

Figure 31: Number of isolates of ESBL-producing Enterobacterales (ESBL-E) collected by ESR. Data for 1996 to 2005 are based on continuous surveillance while data from 2006 to 2016 are annualised based on month-long surveys conducted in these years. The 2006 survey only included urinary *E. coli* and *Klebsiella*, therefore the data for 2006 is not directly comparable with that for other years. No survey was conducted in 2015. Data from ESR.

[620] Institute of Environmental Science and Research Limited (ESR). (2002). *Extended-spectrum ß-lactamases (ESBLs) in Enterobacteriaceae confirmed in 2002*. ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/ESBL/ESBL_2002.pdf
[621] Institute of Environmental Science and Research Limited (ESR). (2005). *Extended-spectrum ß-lactamases (ESBLs) in Enterobacteriaceae confirmed in 2005*. ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/ESBL/ESBL_2005.pdf
[622] Heffernan, H., Woodhouse, R., Draper, J., *et al.* (2018). *2016 survey of extended-spectrum beta-lactamase-producing Enterobacteriaceae*. Porirua, NZ: Institute of Environmental Science and Research Ltd. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/ESBL/ESBL_2016.pdf

Group A *Streptococcus*

Can cause: skin and respiratory infections; infection can lead to rheumatic fever (see evidence synthesis on the OPMCSA website).
AMR trajectory: stable.
Most recent national data: 2015.
See also section 3.4.2.

Data collated from hospital and community laboratories reveals that proportion of group A streptococci infections caused by resistant microbes changed little between 1998 and 2015.[623] Between 2000 and 2015, no isolates were found to be resistant to penicillin, the first-choice antibiotic used for this pathogen. Resistance to second-choice antibiotic erythromycin (commonly used to treat patients who are allergic to penicillin) increased from approximately 1% in the late 1990s to 7.5% in 2010, and in 2015 was recorded as 3.8%.

Haemophilus influenzae (from invasive disease)

Can cause: meningitis, bacteraemia, pneumonia, septic arthritis, cellulitis.
AMR trajectory: stable.
Most recent national data: 2019.

WHO priority organism: MEDIUM

Laboratories throughout Aotearoa New Zealand are requested to refer all invasive isolates of *H. influenzae* to ESR. Between 2002 and 2015, susceptibility was tested and reported on an annual basis but since 2015 this has shifted to testing and reporting every second year. This shift was accompanied by a change in methodology, meaning that proportion of isolates displaying resistance can't be directly compared pre- and post-2015. The reported proportion of isolates displaying resistance for 2017 and 2019 is summarised in Table 10. ESR will not be reporting on *H. influenzae* resistance beyond 2019, having to prioritise AMR reporting in the face of limited resources.[624]

Table 10: Resistance profile of *H. influenzae* isolates from across Aotearoa New Zealand in 2017 and 2019.
NB: Ampicillin is a β-lactam antibiotic that is not used in humans in Aotearoa New Zealand but is structurally extremely similar to the widely used amoxicillin. In this way, resistance to ampicillin is an excellent surrogate for resistance to amoxicillin.

Year	# isolates	Ampicillin resistant	β-lactamase producing	Cefuroxime resistant (Oral / IV)	Cefaclor resistant	# other antibiotics with <10% isolates showing resistance
2019	63	24%	14%	27% / 16%	11%	5
2017	83	28%	20%	20% / 17%	13%	5

ESR will not be reporting on ***H. influenzae*** resistance beyond 2019, having to prioritise AMR reporting in the face of limited resources.

[623] Institute of Environmental Science and Research Limited (ESR). (n.d.). General antimicrobial susceptibility data collected from hospital and community laboratories. Retrieved 2 September, 2021, from https://surv.esr.cri.nz/antimicrobial/general_antimicrobial_susceptibility.php
[624] Institute of Environmental Science & Research Limited. (2021). Personal communication.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Can cause: skin and soft tissue infections, respiratory infections, bone and joint infections, food poisoning, sepsis, pneumonia, meningitis, SSI and bloodstream infections associated with surgical devices and wounds.
AMR trajectory: stable.
Most recent national data: 2017.
See also: case study 4.5.

S. aureus can methicillin resistant (MRSA) or susceptible (MSSA). MSSA is more common is Aotearoa New Zealand than MRSA, but MRSA is of concern given its resistance to β-lactam antibiotics including methicillin (which is not used in Aotearoa New Zealand), flucloxacillin, cefazolin, and cefalexin.

MSSA shows some resistance too

While susceptible to more antibiotics than MRSA, MSSA isolates in Aotearoa New Zealand are resistant to some antibiotics. The most recent AMR surveillance for MSSA comes from the 2017 general antimicrobial susceptibility data.[625] Among MSSA isolates from both bacteraemia and skin and soft tissue infections, more than 80% were not susceptible to penicillin. For all other antimicrobials tested, non-susceptibility was under 20%. Isolates of *S. aureus* that are vancomycin non-susceptible, daptomycin resistant, or linezolid resistant are referred to ESR by labs around the country for enhanced surveillance.[626]

National MRSA surveillance is carried out via prevalence surveys. For these surveys, hospital and community laboratories are requested to refer to ESR all MRSA isolated during a specified period, usually one month. The surveys were carried out on an annual basis between 2000 and 2015. Two further surveys have been completed since in 2017 and 2020, although the 2020 MRSA survey report has not yet been published.

MRSA is most prevalent among young Māori and Pacific peoples.

In 2017, the national prevalence was estimated at 19.9 patients per 100,000 population.[627] This was almost double the prevalence in 2009 (though the 2009 prevalence is likely to be an underestimate); however it was on par with prevalence in the preceding four years.
Of the 956 patients with MRSA in the 2017 survey:

- Nearly 90% were patients in the community, and around 10% in hospital.
- More than 90% of isolates came from skin and soft tissue infection.
- Just under 3% of isolates came from a respiratory source.
- The remainder of isolates came from a range of sources including ears, eyes and invasive surgical or device sites.

Antimicrobial susceptibility data for MRSA from skin and soft tissue infections collected from hospital and community labs in 2017 revealed that 50% were also resistant to the topical

[625] Institute of Environmental Science and Research Limited (ESR). (n.d.). General antimicrobial susceptibility data collected from hospital and community laboratories. Retrieved 2 September, 2021, from https://surv.esr.cri.nz/antimicrobial/general_antimicrobial_susceptibility.php
[626] Institute of Environmental Science and Research Limited (ESR). (n.d.). Our health laboratories. Retrieved 3 September, 2021, from https://www.esr.cri.nz/our-people/our-science-team/our-health-laboratories/
[627] Heffernan, H., & Bakker, S. (2017). *2017 survey of methicillin-resistant Staphylococcus aureus (MRSA)*. Porirua, NZ: Institute of Environmental Science and Research Ltd Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/MRSA/MRSA_2017.pdf

antimicrobial fusidic acid. One study found that the use of the topical antibiotic preparations fusidic acid or mupirocin can co-select for broader antibiotic resistance in *S. aureus*.[628]

MRSA is most prevalent among young Māori and Pacific peoples. Prevalence is also greater in the most socioeconomically deprived patients, and in Northland, Counties Manukau, Lakes, Hawke's Bay, Tairāwhiti, and Waitematā DHBs.

Neisseria gonorrhoeae

Can cause: gonorrhoea, an STI.
AMR trajectory: increasing.
Most recent national data: 2019.

WHO priority organism: HIGH

AMR in *N. gonorrhoeae* is growing both worldwide and in Aotearoa New Zealand. *N. gonorrhoeae* is therefore targeted for enhanced surveillance here. Overseas, reports of isolates resistant to the first-choice treatments ceftriaxone and azithromycin have led to changes in treatment guidelines in the UK (2018) and US (2020), with a switch from dual therapy to using only ceftriaxone, due to increasing azithromycin resistance and concerns about the impact of dual therapy on resistance profiles.[629] In Aotearoa New Zealand, dual therapy with ceftriaxone and azithromycin is recommended as the first-line treatment for gonorrhoea in the *New Zealand Sexual Health Society Gonorrhoea Guideline*.

In the most recent national survey (2018-19) decreased susceptibility to ceftriaxone was detected in only two (out of 344) isolates.[630] Non-susceptibility to azithromycin has increased from 0.5% in 2014-15 to 1.7% in 2018-19.

With a limited number of treatment options available for gonorrhoea, it is important to regularly monitor antimicrobial susceptibility to inform public health interventions. Gonorrhoea is discussed in further detail in section 4.8.

With a limited number of treatment options available for gonorrhoea, it is important to regularly monitor antimicrobial susceptibility to inform public health interventions.

Neisseria meningitidis from invasive disease

Can cause: meningitis, other forms of meningococcal disease such as sepsis.
AMR trajectory: insufficient data.
Most recent national data: 2020.

[628] Nong, Y., Taiaroa, G., Pasricha, S., *et al.* (2021). Clinical relevance of topical antibiotic use in co-selecting for multidrug-resistant *Staphylococcus aureus*: Insights from in vitro and ex vivo models. *Antimicrobial Agents and Chemothery*. https://doi.org/10.1128/aac.02048-20
[629] St. Cyr, S., Barbee, L., Workowski, K.A., *et al.* (2020). Update to CDC's treatment guidelines for gonococcal infection, 2020. *Morbidity and Mortality Weekly Report, 69*(50), 1911-1916.
[630] Straub, C., Thirkell, C., & Dyet, K. (2021). *Antimicrobial resistance and molecular epidemiology of Neisseria gonorrhoeae in New Zealand, 2018-2019*. Porirua, New Zealand: Institute of Environmental Science and Research Ltd. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/Gono/NgonoSurvey2019_FINAL.pdf

During 1991-2008, Aotearoa New Zealand suffered a prolonged meningococcal epidemic caused by a group B strain of *N. meningitidis*. Meningococcal disease case numbers decreased after a strain-specific vaccine was introduced in 2004. This same group B strain continues to cause around one-third of all cases of meningococcal disease, but other strains are also circulating. This includes a distinctive group W strain ('the 2015 strain') first identified in the UK, which shows resistance to penicillin.[631] In part because of this penicillin resistance, the MoH recommended ceftriaxone (instead of penicillin) as the first-choice antibiotic for patients with meningococcal disease.[632]

Meningococcal disease case numbers decreased after a strain-specific vaccine was introduced in 2004.

In 2019, 93 isolates of *N. meningitidis* were tested for antimicrobial susceptibility.[633] Two percent were penicillin resistant, and two-thirds were penicillin non-susceptible. In 2020, 26 isolates of *N. meningitidis* were analysed by ESR for antimicrobial susceptibility.[634] Thirty-nine percent were penicillin resistant, and 64% were penicillin non-susceptible. In both 2019 and 2020, isolates were susceptible to ciprofloxacin, ceftriaxone, or rifampicin.

The substantial increase in observed penicillin resistance between 2019 and 2020 may be in part due to the low numbers reported of *N. meningitidis* in 2020. However, some of this may be a 'real' increase attributable to the group W strain.

Salmonella

Can cause: salmonellosis, an infection of the intestines causing diarrhoea, fever.
AMR trajectory: stable.
Most recent national data: 2016.
See also section 3.6.2.

Labs across the country send *Salmonella* isolates from patients to ESR. Isolates from other sources are gathered too, including from food, animal, and environmental sources. A representative sample of these undergoes AST. The last AMR report published on the ESR website for *Salmonella* is from 2016.[635] In 2016, AST for 10 antimicrobials was conducted on 237 isolates from people with non-typhoidal salmonellosis and 133 from food, animal, or environmental sources.[636] A further 56 isolates from people with typhoid fever were tested against 11 antimicrobials.

The proportion of *Salmonella* isolates that are resistant to first-line antibiotics is generally low. Among the non-typhoidal samples, 87% of human samples and 96% of food, animal, and environmental samples were fully susceptible to all 10 antimicrobials tested. Between 2011 and 2016, the proportion of isolates displaying resistance to the 10 antimicrobials remained relatively

[631] Yang, Z., Ren, X., Davies, H., *et al.* (2021). Genomic surveillance of a globally circulating distinct group W clonal complex 11 meningococcal variant, New Zealand, 2013–2018. *Emerging Infectious Diseases, 27*(4), 1087–1097. https://doi.org/10.3201/eid2704.191716
[632] Ministry of Health. (2018, 30 November). *Change to treatment recommendations for meningococcal disease* [Press release]. Retrieved from https://www.health.govt.nz/news-media/news-items/change-treatment-recommendations-meningococcal-disease
[633] Institute of Environmental Science and Research Limited (ESR). (2019). *Antimicrobial susceptibility of invasive Neisseria meningitidis, 2019*. Porirua, NZ: ESR.
[634] Institute of Environmental Science and Research Limited (ESR). (2020). *Antimicrobial susceptibility of invasive Neisseria meningitidis, 2020.* Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/NME/NME_2020.pdf
[635] Institute of Environmental Science and Research Limited (ESR). (n.d.). Salmonella. Retrieved 3 September, 2021, from https://surv.esr.cri.nz/antimicrobial/salmonella.php
[635] ibid.

stable. Samples from people who had recently travelled overseas were consistently more resistant, or multidrug resistant, than those from people who had not been overseas.

A high proportion of the typhoidal samples displayed ciprofloxacin resistance (>60%). Due to the emergence of ciprofloxacin non-susceptibility, azithromycin is now the recommended first-choice treatment for typhoid fever (depending on where the infection was acquired). No resistance to azithromycin was detected in 2016.

Streptococcus pneumoniae from invasive disease

WHO priority organism: MEDIUM

Can cause: meningitis, pneumonia, septicaemia.
AMR trajectory: stable.
Most recent national data: 2019.

Labs across the country refer all isolates of *S. pneumoniae* that have caused invasive disease to ESR. The antimicrobial susceptibility of these isolates is routinely tested at ESR. Of the 233 isolates tested in 2019, 27.5% were resistant to penicillin, up from 24% in 2016.[637] More than 20% of these penicillin-resistant strains were also resistant to three or more other antibiotics tested. No isolates displayed resistance to cefotaxime. Penicillin resistance has increased between 2011 and 2019, but cefotaxime resistance decreased. In 2016, the proportion of isolates displaying penicillin resistance varied geographically, from 13% in the central region to nearly 30% in the northern region.[638]

What about non-invasive disease?

S. pneumoniae can also cause non-invasive disease (e.g. pneumonia, ear infections, sinus infections). Isolates of *S. pneumoniae* causing non-invasive disease were included in general antimicrobial susceptibility data until 2015.[639] Resistance to penicillin, erythromycin, tetracycline, and trimethoprim + sulfamethoxazole hovered around 20%.

Mycobacterium tuberculosis

Can cause: TB, most commonly a respiratory infection.
AMR trajectory: increasing.
Most recent national data: 2017.

In 2017, there were five cases of multidrug-resistant TB, defined as being resistant to both isoniazid and rifampicin.

In 2017, 261 isolates of *M. tuberculosis* were tested for antimicrobial susceptibility.[640] Nearly 85% of isolates were susceptible to all five antimicrobials tested (isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin). In the ten years leading up to 2017, pyrazinamide resistance decreased, while streptomycin resistance increased. In 2017, there were five cases of multidrug-resistant TB, defined as being resistant to both isoniazid and rifampicin. The slow growth of *M. tuberculosis* means that culture-based susceptibility tests take more time to yield susceptibility results.[641] TB is discussed further in section 4.7.

[637] Institute of Environmental Science and Research Limited (ESR). (2019). *Invasive pneumococcal disease in New Zealand, 2016*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/IPD/2016/2016IPDAnnualReport.pdf
[638] Ibid.
[639] Institute of Environmental Science and Research Limited (ESR). (n.d.). General antimicrobial susceptibility data collected from hospital and community laboratories. Retrieved 2 September, 2021, from https://surv.esr.cri.nz/antimicrobial/general_antimicrobial_susceptibility.php
[640] Institute of Environmental Science and Research Limited (ESR). (2021). *Tuberculosis in New Zealand: Annual report 2017*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/AnnTBReports/TBAnnualReport2017.pdf
[641] Walker, T.M., Kohl, T.A., Omar, S.V., *et al.* (2015). Whole-genome sequencing for prediction of *Mycobacterium tuberculosis* drug susceptibility and resistance: A retrospective cohort study. *The Lancet Infectious Diseases, 15*(10), 1193-1202. https://doi.org/10.1016/S1473-3099(15)00062-6

Vancomycin-resistant enterococci (VRE)

Can cause: UTIs, bacteraemia, wound infections.
AMR trajectory: no clear trend.
Most recent national data: 2020.

WHO priority organism: HIGH

Vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* are targeted for enhanced surveillance by ESR, with labs around the country referring isolates to them for AST. In 2020, 38 VRE isolates from 36 patients were referred to ESR. This is the lowest number of isolates since 2012 and follows a steady rise between 2017 and 2019. Over 90% of the 2020 isolates were resistant to at least three classes of antibiotics.[642]

Helicobacter pylori

Can cause: chronic gastritis, stomach ulcers.
AMR trajectory: increasing.
Most recent national data: 2020 (a systematic review covering Australasia).

WHO priority organism: HIGH

Resistance to both clarithromycin and metronidazole have been identified in *H. pylori* in Aotearoa New Zealand.[643] Across Australasia, the prevalence of resistance to clarithromycin is increasing – a concerning trend given that clarithromycin is the first-choice antibiotic for an *H. pylori* infection, in combination with either metronidazole or amoxicillin.[644] There is currently no routine surveillance for *H. pylori*: most labs do not culture it as it is tricky to grow. Cases are diagnosed using a stool antigen test, which does not capture AST information.

Shigella spp.

Can cause: shigellosis, a type of food poisoning.
AMR trajectory: increasing.
Most recent national data: 2016.

WHO priority organism: MEDIUM

The Public Health Surveillance website, jointly run by ESR and MoH, states that AMR surveillance of *Shigella* spp. is to be reported on a three-yearly basis. However, the last available report is from five years ago. The 2016 report, covering 263 isolates referred to ESR over 2015 and 2016, found that 46% were resistant to at least three antibiotics tested.[645] The first-choice antibiotics for shigellosis are trimethoprim + sulfamethoxazole and fluoroquinolones such as ciprofloxacin. The proportion of isolates displaying resistance to these antibiotics were 57% and 23% respectively. The second-choice treatment is azithromycin. Eleven percent of isolates tested harboured a mechanism capable of disabling azithromycin, which for at least some of those isolates was likely to confer clinical resistance. These concerning findings – of emerging resistance to a second-line antibiotic – led to a call for revised treatment guidelines and continued culturing capability to monitor resistance in *Shigella* spp.[646]

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[642] Institute of Environmental Science and Research Limited (ESR). (2020). *Vancomycin-resistant enterococci, 2020*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/VRE/VRE_2020.pdf
[643] Schubert, J.P., Gehlert, J., Rayner, C.K.*, et al.* (2021). Antibiotic resistance of *Helicobacter pylori* in Australia and New Zealand: A systematic review and meta-analysis. *Journal of Gastroenterology and Hepatology*. https://doi.org/10.1111/jgh.15352
[644] bpac nz. (2014). The changing face of *Helicobacter pylori* testing. *Best Tests*, 20-25. Retrieved from https://bpac.org.nz/BT/2014/May/docs/BT23-h-pylori.pdf
[645] Heffernan, H., & Woodhouse, R. (2017). *Antimicrobial susceptibility of Shigella, 2015 and 2016*. Porirua, NZ: Institute of Environmental Science Research Ltd. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/SHIG/201516ShigellaAMRreport.pdf
[646] Heffernan, H., Woodhouse, R., Hewison, C.*, et al.* (2018). Antimicrobial resistance among *Shigella* in New Zealand. *New Zealand Medical Journal, 131*(1477), 56-62.

Aspergillus fumigatus complex

Can cause: invasive fungal infection.
AMR trajectory: stable.
Most recent national data: 2020.

The *A. fumigatus* complex is a common cause of invasive fungal disease worldwide. An analysis of 260 isolates collected in Aotearoa New Zealand between 2000 and 2020 revealed that only around 1-2% were resistant to various azole antifungal treatments.[647] There was one recorded case of a patient with *A. fumigatus* resistant to all azole antifungal treatments.

There are blind spots in our understand of AMR in human health

While the above information about AMR in human health in Aotearoa New Zealand is helpful, some of it is outdated (particularly given what is known about how rapidly AMR can arise and spread). Surveillance isn't as regular as it could be for pathogens or resistance mechanisms of concern. Plus, there is usually a time delay between the first report of an organism in Aotearoa New Zealand and the start of formalised reporting. For example, colistin resistance (resistance to a last-line antibiotic) has thus far been included in the surveillance report for acquired carbapenemase genes (because some CPEs happen to have colistin resistance genes as well). But colistin resistance may soon warrant its own standalone report. These issues leave us with blind spots, compromising our ability to fully understand the AMR riskscape for human health and to assess the effectiveness of interventions.

These blind spots are largely the result of competing demands in an under-resourced environment, coupled with a growing number of AMR threats to monitor.

These blind spots are largely the result of competing demands in an under-resourced environment, coupled with a growing number of AMR threats to monitor. The healthcare system would benefit greatly from the ability to carry out more timely, regular and prioritised surveillance and reporting, as well as a central database to collate data over time. Passive surveillance of key organisms from diagnostic labs across the country could feed into a centralised system akin to that in place for COVID-19 reporting. Such a centralised system would need to be carefully set up and resourced to prevent reporting from lagging several years behind. This system should be supplemented by a real-time alert mechanism for important resistance types that are not currently notifiable (e.g. CPEs).

ESR needs to be properly resourced to achieve this comprehensive level of surveillance. In the *New Zealand AMR Action Plan*, one of the listed activities to be completed by 2022 was to "develop the business case and implement a standardised surveillance system for AMR in human health, including a review of workforce capacity, capability and training and an appropriate compatible data

[647] McKinney, W.P., Vesty, A., Sood, J., *et al.* (2021). The emergence of azole resistance in *Aspergillus fumigatus* complex in New Zealand. *The New Zealand Medical Journal, 134*(1536), 41-51.

repository or data management system to address the requirements identified."[648] As of writing, there has not been any progress made on this activity.

Resistant organisms can be introduced to Aotearoa New Zealand from overseas

As discussed in section 2.3.3, global connections facilitate the spread of AMR, and resistant microbes that have arisen overseas have spread to Aotearoa New Zealand. Rates of AMR are higher overseas than in Aotearoa New Zealand, and these global connections highlight the importance of global collaboration and action to tackle AMR. Some examples of evidence for overseas-acquired resistant microbes are provided below. In some instances, spread from travellers to others in Aotearoa New Zealand with no history of travel has been observed.

- Positive correlations have been observed between ESBL-producing *E. coli* and overseas-born new arrivals to Aotearoa New Zealand.[649]
- Two patients in Ōtautahi Christchurch were found to be infected with the same clone of a CPE (see section above for more details). One patient was likely to have acquired the infection while in Cambodia, while the second (who lived in the same district of Ōtautahi Christchurch) may have become infected through association with the traveller (although a clear link was never established).[650]
- In Tāmaki Makaurau Auckland, a patient who hadn't travelled overseas introduced an extensively antibiotic-resistant carbapenemase-producing *E. coli* to a hospital. Researchers concluded that the person caught it from their household contact who had recently returned from India.[651]

This is far from a complete list. Our current hospital screening practices are unlikely to detect all instances where patients have acquired resistant microbes overseas or through association with travellers.

Predicting the AMR burden of the future is very difficult

There has not been any in-depth modelling specific to Aotearoa New Zealand on future burden of AMR on human health.[652] However, a 2019 modelling study looking at 52 different countries including Aotearoa New Zealand attempted to estimate future resistance proportions for eight antibiotic-bacteria combinations between 2015 and 2030, selected based on their health burden and WHO prioritisation.[653]

To make their predictions, the modellers used available data on AMR prevalence and antibiotic use, as well as a range of sociodemographic predictors of AMR and antibiotic use (e.g. GDP, out-of-pocket health spend, population age profile). They added the caveat that the predictions were based on incomplete data and also relied on the assumption that past trends and relationships would persist in relation to antibiotic consumption, economic and population growth, and health spending. As a

[648] Ministry of Health and Ministry for Primary Industries. (2017). *New Zealand Antimicrobial Resistance Action Plan*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/publication/new-zealand-antimicrobial-resistance-action-plan

[649] Blakiston, M.R., & Freeman, J.T. (2020). Population-level exposures associated with MRSA and ESBL-*E. coli* infection across district health boards in Aotearoa New Zealand: An ecological study. *The New Zealand Medical Journal, 133*(1510), 62-69.

[650] Howard, J.C., Anderson, T., Creighton, J.*, et al.* (2018). Geographical and temporal clustering of OXA-48-producing *Escherichia coli* ST410 causing community-onset urinary tract infection in Christchurch, New Zealand. *Journal of Antimicrobial Chemotherapy, 73*(10), 2900-2901. https://doi.org/10.1093/jac/dky269

[651] Blakiston, M., Roberts, S.A., Freeman, J.T.*, et al.* (2017). Household transmission of NDM-producing *E. coli* in New Zealand. *The New Zealand Medical Journal, 130*(1452), 63-65.

[652] Pullon, H.W., Gommans, J., Thomas, M.G.*, et al.* (2016). Antimicrobial resistance in New Zealand: The evidence and a call for action. *The New Zealand Medical Journal, 129*(1444), 103-110.

[653] Hashiguchi, T.C.O., Ait Ouakrim, D., Padget, M.*, et al.* (2019). Resistance proportions for eight priority antibiotic-bacterium combinations in OECD, EU/EEA and G20 countries 2000 to 2030: A modelling study. *Eurosurveillance, 24*(20). https://doi.org/10.2807/1560-7917.es.2019.24.20.1800445

result, there is considerable uncertainty associated with the following predictions made for Aotearoa New Zealand.

For CPOs, the modelling study estimated that the proportion of infections caused by third-generation cephalosporin-resistant *K. pneumoniae* and *E. coli* would increase between 2015 and 2030.

- The study estimated that 26% of *K. pneumoniae* infections would be caused by bacteria resistant to third-generation cephalosporins in 2030 (up from an estimated 21% in 2015), and 14% of *E. coli* infections would be caused by bacteria resistant to third-generation cephalosporins by 2030 (up from an estimated 7% in 2015).
- The study predicted no change in resistance proportion for carbapenem-resistant *P. aeruginosa* or *K. pneumoniae* for the same period.

For other resistant organisms, the modellers estimated that there would be increases in the proportion of infections caused by resistant bacteria by 2030 for one and decreases for three others.

- The study estimated that 12% of *E. coli* infections would be caused by bacteria resistant to fluoroquinolones by 2030 (up from an estimated 10% in 2015).
- The study estimated that 32% of *S. aureus* infections would be caused by bacteria resistant to methicillin by 2030 (down from an estimated 36% in 2015).
- The study estimated that 16% of *S. pneumoniae* infections would be caused by bacteria resistant to penicillin by 2030 (down from an estimated 19% in 2015).
- The study estimated that 15% of *E. faecalis* and *E. faecium* infections will be caused by bacteria resistant to vancomycin by 2030 (down from an estimated 17% in 2015).

However, the uncertainty associated with these estimates is considerable. For example, actions taken to curb AMR could see actual prevalence in 2030 fall short of predictions. Meanwhile, inaction or a worsening of the state of play in relation to use of antimicrobials, infection prevention measures, and healthcare could see our AMR burden exceed predictions considerably.

4.3.2 Evidence of AMR in animals and food in Aotearoa New Zealand

AMR also affects animals in Aotearoa New Zealand, which has implications for animal health and wellbeing, agricultural productivity, and human health (see section 2.3.2 for more details, including on the human-animal interface). However, data on AMR in animals in Aotearoa New Zealand isn't systematically collected and reported. What we know about AMR in this country is derived from a series of ad hoc surveys and academic publications (see Table 11).

A review in 2018 commissioned by the Australian Government Department of Health covers available AMR data from Aotearoa New Zealand food animals and plants, and outlines knowledge gaps and recommendations for both Australia and New Zealand.[654] This review found that AMR data

… data on AMR in animals in Aotearoa New Zealand isn't systematically collected and reported.

[654] Australian Government Department of Health. (2018). *Review of published and grey literature on the presence of antimicrobial resistance in food in Australia and New Zealand*. Retrieved from https://www.amr.gov.au/resources/review-published-and-grey-literature-presence-antimicrobial-resistance-food-australia-and

for the dairy, red meat, pork and chicken meat sectors was of moderate completeness but there was limited data for horticulture and no data for eggs or seafood.

MPI oversees the National Microbiological Database programme, which poultry and red meat operators participate in. While the programme measures microorganisms that present a food safety risk, it does not routinely currently consider AMR or susceptibility testing. ESR occasionally requests susceptibility testing for isolates from food.

Pathogens sent to private veterinary labs are also a source of AMR data. However, protocols are not in place to obtain the full spectrum of data, with only exotic samples currently notifiable to MPI. AST of samples sent to labs does not always happen for animal isolates. For example, only 18% of the samples taken from pigs between 2003-2016 had AST data available[655] For cows, this was only 9.2%.[656] Some studies have mined commercial veterinary pathology laboratory records for data to understand the prevalence of AMR.[657]

Aotearoa New Zealand would benefit from coordinated surveillance in animals (particularly in food-producing animals, but companion animals should not be overlooked either). Scoping for an Aotearoa New Zealand AMR surveillance programme in food-producing animals was undertaken in 2006.[658] The scoping work reviewed a range of international surveillance programmes and identified Denmark and the US as having surveillance systems potentially most useful and applicable to Aotearoa New Zealand's context.

A baseline survey was undertaken following this work that focused on antibiotic resistance from food-producing animals in 2009/2010.[659] Three animal groups were included in this survey: very young calves, pigs and broiler poultry. This survey is currently being repeated by ESR and MPI, with a final report expected by the end of 2022.[660]

[655] Riley, C.B., Chidgey, K.L., Bridges, J.P*., et al.* (2020). Isolates, antimicrobial susceptibility profiles and multidrug resistance of bacteria cultured from pig submissions in New Zealand. *Animals, 10*(8), 1427.
[656] Lawrence, K., Wakeford, L., Toombs-Ruane, L*., et al.* (2019). Bacterial isolates, antimicrobial susceptibility and multidrug resistance in cultures from samples collected from beef and pre-production dairy cattle in New Zealand (2003–2016). *New Zealand Veterinary Journal, 67*(4), 180-187. https://doi.org/10.1080/00480169.2019.1605943
[657] McMeekin, C., Hill, K., Gibson, I*., et al.* (2017). Antimicrobial resistance patterns of bacteria isolated from canine urinary samples submitted to a New Zealand veterinary diagnostic laboratory between 2005–2012. *New Zealand Veterinary Journal, 65*(2), 99-104. https://doi.org/10.1080/00480169.2016.1259594; Toombs-Ruane, L., Riley, C., Kendall, A*., et al.* (2016). Antimicrobial susceptibility of bacteria isolated from neonatal foal samples submitted to a New Zealand veterinary pathology laboratory (2004 to 2013). *New Zealand Veterinary Journal, 64*(2), 107-111. https://doi.org/10.1080/00480169.2015.1109006
[658] Read, D.A. (2006). *Scoping a New Zealand antimicrobial resistance surveillance programme in food*. Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/26195-Scoping-a-New-Zealand-antimicrobial-resistance-surveillance-programme-in-food
[659] Heffernan, H., Wong, T.L., Lindsay, J*., et al.* (2011). *A baseline survey of antimicrobial resistance in bacteria in selected New Zealand foods, 2009-2010*. Wellington, NZ: Ministry of Agriculture and Forestry. Retrieved from https://www.mpi.govt.nz/dmsdocument/21464-A-baseline-survey-of-antimicrobial-resistance-in-bacteria-from-selected-New-Zealand-foods-2009-2010
[660] MPI. (2021). Personal communication.

Table 11: A selection of publications relating to AMR in animals in Aotearoa New Zealand

Animal	Specific AMR findings in Aotearoa New Zealand
Pigs	A 2020 study characterised samples gathered from commercial veterinary pathology labs between 2003 and 2016, yielding a range of bacterial isolates. Sample type was recorded for three-quarters, with samples most commonly collected from pig lungs, faeces, or intestines. MDROs (i.e. resistant to three or more antibiotic classes) was present in 43% of isolates for which susceptibility was available.[661] A 2008 study found that overall levels of resistance in *E. coli* and *Enterococcus* spp. isolated from faeces on conventional pig farms were similar to those reported in Europe. There were higher levels of resistance in the *E. coli* and *Enterococcus* spp. from the conventionally farmed pig faeces compared with an organic farm that didn't use antibiotics.[662] A livestock-associated strain of MRSA, originally identified in pigs in Northern European countries, was identified in Aotearoa New Zealand in 2011. It has since been isolated from several people involved in pig farming or the abattoir industry in the Canterbury region.[663]
Poultry	Analysis of faecal samples from poultry in the early 2000s identified VRE in isolates recovered from farms that had used avoparcin.[664] Between 1977 and 2000, avoparcin – which is structurally similar to vancomycin, an antibiotic used in people – was used prophylactically in broiler chickens. A further survey in the early 2000s of faecal samples from 147 broiler farms detected 382 isolates of enterococci, with around 6% being VRE.[665] Around 65% were resistant to erythromycin (a macrolide antibiotic used in humans). A further 15% were resistant to avilamycin and 99% resistant to bacitracin. Vancomycin resistance is linked to macrolide resistance[666] (e.g. erythromycin, tylosin) so the continued use of prophylactic macrolides may co-select for VREs even after the discontinuation of avoparcin. A recent genomic analysis of VRE based on poultry and human isolates cultured between 1998 and 2009 found strict delineation between human and poultry isolates of *Enterococcus faecium*. [667] In contrast, there was overlap of a particular strain of *Enterococcus faecalis* between human and poultry isolates. This was the predominant strain in both human and poultry isolates in the three years after discontinuation of avoparcin use and suggested that is strain may have originated in poultry and spread to humans. Sequencing also found that genes encoding resistance to vancomycin, bacitracin, and erythromycin were colocalised in some isolates, meaning that continued use of bacitracin or macrolides could inadvertently select for vancomycin resistance. In 2006, *E. faecium* and *E. faecalis* were isolated from carcass rinse samples from five poultry processing plants.[668] Bacitracin resistance was high (97% in *E. faecium* and 88% in *E. faecalis*). Resistance to tetracycline and erythromycin was similar between the two species, ranging between 32% and 48%. Clusters of *E. faecium* resistance patterns were linked to on-farm practices including use of in-feed drugs at sub-therapeutic levels and the chicken lineage. Other results included: • Furazolidone resistance: 96% *E. faecium*, 21% *E. faecalis* • Ampicillin resistance: 12% *E. faecium*, 0% *E. faecalis* • Quinupristin + dalfopristin resistance: 14% *E. faecium*, 83% *E. faecalis* • Three isolates displayed gentamicin resistance and four were VREs.

[661] Riley, C.B., Chidgey, K.L., Bridges, J.P*., et al.* (2020). Isolates, antimicrobial susceptibility profiles and multidrug resistance of bacteria cultured from pig submissions in New Zealand. *Animals, 10*(8), 1427.

[662] Nulsen, M., Mor, M., & Lawton, D. (2008). Antibiotic resistance among indicator bacteria isolated from healthy pigs in New Zealand. *New Zealand Veterinary Journal, 56*(1), 29-35. https://doi.org/10.1080/00480169.2008.36801

[663] Heffernan, H., & Bakker, S. (2017). *2017 survey of methicillin-resistant Staphylococcus aureus (MRSA)*. Porirua, NZ: Institute of Environmental Science and Research Ltd Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/MRSA/MRSA_2017.pdf

[664] Manson, J.M., Keis, S., Smith, J.M.B*., et al.* (2003). A clonal lineage of VanA-type *Enterococcus faecalis* predominates in vancomycin-resistant enterococci isolated in New Zealand. *Antimicrobial Agents and Chemotherapy, 47*(1), 204-210. https://doi.org/10.1128/AAC.47.1.204-210.2003

[665] Manson, J.M., Smith, J.M.B., & Cook, G.M. (2004). Persistence of vancomycin-resistant enterococci in New Zealand broilers after discontinuation of avoparcin use. *Applied and Environmental Microbiology, 70*(10), 5764-5768. https://doi.org/10.1128/AEM.70.10.5764-5768.2004

[666] Manson, J.M., Keis, S., Smith, J.M.B*., et al.* (2003). A clonal lineage of VanA-type *Enterococcus faecalis* predominates in vancomycin-resistant enterococci isolated in New Zealand. *Antimicrobial Agents and Chemotherapy, 47*(1), 204-210. https://doi.org/10.1128/AAC.47.1.204-210.2003

[667] Rushton-Green, R., Darnell Rachel, L., Taiaroa, G*., et al.* Agricultural origins of a highly persistent lineage of vancomycin-resistant *Enterococcus faecalis* in New Zealand. *Applied and Environmental Microbiology, 85*(13), e00137-00119. https://doi.org/10.1128/AEM.00137-19

[668] Pleydell, E., Rogers, L., Kwan, E*., et al.* (2010). Evidence for the clustering of antibacterial resistance phenotypes of enterococci within integrated poultry companies. *Microbial Ecology, 59*(4), 678-688. https://doi.org/10.1007/s00248-009-9625-6

Animal	Specific AMR findings in Aotearoa New Zealand
	In 2014, a strain of *Campylobacter jejuni* (ST-6964) resistant to fluoroquinolones and tetracycline emerged in three poultry companies and was transmitted to humans via the food chain.[669] ST-6964 continues to be detected in both poultry and humans.[670]
Dairy cattle	A 2017 review provides a good overview of what we know and don't know about antimicrobial-resistant bacteria in dairy cattle.[671] The review states: "In New Zealand there is no evidence to date that the use of antimicrobials in dairy cattle has resulted in the emergence of pathogens that are multidrug resistant. At present the risk of AMR developing in bacteria carried by dairy cattle and potential transmission to humans is not able to be assessed because of the lack of New Zealand data. However, research carried out overseas suggests that there is the potential for AMR to increase due to the use of antimicrobials in the dairy industry, particularly through the use of third and fourth generation cephalosporins. Although there is limited evidence for the transmission of antimicrobial resistant bacteria and their genes between dairy cattle and humans, it is clear that antimicrobial use can lead to bacteria in the gut of dairy cattle developing AMR." A 2021 study found ESBL-producing *E. coli* in faecal swabs from cows on one of 15 farms tested, while plasmid-mediated AmpC β-lactamase-producing *E. coli* were found on three farms.[672] Vet labs across Aotearoa New Zealand have been reporting the emergence of increased minimum inhibitory concentrations to β-lactam antibiotics in *Streptococcus uberis*, which commonly causes mastitis. According to a 2020 study, 53% of 265 *S. uberis* isolates collected were oxacillin resistant (similar to flucloxacillin, a widely used antibiotic in humans in Aotearoa New Zealand).[673] A 2014 study found that, of 364 *S. aureus* isolates from cases of bovine mastitis, 28% were penicillin resistant, 2% were ampicillin resistant, and 0.5% were trimethoprim + sulfamethoxazole resistant. Of 65 *Streptococcus dysgalactiae* isolates, 17% were trimethoprim + sulfamethoxazole resistant. Of 102 *S. uberis* isolates, 13% were trimethoprim + sulfamethoxazole resistant.[674] In a 2015 study looking at isolates from bovine milk samples from five commercial vet labs around NZ: • Of 106 *S. uberis* isolates, over 10% showed resistance to ampicillin (11.3%), lincomycin (60.4%), neomycin (100%), streptomycin (99.1%), and enrofloxacin (37.7%) • Of 107 *S. aureus* isolates, over 10% showed resistance to amoxicillin (21.6%), ampicillin (19.6%), penicillin (19.6%), and lincomycin (99.1%) • Of 41 *Str. dysgalactiae* isolates, over 10% showed resistance to lincomycin (100%), neomycin (100%), streptomycin (19.3%), tetracycline (97.6%), and enrofloxacin (68.3%).[675] A 2013 paper showed that, of 55 isolates of *S. aureus* from cows with mastitis in the Waikato region, 45% were resistant to penicillin.[676]

[669] French, N., Zhang, J., Carter, G.*, et al.* (2019). Genomic analysis of fluoroquinolone- and tetracycline-resistant *Campylobacter jejuni* sequence type 6964 in humans and poultry, New Zealand, 2014–2016. *Emerging Infectious Diseases, 25*(12), 2226. https://doi.org/10.3201/eid2512.190267

[670] Lake, R., Ashmore, E., Cressey, P.*, et al.* (2020). *Source assigned campylobacteriosis in New Zealand study*. Wellington, NZ: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/39896-Source-Assigned-Campylobacteriosis-in-New-Zealand-Study-SACNZS-Report; Lake, R.J., Campbell, D.M., Hathaway, S.C.*, et al.* (2021). Source attributed case-control study of campylobacteriosis in New Zealand. *International Journal of Infectious Diseases, 103*, 268-277. https://doi.org/10.1016/j.ijid.2020.11.167

[671] Burgess, S., & French, N. (2017). *Antimicrobial resistant bacteria in dairy cattle: A review*. Palmerston North, NZ: New Zealand Food Safety and Science Research Centre. Retrieved from https://www.nzfssrc.org.nz/node/79

[672] Burgess, S.A., Aplin, J., Biggs, P.J.*, et al.* (2021). Characterisation of AmpC and extended-spectrum beta-lactamase producing *E. coli* from New Zealand dairy farms. *International Dairy Journal, 117*, 104998. https://doi.org/10.1016/j.idairyj.2021.104998

[673] McDougall, S., Clausen, L., Ha, H.-J.*, et al.* (2020). Mechanisms of β-lactam resistance of *Streptococcus uberis* isolated from bovine mastitis cases. *Veterinary Microbiology, 242*, 108592. https://doi.org/10.1016/j.vetmic.2020.108592

[674] McDougall, S., Hussein, H., & Petrovski, K. (2014). Antimicrobial resistance in *Staphylococcus aureus*, *Streptococcus uberis* and *Streptococcus dysgalactiae* from dairy cows with mastitis. *New Zealand Veterinary Journal, 62*(2), 68-76. https://doi.org/10.1080/00480169.2013.843135

[675] Petrovski, K., Grinberg, A., Williamson, N.*, et al.* (2015). Susceptibility to antimicrobials of mastitis-causing *Staphylococcus aureus*, *Streptococcus uberis* and *Str. dysgalactiae* from New Zealand and the USA as assessed by the disk diffusion test. *Australian Veterinary Journal, 93*(7), 227-233. https://doi.org/10.1111/avj.12340

[676] Steele, N., & McDougall, S. (2014). Effect of prolonged duration therapy of subclinical mastitis in lactating dairy cows using penethamate hydriodide. *New Zealand Veterinary Journal, 62*(1), 38-46. https://doi.org/10.1080/00480169.2013.830350

Animal	Specific AMR findings in Aotearoa New Zealand
	All 209 *E. coli* isolates from the uteri of post-partum dairy cows demonstrated low (<7%) or no resistance to ampicillin, ticarcillin + clavulanic acid, ceftiofur, cefuroxime, cephapirin, enrofloxacin and oxytetracycline, based on a 2015 study.[677]
Beef and pre-production dairy cattle	In a sample of 251 isolates collated from commercial vet labs between 2003 and 2016, 21% were resistant to three or more antibiotics (i.e. multidrug resistant).[678] Multidrug resistance was most common for *Enterococcus* spp. (12/17, 71%) and *E. coli* (13/30, 43%). These samples came from a range of sources, with the most common being faeces (32%).
Sheep	Bacterial isolates submitted to veterinary labs from sheep in Aotearoa New Zealand between 2003 and 2016 were assessed for AMR. Multidrug resistance was found in 24 out of 117 isolates (20.5%), and was more frequently found among *Enterococcus* spp., *Bacillus* spp., and *Proteus mirabilis* isolates. Multidrug resistance was infrequent in isolates of *S. aureus*, alpha-haemolytic streptococci, *E. coli*, and *Enterobacter* spp.[679] A 2021 study found genes associated with β-lactamase enzymes in 41 of 44 *Campylobacter* collected from sheep carcasses.[680]
Horses	Thirty-nine percent of the 774 bacterial isolates cultured from 237 young horses had multidrug-resistant strains of bacteria, based on a 2015 study.[681] Twenty-six percent of 126 isolates collected from foals and submitted to a veterinary pathology lab between 2004 and 2013 were MDROs.[682]
Cats and dogs	Between 2005 and 2012 there was an increase in resistance to some commonly used antimicrobials in the treatment of UTIs in dogs. The percentage of *E. coli* isolates resistant to amoxicillin and cephalothin increased between 2005 and 2012, as did resistance to enrofloxacin, but there was no change in resistance to trimethoprim + sulfamethoxazole.[683] Multidrug-resistant *Staphylococcus pseudintermedius* was identified in a dog taken to the vet in Waikato in 2016.[684] Clinical infections of MRSA in cats and dogs in Aotearoa New Zealand are sporadic, according to a study that collated isolates from participating vet labs and tested a cross-section of samples from both cats and dogs between June 2012 and June 2013.[685] MRSA isolates were reported from five dogs over the one-year study period, displaying diverse resistance profiles. According to a 2019 study, ESBL- and β-lactamase-producing *E. coli* were isolated from faecal swabs from cats and dogs at a prevalence close to the prevalence of faecal carriage in humans.[686]

[677] De Boer, M., Heuer, C., Hussein, H.*, et al.* (2015). Minimum inhibitory concentrations of selected antimicrobials against *Escherichia coli* and *Trueperella pyogenes* of bovine uterine origin. *Journal of Dairy Science, 98*(7), 4427-4438. https://doi.org/10.3168/jds.2014-8890

[678] Lawrence, K., Wakeford, L., Toombs-Ruane, L.*, et al.* (2019). Bacterial isolates, antimicrobial susceptibility and multidrug resistance in cultures from samples collected from beef and pre-production dairy cattle in New Zealand (2003–2016). *New Zealand Veterinary Journal, 67*(4), 180-187. https://doi.org/10.1080/00480169.2019.1605943

[679] Riley, C.B., Chidgey, K.L., Bridges, J.P.*, et al.* (2020). Isolates, antimicrobial susceptibility profiles and multidrug resistance of bacteria cultured from pig submissions in New Zealand. *Animals, 10*(8), 1427.

[680] Rivas, L., Dupont, P.-Y., Gilpin, B.*, et al.* (2021). Prevalence and genotyping of *Campylobacter jejuni* and *Campylobacter coli* from ovine carcasses in New Zealand. *Journal of Food Protection, 84*(1), 14-22. https://doi.org/10.4315/jfp-20-220

[681] Toombs-Ruane, L.J., Riley, C.B., Kendall, A.T.*, et al.* (2015). Antimicrobial susceptibilities of aerobic isolates from respiratory samples of young New Zealand horses. *Journal of Veterinary Internal Medicine, 29*(6), 1700-1706. https://doi.org/10.1111/jvim.13600

[682] Toombs-Ruane, L., Riley, C., Kendall, A.*, et al.* (2016). Antimicrobial susceptibility of bacteria isolated from neonatal foal samples submitted to a New Zealand veterinary pathology laboratory (2004 to 2013). *New Zealand Veterinary Journal, 64*(2), 107-111. https://doi.org/10.1080/00480169.2015.1109006

[683] McMeekin, C., Hill, K., Gibson, I.*, et al.* (2017). Antimicrobial resistance patterns of bacteria isolated from canine urinary samples submitted to a New Zealand veterinary diagnostic laboratory between 2005–2012. *New Zealand Veterinary Journal, 65*(2), 99-104. https://doi.org/10.1080/00480169.2016.1259594

[684] Bell, A., Coombs, G., Cater, B.*, et al.* (2016). First report of a mecA-positive multidrug-resistant *Staphylococcus pseudintermedius* isolated from a dog in New Zealand. *New Zealand Veterinary Journal, 64*(4), 253-256. https://doi.org/10.1080/00480169.2016.1146171

[685] Karkaba, A., Benschop, J., Hill, K.*, et al.* (2017). Characterisation of methicillin-resistant *Staphylococcus aureus* clinical isolates from animals in New Zealand, 2012–2013, and subclinical colonisation in dogs and cats in Auckland. *New Zealand Veterinary Journal, 65*(2), 78-83. https://doi.org/10.1080/00480169.2016.1222919

[686] Karkaba, A., Hill, K., Benschop, J.*, et al.* (2019). Carriage and population genetics of extended spectrum β-lactamase-producing *Escherichia coli* in cats and dogs in New Zealand. *Veterinary Microbiology, 233*, 61-67. https://doi.org/10.1016/j.vetmic.2019.04.015

Animal	Specific AMR findings in Aotearoa New Zealand
	A separate study published in 2019 found methicillin-resistant and multidrug-resistant *Staphylococcus pseudintermedius* in isolates collected from dogs in Aotearoa New Zealand.[687]
Bees	Resistance to two miticides used to treat varroa (fluvalinate and flumethrin) was detected in 2010 study. It is not known whether resistance developed in Aotearoa New Zealand (e.g. due to incorrect dosage and duration of treatments, failure to alternate miticides) or partially resistant mites were introduced.[688]

4.3.3 Evidence of AMR in plants in Aotearoa New Zealand

Internationally, surveillance of AMR in plants is poor, and Aotearoa New Zealand is no exception. While there are international guidelines for the surveillance of AMR in food-producing animals, there are no similar guidelines for the surveillance of AMR in plants.[689] The FAO has stated that surveillance and further testing are needed to undertake risk assessments and monitor progress in implementing more sustainable plant health practices that reduce reliance on antimicrobials (see section 5.5.5).[690] While many antimicrobials used in horticulture are not used in human medicine, AMR among microbes that infect plants is still a concern due to the impacts it can have on agricultural productivity and native flora. Furthermore, for some antimicrobials used in plants (e.g. azoles) there are potential human health implications[691] (see section 2.3.2 for more details).

While there are international guidelines for the surveillance of AMR in food-producing animals, there are no similar guidelines for the surveillance of AMR in plants.

There is no routine monitoring and surveillance for AMR in horticulture and limited studies of the presence of AMR in plants in Aotearoa New Zealand. The extent to which antimicrobial use in plant production selects for the emergence and maintenance of AMR organisms is unclear,[692] as is any relationship with AMR in animal and human health.

In horticulture, copper-based sprays are widely used to protect plants from a range of diseases. When the kiwifruit disease Psa arrived in Aotearoa New Zealand in 2010, it was susceptible to

[687] Nisa, S., Bercker, C., Midwinter, A.C., *et al.* (2019). Combining MALDI-TOF and genomics in the study of methicillin resistant and multidrug resistant *Staphylococcus pseudintermedius* in New Zealand. *Scientific Reports, 9*(1), 1-13.
[688] Goodwin, R.M., Taylor, M.A., McBrydie, H.M., *et al.* (2005). Base levels of resistance to common control compounds by a New Zealand population of *Varroa destructor*. *New Zealand Journal of Crop and Horticultural Science, 33*(4), 347-352. https://doi.org/10.1080/01140671.2005.9514369
[689] Interagency Coordination Group on Antimicrobial Resistance. (2018). *Surveillance and monitoring for antimicrobial use and resistance*. Retrieved from https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_Surveillance_and_Monitoring_for_AMU_and_AMR_110618.pdf
[690] Food and Agriculture Organization Antimicrobial Resistance Working Group. (2018). *Antimicrobial resistance and foods of plant origin: Summary report of an FAO meeting of experts*. Retrieved from http://www.fao.org/3/BU657en/bu657en.pdf
[691] Dalhoff, A. (2018). Does the use of antifungal agents in agriculture and food foster polyene resistance development? A reason for concern. *Journal of Global Antimicrobial Resistance, 13*, 40-48. https://doi.org/10.1016/j.jgar.2017.10.024; Brauer, V.S., Rezende, C.P., Pessoni, A.M., *et al.* (2019). Antifungal agents in agriculture: Friends and foes of public health. *Biomolecules, 9*(10), 521. https://doi.org/10.3390/biom9100521
[692] Food and Agriculture Organization Antimicrobial Resistance Working Group. (2018). *Antimicrobial resistance and foods of plant origin: Summary report of an FAO meeting of experts*. Retrieved from http://www.fao.org/3/BU657en/bu657en.pdf

copper. However, in 2015-16, one quarter of Psa isolates collected were copper resistant.[693] Psa is discussed further in section 3.5.1.

Streptomycin resistance has been identified in microbes that affect stone fruit and pip fruit in Aotearoa New Zealand. In 1995, streptomycin resistance, conferred by a mutation in the *rpsL* gene that encodes the ribosomal target protein for streptomycin, was found in populations of *Erwinia amylovora* (the pathogen that causes fire blight).[694] In a 2008 study, 50 of the 54 *Pseudomonas syringae* strains had the genes that confer resistance to streptomycin. Other strains, including all strains of *Erwinia amylovora*, were streptomycin resistant due to a mutation in the *rpsL* gene.[695]

It's not just the direct use of antimicrobials in plants that matters, as resistance can come from contaminated sources in the wider environment (see sections 2.3.2 and 4.3.4). Genes conferring resistance to antimicrobials, including resistance to drugs used to treat human and animal infections, have been found among bacteria isolated from foods of plant origin. Soil, water, insects, animal intrusion, manure used as fertiliser, and human handling are probable sources of contamination in plants.[696] Animals can be similarly affected – exposure is across the whole system and requires a holistic approach. Research is also needed to determine whether insects and invertebrates are vectors of resistance.

4.3.4 Evidence of AMR in the environment in Aotearoa New Zealand

Antimicrobial-resistant microbes are known to exist in the environment (e.g. in soil and water), including in Aotearoa New Zealand. Resistant microbes can evolve in response to naturally occurring or anthropogenically introduced antimicrobial compounds in the environment or could enter the environment after evolving in humans, animals, or plants (see section 2.3.2 for more details).

Aotearoa New Zealand does not routinely or methodically test the environment for the presence of AMR. The lack of environmental monitoring or inclusion of environmental aspects within our holistic approach was identified as a gap in our self-reported progress on AMR action for the Tripartite survey.[697] As with AMR in plants, any relationship between AMR in the environment and AMR in animal and human health is poorly understood.

Aotearoa New Zealand does not routinely or methodically test the environment for the presence of drug-resistant bacteria… there are specific knowledge gaps that need to be filled.

[693] Colombi, E., Straub, C., Künzel, S., *et al.* (2017). Evolution of copper resistance in the kiwifruit pathogen *Pseudomonas syringae pv. actinidiae* through acquisition of integrative conjugative elements and plasmids. *Environmental Microbiology, 19*(2), 819-832. https://doi.org/10.1111/1462-2920.13662; Zhao, M., Butler, M., Taiaroa, G., *et al.* (2018). *Conjugation in Pseudomonas syringae pv. actinidiae (Psa).* Paper presented at the IX International Symposium on Kiwifruit, Porto, Portugal.

[694] Chiou, C.-S., & Jones, A. (1995). Molecular analysis of high-level streptomycin resistance in *Erwinia amylovora*. *Phytopathology, 85*(3), 324-328.

[695] Vanneste, J.L., Voyle, M.D., Yu, J., *et al.* (2008). Copper and streptomycin resistance in *Pseudomonas* strains isolated from pipfruit and stone fruit orchards in New Zealand (pp. 81-90): Springer Netherlands.

[696] Food and Agriculture Organization Antimicrobial Resistance Working Group. (2018). *Antimicrobial resistance and foods of plant origin: Summary report of an FAO meeting of experts*. Retrieved from http://www.fao.org/3/BU657en/bu657en.pdf

[697] World Health Organization, Food and Agriculture Organization of the United Nations, & World Organisation for Animal Health. (2021). *Monitoring global progress on antimicrobial resistance: tripartite AMR country self-assessment survey (TrACSS) 2019–2020. Global analysis report*.

Drug-resistant microbes in our water

ESBL-producing *E. coli* isolates (see section 4.3.1 above) have been found in our waterways.[698] For example, ESBL-producing *E. coli* have been isolated from the Avon River in Ōtauathi Christchurch.[699] Other waterways in and near Ōtautahi Christchurch have also been the subject of testing: a study of one urban river and one agricultural river near Ōtautahi Christchurch found *E. coli* resistant to one or more of nine different antimicrobials, with variation between rivers.[700] Sampling of the Waimakariri River in Waitaha North Canterbury in 2004 and 2012 revealed an increase in the number of sample sites with multidrug-resistant *E. coli*.[701]

In another waterway study in 2010 and 2011, 480 samples from 20 freshwater waterways across southern Aotearoa New Zealand were collected. Low levels of AMR genes were found to be widespread throughout the year (1.3% overall detection rate).[702]

An analysis of sewage samples shows that compared with some countries our environment has low levels of drug-resistant pathogens (especially when compared with those that manufacture antimicrobials). This study found that sewage samples from North America, Western Europe, Australia, and Aotearoa New Zealand generally had the lowest levels of AMR, while Asia, Africa, and South America had the highest levels. Brazil, India, and Vietnam had the greatest diversity in AMR genes, while Australia and Aotearoa New Zealand had the lowest.[703] However, only one sample from Ōtepoti Dunedin was included for Aotearoa New Zealand so its findings cannot be extrapolated too far. For more on wastewater testing, see section 5.4.1.

While there is evidence of drug-resistant bacteria in some environments tested in Aotearoa New Zealand, there are specific knowledge gaps that need to be filled. The risk of exposure to AMR through different sources (e.g. recreational use of rivers, untreated water, different foods) is not understood and enhancing this understanding could inform preventative interventions. Anthropogenic inputs may select for and increase the spread of AMR in certain environments (e.g. from heavy metal seepage, old rubbish dumps, industry waste) however, these inputs and their impact are not well understood. Comparing environmental AMR between sites (e.g. landfill vs national park) could help to understand the impacts of human activities on environmental AMR.

[698] Burgess, S.A., Francois, M., Midwinter, A.C., *et al.* (2021). Draft genome sequences of seven extended-spectrum β-lactamase-producing *Escherichia coli* strains isolated from New Zealand waterways. *Microbiology Resource Announcements, 10*(11). ; Gray, H.A., Biggs, P.J., Midwinter, A.C., *et al.* (2021). Genome sequences for extended-spectrum beta-lactamase-producing *Escherichia coli* strains isolated from different water sources. *Microbiology Resource Announcements, 10*(24), e00328-00321. https://doi.org/10.1128/MRA.00328-21

[699] Adewale, M.E. (2018). *Distribution of antibiotic resistant bacteria that are human pathogens and tritagonists in waterways.* (Master of Science), University of Canterbury, Christchurch, NZ. Retrieved from https://ir.canterbury.ac.nz/bitstream/handle/10092/15096/Adewale%2C%20Emmanuel_Master%27s%20Thesis.pdf?sequence=1&isAllowed=y

[700] Van Hamelsveld, S., Adewale, M.E., Kurenbach, B., *et al.* (2019). Prevalence of antibiotic-resistant *Escherichia coli* isolated from urban and agricultural streams in Canterbury, New Zealand. *FEMS Microbiology Letters, 366*(8). https://doi.org/10.1093/femsle/fnz104

[701] Schousboe, M.I., Aitken, J., & Welsh, T.J. Increase in antibiotic resistant *Escherichia coli* in a major New Zealand river: Comparison between 2004 and 2012 - an interval of 8 years. *New Zealand Journal of Medical Laboratory Science*. https://doi.org/10.3316/informit.150167245785565

[702] Winkworth-Lawrence, C., & Lange, K. (2016). Antibiotic resistance genes in freshwater biofilms may reflect influences from high-intensity agriculture. *Microbial Ecology, 72*(4), 763-772. https://doi.org/10.1007/s00248-016-0740-x

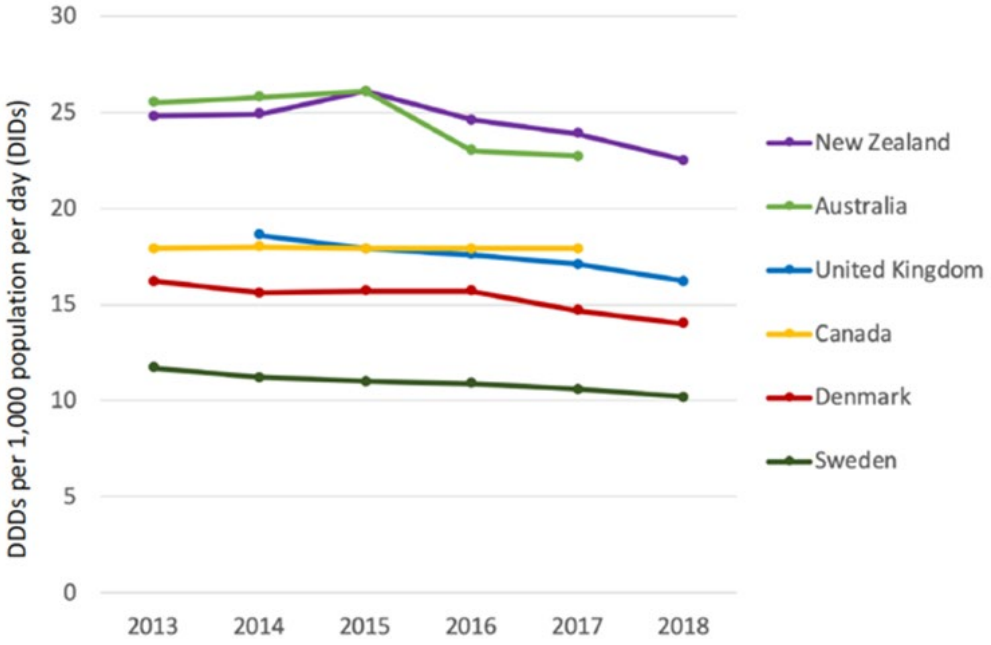
[703] Hendriksen, R.S., Munk, P., Njage, P., *et al.* (2019). Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nature Communications, 10*(1), 1124. https://doi.org/10.1038/s41467-019-08853-3

4.4 Use of antimicrobials in Aotearoa New Zealand

As detailed in section 2.3.2, antimicrobial use drives AMR by creating a selection pressure that leads to the survival and proliferation of resistant microbes. While antimicrobial use is crucial to protecting human, animal, and plant health, in some circumstances antimicrobials are overused or used inappropriately. Identifying the quantity of antimicrobials used, the quality of that use (e.g. whether the prescription is appropriate for the indication, whether course duration is suitable, etc.), the distribution of use (e.g. across regions, sectors, or population subgroups), and trends in use is key to identifying opportunities to improve AMS. In this section, we summarise what is known about antimicrobial use across human, animal, and plant health, as well as the presence of antimicrobials in the environment. As with section 4.3 on AMR, we highlight data gaps where relevant.

4.4.1 Antimicrobial use in human health is high compared with other nations

Compared with other high-income countries, Aotearoa New Zealand has "very high" use of antimicrobials in the community (see Figure 32). In the most recent OECD comparison, Aotearoa New Zealand had the fourth highest level of antibiotic prescribing (measured in defined daily dose per 1,000 people), surpassed only by Greece, Italy, and Korea.[704] In Aotearoa New Zealand, 95% of our total antimicrobial use in humans occurs in the community – again, this is high by international comparisons (see Figure 33).[705] While antimicrobial use in hospitals is far more concentrated compared with the community (around 40% of patients in public hospitals are taking antimicrobials[706]) our use of antimicrobials in hospitals is relatively low.[707]



[704] OECD. (2019). *Health at a Glance 2019*. Retrieved from https://www.oecd-ilibrary.org/content/publication/4dd50c09-en

[705] Duffy, E., Ritchie, S., Metcalfe, S., *et al.* (2018). Antibacterials dispensed in the community comprise 85%-95% of total human antibacterial consumption. *Journal of Clinical Pharmacy and Therapeutics, 43*(1), 59-64. https://doi.org/10.1111/jcpt.12610

[706] Gardiner, S.J., Basevi, A.B., Hamilton, N.L., *et al.* (2020). Point prevalence surveys of antimicrobial use in adult inpatients at Canterbury District Health Board Hospitals. *The New Zealand Medical Journal, 133*(1525), 18-15.

[707] Duffy, E., Ritchie, S., Metcalfe, S., *et al.* (2018). Antibacterials dispensed in the community comprise 85%-95% of total human antibacterial consumption. *Journal of Clinical Pharmacy and Therapeutics, 43*(1), 59-64. https://doi.org/10.1111/jcpt.12610; Duffy, E., Gardiner, S., du Plessis, T., *et al.* (2015). A snapshot of antimicrobial use in New Zealand hospitals: A comparison to Australian and English data. *The New Zealand Medical Journal, 128*(1421), 82-84.

Figure 32: Community antibiotic dispensing measured in defined daily dose (DDD) per 1,000 inhabitants per day during 2013–2018.[708]

[708] Thomas, M., Tomlin, A., Duffy, E.*, et al.* (2020). Reduced community antibiotic dispensing in New Zealand during 2015–2018: Marked variation in relation to primary health organisation. *The New Zealand Medical Journal, 133*(1518), 33.

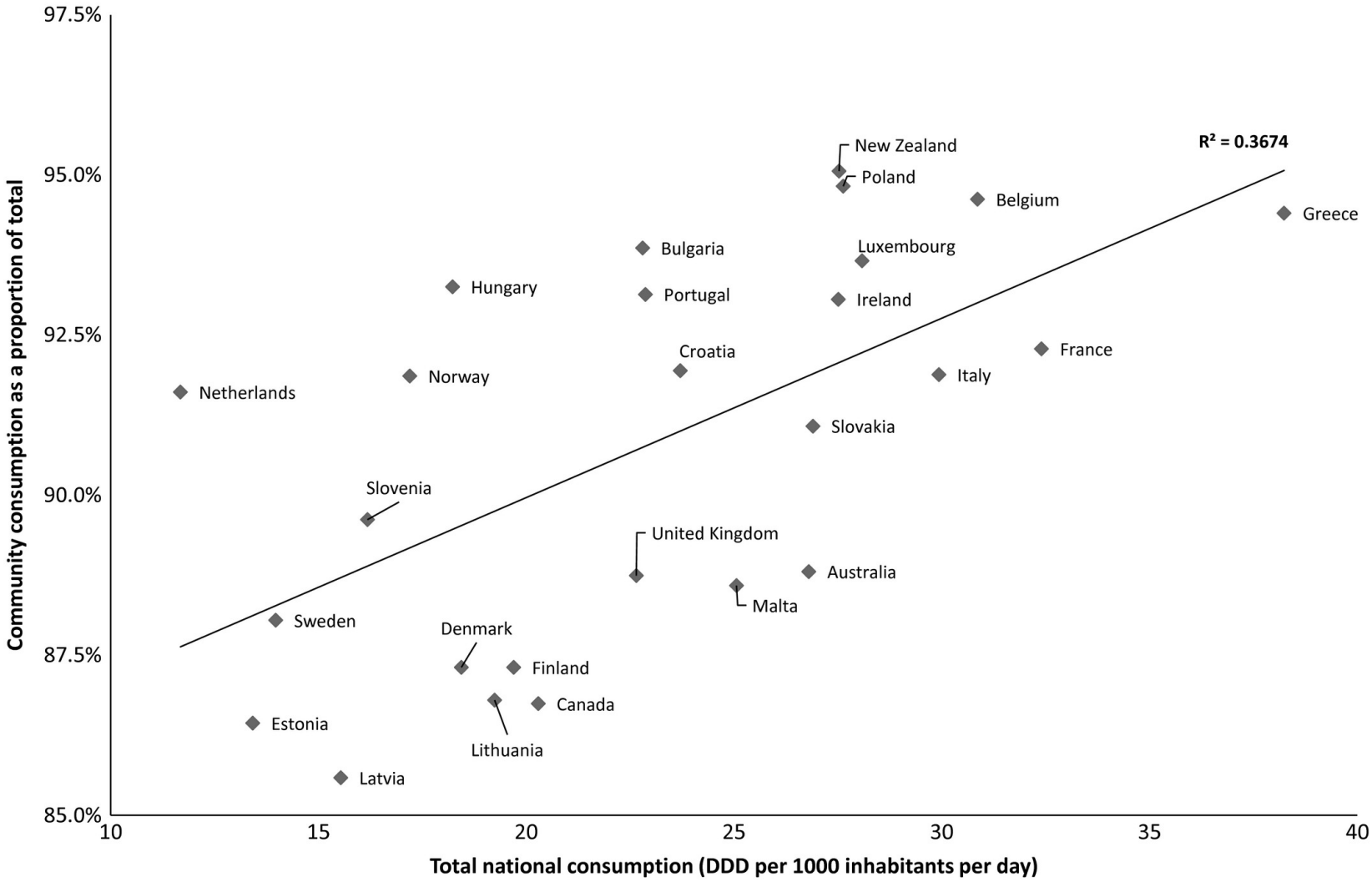


Figure 33: Scatterplot of community antibiotic consumption in relation to total antibiotic consumption, measured in defined daily dose (DDD) per 1000 population per day.[709]

[709] Duffy, E., Ritchie, S., Metcalfe, S.*, et al.* (2018). Antibacterials dispensed in the community comprise 85%-95% of total human antibacterial consumption. *Journal of Clinical Pharmacy and Therapeutics, 43*(1), 59-64. https://doi.org/10.1111/jcpt.12610

Community use is excessive

In 2017, just under half of all New Zealanders were dispensed at least one systemic antibiotic in the community, mostly for oral administration. In the same year, around 1 in 25 people were dispensed topical antibiotics.

In the most recent OECD comparison, Aotearoa New Zealand had the **fourth highest** level of antibiotic prescribing … surpassed only by Greece, Italy, and Korea.

There are differences between DHBs, people of different ages, and ethnic groups. Young people, Pacific and Māori people, and people in the North Island are dispensed more antibiotics.[710] Ninety-seven percent of children in Aotearoa New Zealand have been dispensed at least one antibiotic course by the age of five, and half have had more than seven antibiotic courses.[711] It should be noted that higher relative use doesn't always imply overuse – see section below on under-prescribing, and section 3.4 for details on health inequities.

There was a small, sustained decline in community antibiotic dispensing in Aotearoa New Zealand between 2015 and 2018, with an average 4.6% drop every year (see Figure 32).[712] This overall percentage reduction of 14% across 2015-2018 was comparable to that observed in similar countries. However, Aotearoa New Zealand had a higher starting point. Further, this period of decline was preceded by a significant increase (49%, standardised to population) in community antibiotic use between 2006 and 2014 across all age groups and ethnicities.[713]

…this period of decline was preceded by a significant increase (49%, standardised to population) in community antibiotic use between 2006 and 2014 across all age groups and ethnicities.

There is seasonal variation observed in antibiotic dispensing rates in Aotearoa New Zealand, with a rise in the winter months corresponding with increased viral respiratory infections (Figure 34).[714] Reducing use of antibiotics to unnecessarily 'treat' these viral infections is an important area of focus.

In Aotearoa New Zealand, community antimicrobial prescribing decreased during the weeks of alert levels three and four in 2020. Antibiotic dispensing rates fell by 36% during this period, with no increase in hospitalisation rates for sentinel infections that could be prevented by antibiotic prescribing. Large reductions were seen with antibiotics mostly used for respiratory infections or UTIs.[715] This finding indicates that antibiotic prescribing in Aotearoa New Zealand could be safely

[710] Health Quality & Safety Commission. (2021). Atlas of Healthcare Variation. Retrieved 15 April, 2021, from https://public.tableau.com/profile/hqi2803#!/vizhome/Communityantibioticusesinglemap/AtlasofHealthcareVariationCommunityantibioticuse

[711] Hobbs, M.R., Grant, C.C., Ritchie, S.R., *et al.* (2017). Antibiotic consumption by New Zealand children: Exposure is near universal by the age of 5 years. *Journal of Antimicrobial Chemotherapy, 72*(6), 1832-1840. https://doi.org/10.1093/jac/dkx060

[712] Thomas, M., Tomlin, A., Duffy, E., *et al.* (2020). Reduced community antibiotic dispensing in New Zealand during 2015–2018: Marked variation in relation to primary health organisation. *The New Zealand Medical Journal, 133*(1518), 33.

[713] Williamson, D.A., Roos, R.F., & Verrall, A. (2016). *Surveillance report: Antibiotic consumption in New Zealand, 2006-2014* (FW15031). Porirua, NZ: ESR.

[714] Whyler, N., Tomlin, A., Tilyard, M., *et al.* (2018). Ethnic disparities in community antibacterial dispensing in New Zealand, 2015. *The New Zealand Medical Journal, 131*(1480), 50-60.

[715] Duffy, E., Thomas, M., Hills, T., *et al.* (2021). The impacts of New Zealand's COVID-19 epidemic response on community antibiotic use and hospitalisation for pneumonia, peritonsillar abscess and rheumatic fever. *The Lancet Regional Health - Western Pacific, 12*, 100162. https://doi.org/10.1016/j.lanwpc.2021.100162

reduced, especially given that a substantial proportion of antibiotic prescribing is for self-limiting respiratory infections. However it should be noted that COVID-19 public health measures likely reduced levels of infection during this time, perhaps accounting for some of the dispensing reduction.

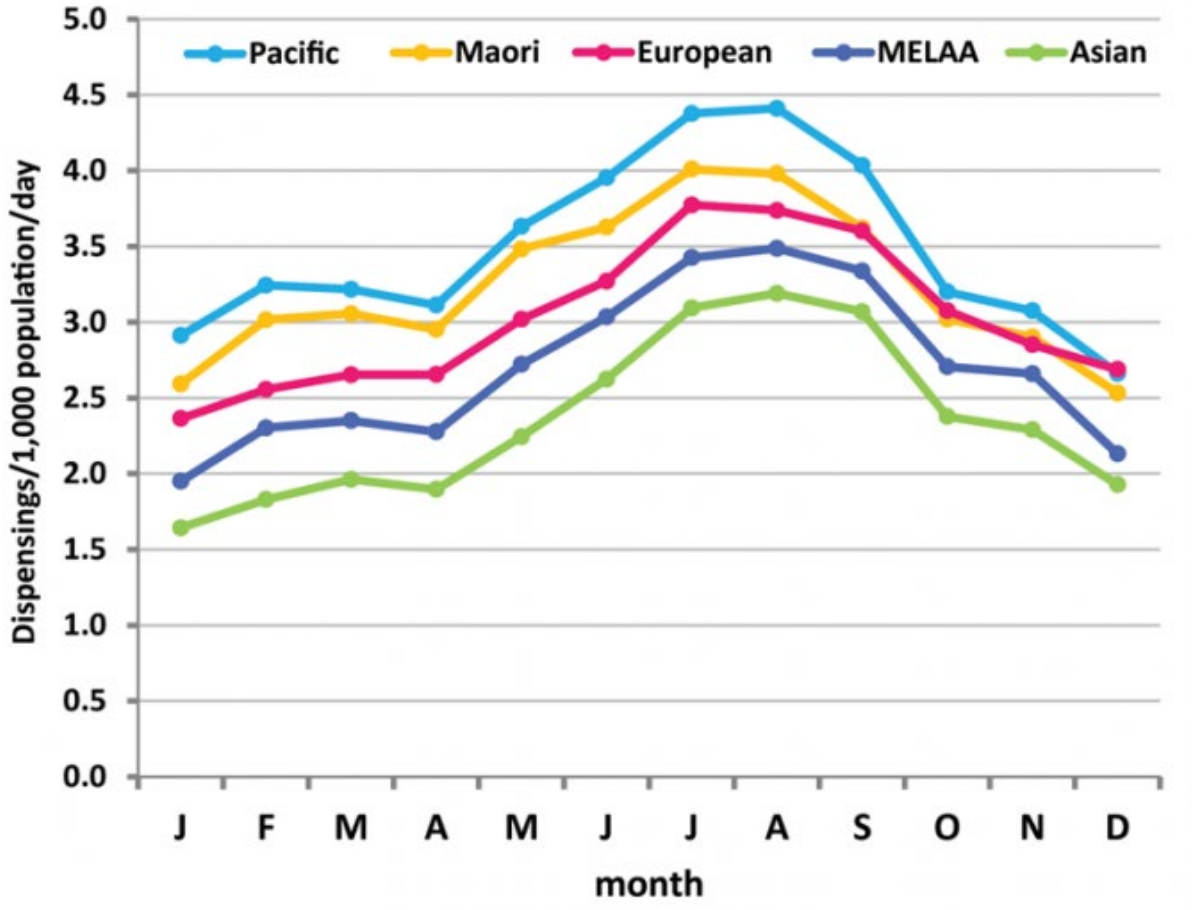


Figure 34: Community antibiotic dispensing (dispensings per 1,000 population per day) by ethnicity and month in New Zealand during 2015. Note the peak in dispensing in winter (June, July, August).[716]

Patient expectations contribute to antimicrobial use

Patient expectations can influence antimicrobial prescribing, potentially leading to inappropriate antimicrobial use. For example, we have heard anecdotally that GPs receive complaints if they refuse to provide antibiotics to a person with a viral sore throat, while others report that their prescribing is influenced by concern about potential complaints if they do not do what the patient demands.[717]

While the proportion of people who feel entitled to antibiotics when visiting the doctor is small, (with 3.7% of people having high feelings of entitlement, 18.5% feeling moderately entitled, and 77.9% having low entitlement[718]), concerns around patient expectations may still impact prescriber behaviour. Supporting GPs to communicate their prescribing decisions is essential and should occur alongside efforts to change patient expectations.

[716] Whyler, N., Tomlin, A., Tilyard, M.*, et al.* (2018). Ethnic disparities in community antibacterial dispensing in New Zealand, 2015. *The New Zealand Medical Journal, 131*(1480), 50-60.
[717] Gardiner, S. (2021). Personal communication.
[718] Lee, C., Norris, P., Duck, I.*, et al.* (2018). Demographic and psychological factors associated with feelings of antibiotic entitlement in New Zealand. *Antibiotics, 7*(3), 82. https://doi.org/10.3390/antibiotics7030082

Aotearoa New Zealand, joined only by the US, lets pharmaceutical companies advertise to consumers. Medicines New Zealand reports that prescription antimicrobials haven't been advertised to New Zealand consumers for at least the past 20 years,[719] so advertising is unlikely to be currently contributing to patient expectations for antimicrobials. If direct-to-consumer advertising of antimicrobials does re-occur at some stage in the future, this may contribute to patient expectations for access to antimicrobial drugs.[720] The Royal New Zealand College of GPs has called for the prohibition of direct-to-consumer advertising of all prescription medications.[721]

Some groups aren't getting the antimicrobials they need

However, it is not as simple as just reducing antibiotic consumption for everyone. The burden of infectious disease is not evenly distributed throughout the population (see section 3.4.2), so even when optimised, antimicrobial use would be expected to vary across population subsets. Any attempts to decrease our use of antimicrobial drugs should ensure that those decreases occur in the right places (i.e. where antimicrobial drugs are being used inappropriately), not among people who could benefit from access.

Any attempts to decrease our use of antimicrobial drugs should ensure that those decreases occur in the right places, not among people who could benefit from access.

Some evidence suggests that Māori and Pacific peoples are under-prescribed antimicrobials, by a margin of up to 29% less than is warranted by their higher infectious disease burden.[722] A 2005-2006 study based in Tairāwhiti found that antibiotic dispensing for Māori was 67% of the level of dispensing for non-Māori,[723] despite higher infection disease prevalence (see section 3.4.2). Under-prescribing is particularly problematic when antimicrobials are required in a timely manner to avoid disease progression, such as in the case of group A *Streptococcus* infections and rheumatic fever, where timely diagnosis and antibiotic access is key to preventing progression to rheumatic heart disease.[724]

Pharmac aspires to eliminate inequities in medicines access by 2025, but this will require collaboration between all parts of the health sector and acknowledgement of the diverse barriers to medicines access.[725] Pharmac's systems and processes are currently being reviewed, including with a focus on whether they help achieve equitable health outcomes for all New Zealanders, including

[719] Medicines New Zealand. (2021). Personal communication.
[720] Franquiz, M.J., & McGuire, A.L. (2021). Direct-to-consumer drug advertisement and prescribing practices: Evidence review and practical guidance for clinicians. *Journal of General Internal Medicine, 36*(5), 1390-1394. https://doi.org/10.1007/s11606-020-06218-x
[721] The Royal New Zealand College of General Practitioners. (2017). Position statement: Prohibition of direct-to-consumer advertising of prescription medications. Retrieved from https://rnzcgp.org.nz/gpdocs/New-website/Advocacy/Position-Statements/2017.03-DTCAPositionStatement.pdf
[722] Metcalfe, S., Vallabh, M., Murray, P., *et al.* (2019). Over and under? Ethnic inequities in community antibacterial prescribing. *The New Zealand Medical Journal, 132*(1488), 65-68. ; Thomas, M., Whyler, N., Tomlin, A., *et al.* (2019). Ethnic disparities in community antibacterial dispensing in New Zealand: Is current antibacterial dispensing for Maori and Pacific people insufficient or excessive, or both? *The New Zealand Medical Journal, 132*(1505). ; Whyler, N., Tomlin, A., Tilyard, M., *et al.* (2018). Ethnic disparities in community antibacterial dispensing in New Zealand, 2015. *The New Zealand Medical Journal, 131*(1480), 50-60.
[723] Norris, P., Horsburgh, S., Keown, S., *et al.* (2011). Too much and too little? Prevalence and extent of antibiotic use in a New Zealand region. *Journal of Antimicrobial Chemotherapy, 66*(8), 1921-1926. https://doi.org/10.1093/jac/dkr194
[724] Anderson, A., Mills, C., & Eggleton, K. (2017). Whānau perceptions and experiences of acute rheumatic fever diagnosis for Māori in Northland, New Zealand. *The New Zealand Medical Journal, 130*(1465), 80-89.
[725] Pharmac. (2019). *Achieving medicine access equity in Aotearoa New Zealand: Towards a theory of change*. Wellington, NZ: Pharmaceutical Management Agency. Retrieved from https://pharmac.govt.nz/assets/achieving-medicine-access-equity-in-aotearoa-new-zealand-towards-a-theory-of-change.pdf

Māori and Pacific peoples and people with disabilities. The interim report was released in December 2021 and assessed that Pharmac has a long way to go towards its goal of improving equitable outcomes.[726]

He Ako Hiringa, a collective of health sector experts, data scientists, equity advisors, clinical educators, clinical writers, and subject matter experts, aims to improve medicines access equity in Aotearoa New Zealand.[727] One of the ways they are working to do this is by making inequities visible to prescribers: they have developed a dashboard, currently available for diabetes prescribing, that allows prescribers to look at their prescribing patterns by age, ethnicity, gender, and deprivation, and compare those patterns to all patients in their practice and a national dataset.[728] This dashboard is discussed further in section 5.5.1.

The fragmented nature of community prescribing makes change challenging

Managing antimicrobial use in the community is far more challenging than in hospital settings because of the wide range of healthcare settings (e.g. private surgical hospitals, ARC facilities, pharmacies, GP clinics, dental clinicals, optometrists).

There are gaps in our knowledge about prescribing by non-medical health practitioners

The proportion of prescriptions from non-medical prescribers (i.e. people who are trained to prescribe drugs but are not doctors) is increasing. One study found that the proportion of prescriptions attributable to non-medical prescribers increased from 1.8% in 2016 to 3.6% in 2019, with antimicrobials among the most prescribed medicines.[729] Among non-medical prescribers, nurse prescribers were the largest contributors between 2016 and 2020 (50% of non-medical prescriptions), followed by dentists (23%), midwives (14%), pharmacists (9%), optometrists (2%), and dieticians (2%). There has been little study of patterns and quality of prescribing among some of these prescribers, such as dentists.

… the proportion of prescriptions attributable to non-medical prescribers increased from 1.8% in 2016 to 3.6% in 2019, with antimicrobials among the most prescribed medicines.

The Optometrists and Dispensing Opticians Board commissions monthly analysis of prescribing patterns.[730] Optometrists are prescribing increasing volumes of antimicrobials every year. Most prescriptions from optometrists are for topical products, with oral medications making up a small proportion of the total prescriptions. Of the oral prescriptions, 60% are antibiotics and more than 7% are antivirals. One antibiotic, azithromycin, accounts for 39% of all oral medications prescribed by optometrists.[731]

The aged care sector faces unique challenges

The aged care sector faces unique challenges to tackle its high rates of antimicrobial prescriptions. There is some data available on antimicrobial use in the aged care setting via the Health Quality &

[726] Pharmac Review Panel. (2021). *Pharmac review: Interim report*. Wellington, NZ: Ministry of Health. Retrieved from https://pharmacreview.health.govt.nz/assets/Pharmac-Review-Interim-report.pdf
[727] He Ako Hiringa. (n.d.). About us. Retrieved 7 December, 2021, from https://www.akohiringa.co.nz/about
[728] He Ako Hiringa. (2021, 31 May). EPiC. Retrieved 18 November, 2021, from https://epic.akohiringa.co.nz/diabetesPatientDemographic
[729] Raghunandan, R., Marra, C.A., Tordoff, J., *et al.* (2021). Examining non-medical prescribing trends in New Zealand: 2016–2020. *BMC Health Services Research, 21*(1). https://doi.org/10.1186/s12913-021-06435-y
[730] Turnbull, P. (2021). Personal communication.
[731] Turnbull, P.R., & Craig, J.P. (2021). Oral medication prescribing by optometrists in New Zealand. *Clinical and Experimental Optometry, 104*(3), 425-427. https://doi.org/10.1111/cxo.13089

Safety Commission's (HQSC's) Atlas of Healthcare Variation (although only spanning 2015-2018). In 2017, 69% of aged care residents in Aotearoa New Zealand received a course of systemic antibiotics, with a reduction in ethnic disparities compared with data from 2015.[732]

Some of these challenges are likely related to the model of prescribing – which is often led by nursing staff or family engagement with a GP, while the GP is potentially prescribing off site. Anecdotally, challenges include:

- Prescribing cover over the weekend, for example, where there might be an increase of 'just-in-case' prescribing on a Friday to cover potential deterioration over the weekend.
- A lot of 'pro re nata' prescribing (i.e. 'take as needed') for convenience (e.g. of topical antifungals or antibiotics that may be started when symptoms like 'red skin' or a 'red eye' occur).
- Prescribing antimicrobials for a UTI on the basis of bacteria detected by a dipstick urine test. This is despite the fact that the presence of bacteria without symptoms does not indicate active infection. While it is acknowledged that it may be hard to detect UTI symptoms in some elderly people, inappropriate antimicrobial treatment for asymptomatic bacteria in the urine may cause adverse effects including potential transition from asymptomatic to symptomatic UTI, as well as driving AMR. The problem of drug-resistant UTIs is further explored in section 4.6.

In Australia, surveys in ARC services have highlighted several areas where significant improvement is needed. This includes addressing the high rates of antimicrobial use for prophylaxis (20% of prescriptions) and 'as needed' (15% of prescriptions), which most commonly relate to topical antimicrobials (90% of that 15%). Following relatively consistent prescribing levels since 2016, there was an increase in documentation of antimicrobial review or stop dates in the prescription (one quality marker for AMS), but a decrease in recording the indication for antimicrobial use in 2019 (where recording an indication is another quality marker for AMS).[733] Similarly, in the UK, high antimicrobial use for prophylaxis has been reported in aged care.[734]

… inappropriate antimicrobial treatment for asymptomatic bacteria in the urine may cause adverse effects including potential transition from asymptomatic to symptomatic UTI, as well as driving AMR.

[732] Health Quality & Safety Commission. (2021). Atlas of Healthcare Variation. Retrieved 15 April, 2021, from https://public.tableau.com/profile/hqi2803#!/vizhome/Communityantibioticusesinglemap/AtlasofHealthcareVariationCommunityantibioticuse

[733] Bennett, N., Walker, K., Buising, K., *et al.* (2021). Topical antimicrobial prescribing patterns in residents of Australian aged-care facilities: use of a national point prevalence survey to identify opportunities for quality improvement. *American Journal of Infection Control*. https://doi.org/https://doi.org/10.1016/j.ajic.2021.03.019; National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care. (2020). *2019 Aged care national antimicrobial prescribing survey report*. Sydney, Australia: Retrieved from https://www.safetyandquality.gov.au/publications-and-resources/resource-library/2019-aged-care-national-antimicrobial-prescribing-survey-report-ac-naps

[734] Thornley, T., Ashiru-Oredope, D., Beech, E., *et al.* (2019). Antimicrobial use in UK long-term care facilities: Results of a point prevalence survey. *Journal of Antimicrobial Chemotherapy, 74*(7), 2083-2090. https://doi.org/10.1093/jac/dkz135

Information we collect on antimicrobial use

Quantity

The majority of community antimicrobial dispensing[735] is captured in the national dispensing database (the Pharmaceutical Collection).[736] This dataset can tell us some important information about how the quantity of antimicrobial use changes with time and with certain patient demographics like age, ethnicity, or region. This dataset has informed some basic understanding of community antimicrobial use, with several ad hoc publications from researchers, and workstreams such as the HQSC Atlas of Healthcare Variation. However, it has not been systematically harnessed for regular reporting.

In 2016, 12 DHBs reported antimicrobial use by at least one defined metric – mostly confined to volume of antimicrobials used.[737] It is difficult to access useful data on the volume of antimicrobials used in public hospitals. Hospital antimicrobial dispensing does not feed into the Pharmaceutical Collection (as the funding model is different) and there is currently no requirement for DHBs to provide this information on antimicrobial prescribing or dispensing in an easy-to-use format. Dispensing data currently offers the best mechanism for between-facility comparisons as electronic prescribing is only used in a minority of DHBs. In Aotearoa New Zealand's public hospitals, the quantity of antimicrobial use (standardised to bed days) is lower than Australia and England, but higher than other countries such as Switzerland and Sweden.[738] That doesn't tell us about quality of prescribing, which can be evaluated by point prevalence surveys (see section below).

… there is no routine reporting of antimicrobial use in human health, and **no target for reduction**.

Currently, the data collection that occurs in the community (Pharmaceutical Collection) and in hospitals (held by DHBs in various formats) is not leveraged optimally to assess quantity of antimicrobial use in human health in Aotearoa New Zealand: there is no routine reporting of antimicrobial use in human health, and no target for reduction. The government's self-assessment, as reported to the recent Tripartite survey, said there was "no national plan or system for monitoring use of antimicrobials" in human health (see appendix 7.5).[739] The *New Zealand AMR Action Plan* published in 2017 included an action to "develop the business case and implement a standardised surveillance system for monitoring antimicrobial prescribing in the community and in hospitals, to be completed by 2022.[740] This work has not been completed.

[735] Note that dispensing does not necessarily correlate with consumption. For example, there are gaps – some people may collect a script but never take it or may take part of it (stopping when lab results come back, or when they feel better). In this way, dispensing is only a surrogate for consumption, but probably the best we can do.
[736] Ministry of Health. (n.d.). Pharmaceutical data web tool. Retrieved 27 October, 2021, from https://minhealthnz.shinyapps.io/pharmaceutical_data_web_tool/
[737] Gardiner, S.J., Pryer, J.A., & Duffy, E.J. (2017). Survey of antimicrobial stewardship practices in public hospitals in New Zealand district health boards. *The New Zealand Medical Journal, 130*(1458), 27-41.
[738] Duffy, E., Gardiner, S., du Plessis, T.*, et al.* (2015). A snapshot of antimicrobial use in New Zealand hospitals: A comparison to Australian and English data. *The New Zealand Medical Journal, 128*(1421), 82-84.
[739] World Health Organization. (2020). Global database for the tripartite antimicrobial resistance (AMR) country self-assessment survey (TrACSS). Retrieved 4 August 2021 https://amrcountryprogress.org/
[740] Ministry of Health and Ministry for Primary Industries. (2017). *New Zealand Antimicrobial Resistance Action Plan*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/publication/new-zealand-antimicrobial-resistance-action-plan

Other data gaps

We don't know how easy it is to access antimicrobials without a prescription in Aotearoa New Zealand. A UK study demonstrated the availability of antibiotics online without a prescription, highlighting the risk that online antibiotic suppliers pose to AMS and patient safety.[741]

Internet sales of antimicrobials are governed by the same rules as in-person sales – that is, a prescription from an Aotearoa New Zealand registered doctor is needed for most systemic antimicrobials to be shipped from overseas. However, we don't know whether this is enforced in practice.

Some antimicrobials are available 'over the counter'. These are not captured in the Pharmaceutical Collection. Examples include:

- Trimethoprim – pharmacist only.
- Chloramphenicol eye drops – pharmacist only.
- Topical antifungals like clotrimazole or miconazole – from pharmacist only (vaginal or oral products) to general sale.
- Oral fluconazole (single dose) – pharmacist only.
- Acyclovir and penciclovir creams.
- Nystatin oral liquid and vaginal cream.
- Malathion topical shampoo or liquid spray.

Assessing the quality of prescribing

Most of the available data focuses on the quantity of antimicrobials dispensed, while information about the quality of antimicrobial use is lacking. This makes it hard to assess at the national level whether people are prescribed the right antimicrobials, at the right time, via the right route, at the right dose, and for the right duration.

Hospitals and the National Antimicrobial Prescribing Survey

Some quality improvement initiatives, such as the HQSC's SSI Improvement programme or individual DHBs undertaking point prevalence surveys, do provide information on quality of prescribing in the hospital setting.[742]

For example, the New Zealand SSI Improvement Programme, instituted by HQSC and covering both public and private hospitals, provided guidance for two surgical specialities (orthopaedic and cardiac surgery) and reported improved prescribing for routine antibiotic prophylaxis for orthopaedic surgery.[743]

In Australia, the National Centre for Antimicrobial Stewardship provides guidance and auditing tools to survey antimicrobial use and collates findings.[744] The results of the National Antimicrobial Prescribing Survey (NAPS) are published annually. The 2019 report for hospitals shows some

[741] Boyd, S.E., Moore, L.S.P., Gilchrist, M., *et al.* (2017). Obtaining antibiotics online from within the UK: A cross-sectional study. *Journal of Antimicrobial Chemotherapy, 72*(5), 1521-1528. https://doi.org/10.1093/jac/dkx003

[742] Morris, A.J., Roberts, S.A., Grae, N., *et al.* (2018). The New Zealand Surgical Site Infection Improvement (SSII) programme: A national quality improvement programme reducing orthopaedic surgical site infections. *The New Zealand Medical Journal, 131*(1479), 45-56. ; Gardiner, S.J., Basevi, A.B., Hamilton, N.L., *et al.* (2020). Point prevalence surveys of antimicrobial use in adult inpatients at Canterbury District Health Board Hospitals. *The New Zealand Medical Journal, 133*(1525), 18-15.

[743] Morris, A.J., Roberts, S.A., Grae, N., *et al.* (2018). The New Zealand Surgical Site Infection Improvement (SSII) programme: A national quality improvement programme reducing orthopaedic surgical site infections. *The New Zealand Medical Journal, 131*(1479), 45-56. ; Artus, J., Blick, G., & Ryan, M. (2018). *Evaluation of the surgical site infection improvement programme: Final (summative) report*. Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/Surgical-Site-Infection-Surveillance/SSIIP-evaluation-report-27Aug2018-FINAL.pdf

[744] National Centre for Antimicrobial Stewardship. (n.d.). National Centre for Antimicrobial Stewardship. Retrieved 29 October, 2021, from https://www.ncas-australia.org/

improvements since this process began, for example: documenting the indication for prescriptions in the clinical record in hospitals has increased from 70.5% in 2013 to 84.2% in 2019, but there are other areas where there are no improvements or even declines (e.g. compliance with prescription guidelines decreased from 72.1% in 2013 to 65.3% in 2019).[745]

Since 2015, Aotearoa New Zealand has had access to the Australian NAPS, initially provided as a pilot study. A recent survey of antimicrobial use in Canterbury DHB using the NAPS approach found that 74% of prescriptions were compliant with guidelines and 83% were appropriate.[746] Some 17 hospitals and 139 individual auditors have registered to use NAPS in Aotearoa New Zealand. However, as it has not been applied as a national system, there is no overarching visibility of audit findings, meaning we cannot compare between facilities. A contract for continued NAPS use is under negotiation, with continued access until early 2022 while negotiations are ongoing. The pressures of preparing for and responding to the COVID-19 pandemic likely means that many DHBs won't have undertaken NAPS in 2021.

We lack understanding of the quality of prescribing

We lack data on the quality of antimicrobial prescribing in most community and hospital settings. Our software systems do not link the antimicrobial prescribed or dispensed with what the antimicrobial was used for (i.e. the indication). In addition, not all healthcare providers use electronic prescribing methods, instead relying on paper-based systems. Plus, prescribers are not required to record the indication. This means we can't tell whether the particular antimicrobial prescribed is appropriate for the patient's ailment and consistent with prescribing guidelines. Overseas evidence shows that a significant proportion of community prescriptions are inappropriate. For example, in a US study, only 23% were appropriate and 36% were 'potentially appropriate'.[747]

As well as providing information about the quality of prescribing, requiring prescribers to record an indication promotes thoughtful prescribing and may therefore in itself support good AMS practices. See section 5.5.1 for more on recording an indication and AMS more generally.

Prescribers are not required to record the indication. This means **we can't tell whether the particular antimicrobial prescribed is appropriate** for the patient's ailment and consistent with prescribing guidelines.

[745] National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care. (2021). *Antimicrobial prescribing practice in Australian Hospitals Results of the 2019 Hospital National Antimicrobial Prescribing Survey*. Sydney, Australia: ACSQHC.
[746] Gardiner, S.J., Basevi, A.B., Hamilton, N.L*., et al.* (2020). Point prevalence surveys of antimicrobial use in adult inpatients at Canterbury District Health Board Hospitals. *The New Zealand Medical Journal, 133*(1525), 18-15.
[747] Chua, K.-P., Fischer, M.A., & Linder, J.A. (2019). Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study. *BMJ*, k5092. https://doi.org/10.1136/bmj.k5092

4.4.2 Antimicrobial use in animals is low but could still be improved

Our context and farming systems are unique, which can make it difficult to compare our rates of antimicrobial use in food-producing animals with other countries. For example, the profile of agricultural diseases present in Aotearoa New Zealand differs to other countries, as well as our geography and farming techniques.

While comparison between countries is difficult, Aotearoa New Zealand has a comparatively low rate of antimicrobial use in animals. For example, a local study that considered antimicrobial use in animals in 26 countries up to 2012 ranked our overall use the third lowest.[748] This study used data on the volume of antimicrobials sold compared to the biomass of animals, with only Norway and Iceland having an overall lower use rate than Aotearoa New Zealand.

A local study that considered antimicrobial use in animals in 26 countries up to 2012 ranked our overall use the **third lowest**.

Low antimicrobial use is an important target but needs to be considered in conjunction with animal welfare concerns, food safety concerns, and productivity. Targeting reductions to specific types of use (e.g. types of prophylaxis) is more beneficial than overall reduction targets alone.

Ideally, each type of animal farming would be considered on its own (rather than combined for the agricultural sector as a whole) to account for differences and to inform specific, effective actions. For example, while our non-intensive pastoral farming approach enables low antimicrobial use in animals such as sheep and cattle, the intensive nature of pig and poultry farming can lead to more spread of infectious disease that necessitates antimicrobial use. There is also variability between farms based on factors such as their chosen farming techniques.

In absolute terms, the majority of antimicrobial use in Aotearoa New Zealand is in the pig and poultry meat industries – with the bulk coming from zinc bacitracin use in poultry meat (which is rapidly declining due to industry initiatives – see discussion below). Poultry are farmed in large numbers and in close contact – even on free-range farms, poultry will not necessarily utilise all space provided and remain in close groups.[749] Pig farming is similarly intensified; the pork industry reports that around 3% of pigs in Aotearoa New Zealand are free range and 42% are in free-farmed systems (and even outdoor-dwelling pigs are susceptible to disease).[750]

In the poultry and pig industries, antibiotics are estimated to be used at a rate of more than 500 mg per kg of animal biomass (known as 'mg/PCU'), which is fifty times higher than the overall rate of 10.2 mg/PCU across all use in food animals in Aotearoa New Zealand (from 2014-2018).[751] This

[748] Hillerton, J.E., Irvine, C.R., Bryan, M.A., *et al.* (2017). Use of antimicrobials for animals in New Zealand, and in comparison with other countries. *New Zealand Veterinary Journal, 65*(2), 71-77. https://doi.org/10.1080/00480169.2016.1171736
[749] Pettersson, I., Freire, R., & Nicol, C.J. (2016). Factors affecting ranging behaviour in commercial free-range hens. *World's Poultry Science Journal, 72*(1), 137-150. https://doi.org/10.1017/S0043933915002664
[750] NZ Pork. (n.d.). Farming styles in New Zealand. Retrieved 7 December, 2021, from https://www.nzpork.co.nz/farmers/pork-farming-styles-in-new-zealand
[751] Hillerton, J.E., Bryan, M.A., Beattie, B.H., *et al.* (2021). Use of antimicrobials for food animals in New Zealand; updated estimates to identify a baseline to measure targeted reductions. *New Zealand Veterinary Journal*, 1-6. https://doi.org/10.1080/00480169.2021.1890648

estimate has been disputed by industry.[752] Further, mg/PCU does not take into account the amount of meat produced, with more kilograms of meat produced per PCU on pig farms compared to some sheep and beef farms.[753]

Across all animals, Aotearoa New Zealand uses proportionally more cephalosporins and macrolides, but less fluoroquinolones compared with European countries. Third and fourth generation cephalosporins, macrolides, and fluoroquinolones are all considered by the WHO to be critically important antimicrobials for human health (along with ketolides, and glycopeptides, see appendix 7.3).[754] However, macrolides are rated as having lower importance to human health in other jurisdictions, including Europe and Australia.[755]

Trends in antimicrobial use in animals

Between 2012 and 2017, Aotearoa New Zealand's total antimicrobial sales for use in animals was increasing, but since 2017 there has been a promising decline.[756] Similarly, sales of critically important antibiotics have also decreased between 2017 and 2019, by 22%. Some of this decline may be due to a decrease in animal numbers, but much has been driven by concerted efforts in the pig and poultry industries to reduce use of the polypeptide zinc bacitracin and the macrolide tylosin.[757]

When comparing trends in food animal use from 2012-2018, Aotearoa New Zealand's use increased 11% since 2012 but has stabilised and is still **comparatively low**.

In Aotearoa New Zealand in 2019, more than 61 tonnes of antimicrobials were sold for animals.[758] While this can form the basis for establishing a baseline against which to measure overall improvements, we need data specific to different sectors to measure improvement that considers the different farming contexts. In addition, reporting use in relation to animal biomass would allow for more ready comparison between years and sectors.

At a global level, the countries that provided data to the OIE for 2015-2017 reported an overall decrease of 34% in antimicrobial use rate.[759] When comparing trends in food animal use from 2012-2018, Aotearoa New Zealand's use increased 11% since 2012 but has stabilised and is still comparatively low. Several European nations had decreased use (Norway by 23%, Sweden by 7%, UK

[752] PIANZ. (2021). Personal communication.
[753] NZ Pork. (2021). Personal communication.
[754] Collignon, P.C., Conly, J.M., Andremont, A., *et al.* (2016). World Health Organization ranking of antimicrobials according to their importance in human medicine: A critical step for developing risk management strategies to control antimicrobial resistance from food animal production. *Clinical Infectious Diseases, 63*(8), 1087-1093. https://doi.org/10.1093/cid/ciw475
[755] Trott, D.J., Turnidge, J., Kovac, J.H., *et al.* (2021). Comparative macrolide use in humans and animals: should macrolides be moved off the World Health Organisation's critically important antimicrobial list? *Journal of Antimicrobial Chemotherapy, 76*(8), 1955-1961. https://doi.org/10.1093/jac/dkab120
[756] The Agricultural Compounds and Veterinary Medicines Team. (2021). *2019 antibiotic agricultural compound sales analysis*. Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/48622-2019-Antibiotic-Agricultural-Compound-Sales-Analysis
[757] Ibid.
[758] Hillerton, J.E., Bryan, M.A., Beattie, B.H., *et al.* (2021). Use of antimicrobials for food animals in New Zealand; updated estimates to identify a baseline to measure targeted reductions. *New Zealand Veterinary Journal*, 1-6. https://doi.org/10.1080/00480169.2021.1890648; The Agricultural Compounds and Veterinary Medicines Team (New Zealand Food Safety). (2020). *Antibiotic sales analysis 2018*. Wellington, New Zealand: Ministry for Primary Industries.
[759] World Organisation for Animal Health (OIE). (2021). *OIE annual report on antimicrobial agents intended for use in animals: Fifth report*. Paris, France: World Organisation for Animal Health (OIE). Retrieved from https://www.oie.int/app/uploads/2021/05/a-fifth-annual-report-amr.pdf

by 56%, Netherlands by 23%, Italy by 28%) while others had increased use (e.g. 14% in Slovakia and 27% in Poland).[760]

Antibiotic use is highest in pig and poultry sectors

In 2019, zinc bacitracin was the highest selling individual compound available in Aotearoa New Zealand accounting for around 38% of the antibiotics sold.[761] It is registered for use in both pigs and poultry. MPI data does not contain information on the proportion used in each industry, however we understand that both industries collect their own data. Zinc bacitracin use in pigs has declined markedly over the last 3-5 years as a result of major improvements in the management of enteric diseases, and since 2019 there has been no recorded use of this antimicrobial in the pig industry.[762]

Active efforts to reduce use are ongoing and the poultry industry expects that 90% of meat chicken production won't use zinc bacitracin in 2022.

Zinc bacitracin is still used in the meat poultry industry to control necrotic enteritis, a major disease in poultry worldwide that is often caused by coccidiosis parasite infection. However, active efforts to reduce use in Aotearoa New Zealand are ongoing and the industry expects that 90% of meat chicken production won't use zinc bacitracin in 2022.[763] Instead, there are a range of non-antimicrobial products designed to support chicken gut integrity that can be deployed, although it can reportedly be a difficult process to register some of these alternative products in Aotearoa New Zealand.[764] There are coccidiosis vaccines available for use in poultry (e.g. Eimeriavax 4m) and these are used in layer poultry, while use in short-lived meat chickens still poses issues. Zinc bacitracin is not of critical importance to human health.

Pig industry

All antibiotic use on pig farms should be under the direction of a vet, with farmers observing and treating illness on-farm based on information provided during a vet consultation. Vets train workers on-farm to recognise signs of disease and how to identify and use appropriate treatments. While common antibiotics, such as penicillin, are often effective in pigs, a small proportion are treated with antibiotics that may be of more concern from a human health perspective. In 2017, the New Zealand pork industry implemented a voluntary position not to use fluoroquinolones and third and fourth generation cephalosporin antibiotics on their farms, except under exceptional circumstances.[765]

Zinc bacitracin use in pigs in Aotearoa New Zealand has declined markedly over the last 3-5 years as a result of major improvements in the management of enteric diseases.

[760] Hillerton, J.E., Bryan, M.A., Beattie, B.H., *et al.* (2021). Use of antimicrobials for food animals in New Zealand; updated estimates to identify a baseline to measure targeted reductions. *New Zealand Veterinary Journal*, 1-6. https://doi.org/10.1080/00480169.2021.1890648

[761] The Agricultural Compounds and Veterinary Medicines Team. (2021). *2019 antibiotic agricultural compound sales analysis*. Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/48622-2019-Antibiotic-Agricultural-Compound-Sales-Analysis

[762] NZ Pork. (2021). Personal communication.

[763] Mulqueen, K. (2021). Personal communication.

[764] Mulqueen, K. (2021). Personal communication.

[765] NZ Pork. (2021). Personal communication.

Antibiotics for pigs can be used on an individual animal basis but are also sometimes used in feed or water. Although this is a form of prophylaxis, it is frequently targeted at a specific age group where a pathogen is known to emerge (referred to by the industry as 'group treatment').

The macrolide predominantly used in animals in Aotearoa New Zealand is tylosin, and it is generally administered through feed or water.[766] Macrolides are one class of antibiotics used in Aotearoa New Zealand farming that could potentially be targeted to reduce use. Tylosin itself is not used in human health, but resistance in tylosin could potentially cause resistance in other macrolide antibiotics that are used in human health.[767] We currently don't have interpretive standards to assess tylosin susceptibility in Enterococci, but high minimum inhibitory concentrations have been detected in samples from poultry, pigs, and calves.[768] Given that this macrolide is often administered in feed or water, there is potential for use to be reduced. The pork industry has advised that active initiatives are in place to drive use of tylosin down.[769]

Tylosin is used to treat diseases such as ileitis (porcine proliferative enteropathy, caused by *Lawsonia intracellularis*) which does not generally resolve without antibiotics. The disease is predictable in terms of when it generally occurs, which is why the industry may sometimes treat a group as a whole through feed or water at a particular growth stage. There is an ileitis vaccine available and uptake of this could improve.

Another example is enzootic pneumonia (caused by *Mycoplasma hyopneumoniae*) which is common in Aotearoa New Zealand's pigs.[770] A vaccine is available for enzootic pneumonia which mitigates much of the need for treatment and tylosin is subsequently seldom used for this type of pneumonia. However, other diseases such as pleuropneumonia (caused by *Actinobacillus pleuropneumoniae*) and *Mycoplasma hyosynoviae* arthritis do require control with use of tylosin.

Growth promotion not permitted in Aotearoa New Zealand

Some antimicrobials administered to animals are also known to have a positive impact on animal growth. Zinc bacitracin and tylosin are both considered to be growth promoters by many countries, though they have important therapeutic uses outside of growth promotion. In Aotearoa New Zealand, these antibiotics (zinc bacitracin and tylosin) cannot be prescribed for the purpose of growth promotion but can be administered via feed or water for therapeutic and prophylactic purposes. Some claim that the boundary between therapeutic, prophylactic and growth promotion use can be difficult to draw.[771]

Similarly, ionophores are a class of drugs that have both antimicrobial activity and growth promotion properties[772] although they are not registered as antibiotics in Aotearoa New Zealand or the EU, while the US FDA considers them to be antibiotics. In the poultry industry, ionophores are used to

[766] The Agricultural Compounds and Veterinary Medicines Team (New Zealand Food Safety). (2020). *Antibiotic sales analysis 2018*. Wellington, New Zealand: Ministry for Primary Industries.
[767] Jackson, C.R., Fedorka-Cray, P.J., Barrett, J.B., *et al.* (2004). Effects of tylosin use on erythromycin resistance in *Enterococci* isolated from swine. *Applied and Environmental Microbiology, 70*(7), 4205-4210. https://doi.org/10.1128/AEM.70.7.4205-4210.2004; Mechesso, A.F., & Park, S.-C. (2020). Tylosin exposure reduces the susceptibility of *Salmonella* Typhimurium to florfenicol and tetracycline. *BMC Veterinary Research, 16*(1), 22. https://doi.org/10.1186/s12917-020-2246-5
[768] Heffernan, H., Wong, T.L., Lindsay, J., *et al.* (2011). *A baseline survey of antimicrobial resistance in bacteria from selected New Zealand foods, 2009-2010*. Wellington, NZ: Ministry of Agriculture and Fisheries.
[769] NZ Pork. (2021). Personal communication.
[770] Lawrence, K., Neumann, E., & Brangenberg, N. (2018). Diseases of backyard pigs in New Zealand. *Surveillance, 45*(2).
[771] Kirchhelle, C. (2018). Pharming animals: a global history of antibiotics in food production (1935–2017). *Palgrave Communications, 4*(1), 96. https://doi.org/10.1057/s41599-018-0152-2
[772] Li, G., De Oliveira, D.M.P., & Walker, M.J. (2021). The antimicrobial and immunomodulatory effects of Ionophores for the treatment of human infection. *Journal of Inorganic Biochemistry*, 111661. https://doi.org/10.1016/j.jinorgbio.2021.111661; Butaye, P., Devriese, L.A., & Haesebrouck, F. (2003). Antimicrobial growth promoters used in animal feed: Effects of less well known antibiotics on gram-positive bacteria. *Clinical Microbiology Reviews, 16*(2), 175-188. https://doi.org/10.1128/CMR.16.2.175-188.2003

control coccidiosis parasite infections. They have been used as growth promoters in ruminants and pigs. In Aotearoa New Zealand, ionophores are advertised as improving feed conversion efficiency in cattle.[773] Ionophores are not widely considered to contribute to AMR in humans but it has been argued that there is insufficient evidence for this conclusion and further research is needed.[774] One study found that ionophore resistance may confer cross resistance to zinc bacitracin[775] (which is not of critical importance to human health, but used in the agricultural sector, see section above).

The EU has a widely publicised 'ban on growth promoters' but as in Aotearoa New Zealand, antibiotics with growth promotion properties (e.g. tylosin) are still used for therapeutic purposes under direction of a vet. The ban of growth promoter use in the EU was based on concerns about the potential for development of AMR genes between animals and humans.[776] The reported ban decreased the overall use of antibiotics but was not without challenges such as increased death rates due to infections.[777] Antibiotic growth promotions is also discussed in section 2.3.2.

Antibiotic use in dairy cows is mainly to prevent and treat mastitis

Beef and dairy farming combined have a much lower estimated stabilised rate of antimicrobial use compared with pigs and poultry, at 6.24 mg/PCU.[778] A separate study of a group of dairy farms estimated use at 8.65 mg/PCU for the 2014-15 season.[779]

Dairy farming uses more antimicrobials than beef farming, mostly to manage mastitis (bacterial infection of the udder). Antimicrobials are used both prophylactically and therapeutically in the dairy industry to manage this condition.

The use of antimicrobials in dairy cows in Aotearoa New Zealand is low by international standards but varies across years and across regions.

The use of antimicrobials in dairy cows in Aotearoa New Zealand is low by international standards but varies across years and across regions. For example, higher use was reported for Murihiku Southland and Otakou South Otago, followed by Manawatū, then Waitaha North Canterbury and Taranaki.[780] Dairy farming in Aotearoa New Zealand is predominantly pastoral, which tends towards lower antibiotic use than housed dairy farming that occurs in many other countries.

A survey of New Zealand dairy farmers in 2017 demonstrated that dairy farmers had limited knowledge or concern about the risk of AMR, particularly outside their farm, with only 47% and 26% agreeing or strongly agreeing that use of antimicrobials on their farm would increase the risk of resistance in their herd and in humans, respectively. Being advised to use antimicrobials was ranked

[773] AgriHealth. (n.d.). Increased milk production. Retrieved 2 December, 2021, from https://agrihealth.co.nz/products/increased-milk-production
[774] Wong, A., & Limbago, B.M. (2019). Unknown risk on the farm: Does agricultural use of ionophores contribute to the burden of antimicrobial resistance? *mSphere, 4*(5), e00433-00419. https://doi.org/doi:10.1128/mSphere.00433-19
[775] Houlihan, A.J., & Russell, J.B. (2003). The susceptibility of ionophore-resistant *Clostridium aminophilum* F to other antibiotics. *Journal of Antimicrobial Chemotherapy, 52*(4), 623-628. https://doi.org/10.1093/jac/dkg398
[776] Castanon, J.I.R. (2007). History of the use of antibiotic as growth promoters in European poultry feeds. *Poultry Science, 86*(11), 2466-2471. https://doi.org/https://doi.org/10.3382/ps.2007-00249
[777] Kim, J., Guevarra, R.B., Nguyen, S.G.*, et al.* (2016). Effects of the antibiotics growth promoter tylosin on swine gut microbiota. *Journal of Microbiology and Biotechnology, 26*(5), 876-882. https://doi.org/10.4014/jmb.1512.12004
[778] Hillerton, J.E., Irvine, C.R., Bryan, M.A.*, et al.* (2017). Use of antimicrobials for animals in New Zealand, and in comparison with other countries. *New Zealand Veterinary Journal, 65*(2), 71-77. https://doi.org/10.1080/00480169.2016.1171736
[779] Bryan, M., & Hea, S. (2017). A survey of antimicrobial use in dairy cows from farms in four regions of New Zealand. *New Zealand Veterinary Journal, 65*(2), 93-98. https://doi.org/10.1080/00480169.2016.1256794
[780] Ibid.; Collis, R.M., Burgess, S.A., Biggs, P.J.*, et al.* (2019). Extended-spectrum beta-lactamase-producing Enterobacteriaceae in dairy farm environments: A New Zealand perspective. *Foodborne Pathogens and Disease, 16*(1), 5-22. https://doi.org/10.1089/fpd.2018.2524

as the most important reason for use by most farmers (87%), but some (68%) ranked their own experience as most important in determining use. For vets, farmers' preferences influenced prescribing for 22% of respondents, but most (82%) prescribed based on diagnosis.[781]

A more recent survey of Aotearoa New Zealand dairy and sheep farmers found differences between these farmers. Dairy farmers had low levels of concern about AMR, were less aware of the need to reduce antimicrobial use and didn't think it was possible to do so. In contrast, more sheep farmers supported restricted use of antimicrobials. Most of the farmers' advice was sourced from vets, the livestock industry, and colleagues.[782]

Dry cow therapy

Dairy cows are susceptible to bacterial infections of the udder, causing udder inflammation known as mastitis. Udder infections can occur during milking or during the 'dry period' when milking stops before calving.[783] Treating and preventing mastitis is the most common reason for antibiotic use in dairy cows.[784] Antibiotics to treat or prevent mastitis are typically administered during the dry period, so is known as antibiotic dry cow treatment or therapy. Previously, dry cow therapy has been applied across whole herds.[785]

While dry cow treatment is beneficial in reducing mastitis, this prophylactic use is poor practice when considering the risk of AMR. Dry cow treatment uses β-lactam antibiotics which are used in human health settings too (including penicillins and first-generation cephalosporins).[786]

In Aotearoa New Zealand, industry body DairyNZ guidelines on dry cow management specify that antimicrobials should be used to treat existing infections (i.e. therapeutic treatment) and any prophylactic use should be targeted at high-risk cows (i.e. those with a history of clinical mastitis or high somatic cell count) rather than at a whole herd level.[787] This is consistent with practice in the Netherlands, which shifted away from blanket antibiotic dry cow therapy in 2012, and Denmark, which banned blanket prophylaxis in the 1990s.

DairyNZ guidelines on dry cow management specify that antimicrobials should be used to treat existing infections … and any prophylactic use should be targeted at high-risk cows.

[781] McDougall, S., Compton, C., & Botha, N. (2017). Factors influencing antimicrobial prescribing by veterinarians and usage by dairy farmers in New Zealand. *New Zealand Veterinary Journal, 65*(2), 84-92. https://doi.org/10.1080/00480169.2016.1246214
[782] Moono, P., Fruean, S.N., McCorkindale, D.*, et al.* (2021). Evaluating farmer attitudes and knowledge on reducing antimicrobial use in dairy and sheep farms in New Zealand. *Preprints*. https://doi.org/10.20944/preprints202106.0588.v1
[783] Neave, F.K., Dodd, F.H., & Henriques, E. (1950). Udder infections in the 'dry period'. *Journal of Dairy Research, 17*(1), 37-49. https://doi.org/10.1017/S0022029900005628
[784] Bates, A., Laven, R., Bork, O.*, et al.* (2020). Selective and deferred treatment of clinical mastitis in seven New Zealand dairy herds. *Preventive Veterinary Medicine, 176*, 104915. https://doi.org/10.1016/j.prevetmed.2020.104915
[785] Turner, S.-A., Williamson, J., Wynn, K.*, et al.* (2011). *Combination effects of teat spraying and dry cow therapy.* Paper presented at the National Mastitis Council Annual Meeting Proceedings, Alexandia, Virginia, US.
[786] Bryan, M., & Hea, S. (2017). A survey of antimicrobial use in dairy cows from farms in four regions of New Zealand. *New Zealand Veterinary Journal, 65*(2), 93-98. https://doi.org/10.1080/00480169.2016.1256794; Collis, R.M., Burgess, S.A., Biggs, P.J.*, et al.* (2019). Extended-spectrum beta-lactamase-producing Enterobacteriaceae in dairy farm environments: A New Zealand perspective. *Foodborne Pathogens and Disease, 16*(1), 5-22. https://doi.org/10.1089/fpd.2018.2524
[787] Dairy NZ. (2020). Guideline 14: Decide dry cow management strategy. (pp. 6): SmartSAMM. Retrieved from https://www.dairynz.co.nz/media/5792839/smartsamm_guideline_14_dry_cow_strategy_march_2020.pdf

Here in Aotearoa New Zealand, the reduction in blanket prophylactic use for a whole herd has largely been enabled by the introduction of internal teat sealants. Teat sealants are a non-antibiotic product that is inserted into and stays within the teat throughout the dry period, providing a physical barrier that can prevent bacteria from moving into the udder and causing infection. A meta-analysis in 2019 found that teat sealant approaches are efficient at preventing new infections and in some circumstances perform better than prophylactic antimicrobial use.[788] It is important that farmworkers are adequately trained and practice good hygiene when inserting the teat sealant, to prevent the introduction of unwanted bacteria.

A meta-analysis in 2019 found that teat sealant approaches are efficient at preventing new infections and in some circumstances **perform better** than prophylactic antimicrobial use.

So far, the use of teat sealants rather than blanket antimicrobial use has been through voluntary mechanisms and the industry has reached the 'tail-end' of behaviour change. It is possible that regulation would be needed to achieve wider uptake. Current research has considered factors that identify individual cows' risk of clinical mastitis, which may support further appropriate use of teat sealants over prophylactic antimicrobial use.[789] Milk testing is used to detect infection and antibiotics are still used for treatment where necessary.

Other farming sectors are of lower concern

Use of antimicrobials in beef and lamb (as opposed to dairy farming) is relatively low, partly due to pastoral farming methods that are associated with lower risk of disease. MPI sales data combines beef and dairy into a single category which means there is a lack of clear data on the use of antimicrobials in the beef industry. Similarly, sheep is within a category that combines both sheep and horses making it difficult to understand volume and trends of use in sheep farming. Vaccine use is common in beef and lamb farming, though uptake varies from vaccine to vaccine due to perceived costs and benefits. Antimicrobials are used in horses in a similar way to companion animals (that is, therapeutically, see section below) and MDROs have been isolated from horses.[790]

There are few antimicrobials specifically registered for use in deer and consequently there is no easily available sales data that provides an overview of antimicrobial usage in this farming system. The multiple species category of antibiotic sales data (which includes deer) accounted for 17% of

[788] Dufour, S., Wellemans, V., Roy, J.P., *et al.* (2019). Non-antimicrobial approaches at drying-off for treating and preventing intramammary infections in dairy cows. Part 1. Meta-analyses of efficacy of using an internal teat sealant without a concomitant antimicrobial treatment. *Animal Health Research Reviews, 20*(1), 86-97. https://doi.org/10.1017/s1466252319000070

[789] McDougall, S., & Castle, R. (2021). Cow-level risk factors for clinical mastitis in the dry period in cows treated with an internal teat sealant alone at the end of lactation. *New Zealand Veterinary Journal*, 1-10. https://doi.org/10.1080/00480169.2021.1938269; McDougall, S., Williamson, J., Gohary, K., *et al.* (2021). Risk factors for clinical or subclinical mastitis following infusion of internal teat sealant alone at the end of lactation in cows with low somatic cell counts. *New Zealand Veterinary Journal*, 1-9. https://doi.org/10.1080/00480169.2021.1977200

[790] Toombs-Ruane, L.J., Riley, C.B., Kendall, A.T., *et al.* (2015). Antimicrobial susceptibilities of aerobic isolates from respiratory samples of young New Zealand horses. *Journal of Veterinary Internal Medicine, 29*(6), 1700-1706. https://doi.org/10.1111/jvim.13600; Toombs-Ruane, L.J., Riley, C.B., Kendall, A.T., *et al.* (2016). Antimicrobial susceptibility of bacteria isolated from neonatal foal samples submitted to a New Zealand veterinary pathology laboratory (2004 to 2013). *New Zealand Veterinary Journal, 64*(2), 107-111. https://doi.org/10.1080/00480169.2015.1109006

sales in 2018. Anecdotally, antimicrobial use is fairly low, and farms may go years without using antibiotics; deer are not particularly susceptible to illness and the pastoral farming system with low stock density does not encourage disease.[791] Deer do experience some illnesses although vaccines are available and are used in the industry.[792] Where velveting occurs, there is a close vet-farmer relationship as oversight of procedures is needed. There is some use of antibiotics that have critical or high importance to human health (e.g. streptomycin, tetracycline).[793]

There are no antimicrobials registered for use in aquaculture in Aotearoa New Zealand and there is no evidence of off-label use occurring.[794] Key aquaculture sectors here include salmon, mussels and oysters.[795] While overseas there are concerns about high usage of antibiotics in farmed fish (see section 2.3.2), Aotearoa New Zealand does not face similar concerns. Due to our environment and lack of particular parasites and diseases, there is no current need for antibiotic use. While there are parasites and diseases associated with shellfish, including zoonotic diseases, there is no use of antibiotics in these industries. Use of antibiotics in shellfish aquaculture is found in other countries.[796] Strategies to grow and intensify aquaculture in Aotearoa New Zealand should consider impact on future need or use of antibiotics.

There are no antimicrobials registered for use in aquaculture in Aotearoa New Zealand and there is no evidence of off-label use occurring.

Companion animals account for a small proportion of antimicrobial use

Pet ownership levels in Aotearoa New Zealand are among the highest in the world. Nearly two-thirds of Aotearoa New Zealand households had at least one companion animal in 2020, with cats (41% of all households) and dogs (34%) being the most common pets.[797] Antimicrobials are used to maintain pet health and welfare. Between 2017 and 2018 there was a 22% increase in antimicrobials sold for use in companion animals, without a clear reason for this increase.[798] The amount has increased again between 2018 and 2019, by a further 18%, but the overall proportion of total animal use remains low, at 2%.[799] Without sufficient data to adjust antimicrobial use in pets for biomass, it is difficult to assess whether antimicrobial use in companion animals is high, low, or comparable to use in agricultural animals.

The proportion of sales of products that are registered for use in companion animals is low compared with total antimicrobial sales for animals and plants but is increasing (1.1% in 2017 to 1.5% in 2018).[800] Most antibiotic classes sold for use in companion animals are penicillins (including

[791] Deer Industry NZ. (2021). Personal communication.
[792] Mackintosh, C.G. (2002). *Diseases of deer for which there are licensed vaccines* (Vol. 15): New Zealand Veterinary Association.
[793] Deer Industry NZ. (2015). *Deer facts: Leptospirosis*. Wellington: Deer Industry New Zealand. Retrieved from https://www.deernz.org/assets/Deer-Facts/DeerFact_Leptospirosis_2015-09.pdf
[794] Australian Government Department of Health. (2018). *Review of published and grey literature on the presence of antimicrobial resistance in food in Australia and New Zealand*. Retrieved from https://www.amr.gov.au/resources/review-published-and-grey-literature-presence-antimicrobial-resistance-food-australia-and
[795] New Zealand Government. (2019). *The New Zealand Government aquaculture strategy*. Retrieved from https://www.mpi.govt.nz/dmsdocument/15895-The-Governments-Aquaculture-Strategy-to-2025
[796] Chen, J., Sun, R., Pan, C.*, et al.* (2020). Antibiotics and food safety in aquaculture. *Journal of Agricultural and Food Chemistry, 68*(43), 11908-11919. https://doi.org/10.1021/acs.jafc.0c03996
[797] Companion Animals New Zealand. (2020). *Companion animals in New Zealand 2020*. Auckland, NZ: Retrieved from https://www.companionanimals.nz/publications
[798] The Agricultural Compounds and Veterinary Medicines Team (New Zealand Food Safety). (2020). *Antibiotic sales analysis 2018*. Wellington, New Zealand: Ministry for Primary Industries.
[799] Agricultural Compounds and Veterinary Medicines Team. [in press] *2019 Antibiotic agricultural compound sales analysis*.
[800] The Agricultural Compounds and Veterinary Medicines Team (New Zealand Food Safety). (2020). *Antibiotic sales analysis 2018*. Wellington, New Zealand: Ministry for Primary Industries.

amoxicillin + clavulanic acid sales), followed by first generation cephalosporins. A survey of companion animal vets conducted in 2008 found that broad-spectrum antimicrobials considered by the WHO to be critically important for human health, such as quinolones and amoxicillin + clavulanic acid (see appendix 7.3), were among the most frequently prescribed antimicrobials, often without submitting a sample for culture and susceptibility testing.[801]

Data and knowledge gaps

Due to the variation between different farming systems, it is important to look at data within each animal sector rather than at a whole-sector level. The main source of antimicrobial usage data is from government and industry reports based on antibiotic sales data. MPI reports annually on antibiotic sales, though reporting tends to lag by two years, which may pose a challenge in immediate action to act on issues and trends.[802] In addition, there is a lack of good data on antimicrobial use in companion animals – while antimicrobial use and AMR in humans falls under MoH and antimicrobial use and AMR in plants and agriculturally important animals falls under MPI, there is no natural 'home' for managing antimicrobial use and AMR in companion animals.

Sales data as a way to monitor antimicrobial use has limitations. It may not reflect what is actually used in that period, and it can't account for different dose requirements for different drugs. We don't have a good system for understanding where antimicrobials go after purchase and an on-farm system could help us know which antimicrobials are used in which animals. Many antibiotics will have registered use for multiple animals – for example, one antibiotic may be used in both pig and poultry industries. MPI reports on pigs and poultry as one sector due to the significant overlap in antibiotic use in these sectors. Other antibiotics might have off-label uses, for example, few antibiotics are specifically registered for deer so MPI is not able to report on this sector's antibiotic use.

There are limitations in using 'total use' to track whether antibiotic sales are changing because variation could also reflect population size changes or changes in disease prevalence. Reporting antimicrobial use as mg of antimicrobial per kg of animal mass is more useful[803] but even this has its limitations, including the fact that it doesn't allow interrogation of the appropriateness of use.

We don't have a good system for understanding where antimicrobials go after purchase and an on-farm system could help us know which antimicrobials are used in which animals.

[801] Pleydell, E., Souphavanh †, K., Hill, K.*, et al.* (2012). Descriptive epidemiological study of the use of antimicrobial drugs by companion animal veterinarians in New Zealand. *New Zealand Veterinary Journal, 60*(2), 115-122. https://doi.org/10.1080/00480169.2011.643733
[802] The Agricultural Compounds and Veterinary Medicines Team (New Zealand Food Safety). (2020). *Antibiotic sales analysis 2018*. Wellington, New Zealand: Ministry for Primary Industries.
[803] Hillerton, J.E., Bryan, M.A., Beattie, B.H.*, et al.* (2021). Use of antimicrobials for food animals in New Zealand; updated estimates to identify a baseline to measure targeted reductions. *New Zealand Veterinary Journal*, 1-6. https://doi.org/10.1080/00480169.2021.1890648

4.4.3 There's limited use of antibiotics in plants but wider use of antifungals

Data on antimicrobial use in plants in Aotearoa New Zealand and globally is limited. The Aotearoa New Zealand government's response in the recent WHO AMR self-assessment survey said there was "no national plan or system for monitoring use of pesticides including antimicrobial pesticides such as bactericides and fungicides used for the purpose of controlling bacteria or fungal diseases" in plant production (see appendix 7.5).[804] Most countries rated themselves lower on this measure than they did for human or animal surveillance.

In Aotearoa New Zealand, there are only two antibiotic products registered for use in plants… Unlike antibiotics for use in humans or animals, antibiotics registered for use in horticulture are available for purchase off the shelf.

Globally, it is typical that few antibiotics have been used for the management of relatively few bacterial plant diseases and are largely restricted to high-value fruit crops because of the expense involved.[805] In Aotearoa New Zealand, there are only two antibiotic products registered for use in plants. Both are aminoglycoside antimicrobials – streptomycin and kasugamycin. Streptomycin is used to manage diseases in stone fruit, pip fruit and tomatoes, and kasugamycin is used to manage Psa infections in kiwifruit.[806] Unlike antibiotics for use in humans or animals, antibiotics registered for use in horticulture are available for purchase off the shelf. Their use is primarily controlled by good agricultural practice, guidance, standards related to residue limits, and market requirements.

MPI reported a 14% increase in sales of antibiotics in horticulture between 2017 and 2018. However, use of products does not always align with the year of purchase, and changes in the land used for particular horticulture can also drive changes in sales.[807] The data does not allow comment on whether or not practices or usage rate have changed in horticulture from year-to-year.

The use of non-antibiotic antimicrobials is more common in the plant sector. For example, copper-based fungicide sprays are used widely and routinely in horticulture and forestry and are also available for use in home gardens.[808] Copper has been found to accumulate in vineyard soils in Aotearoa New Zealand, and total soil copper in a vineyard is related to the number of years copper sprays have been used.[809] Other fungicides used include mercury compounds, zinc, and other

[804] World Health Organization. (2020). Global database for the tripartite antimicrobial resistance (AMR) country self-assessment survey (TrACSS). Retrieved 4 August 2021 https://amrcountryprogress.org/

[805] Sundin, G.W., & Wang, N. (2018). Antibiotic resistance in plant-pathogenic bacteria. *Annual Review of Phytopathology, 56*(1), 161-180. https://doi.org/10.1146/annurev-phyto-080417-045946

[806] The Agricultural Compounds and Veterinary Medicines Team (New Zealand Food Safety). (2020). *Antibiotic sales analysis 2018*. Wellington, New Zealand: Ministry for Primary Industries.

[807] Ibid.

[808] Rolando, C., Baillie, B., Withers, T.*, et al.* (2016). Pesticide use in planted forests in New Zealand. *New Zealand Journal of Forestry, 61*(2), 3-10.

Gaw, S., Wilkins, A., Kim, N.*, et al.* (2006). Trace element and ΣDDT concentrations in horticultural soils from the Tasman, Waikato and Auckland regions of New Zealand. *Science of the total environment, 355*(1-3), 31-47. https://doi.org/10.1016/j.scitotenv.2005.02.020

[809] Morgan, R.K., & Taylor, E. (2004). Copper accumulation in vineyard soils in New Zealand. *Environmental Sciences, 1*(2), 139-167. https://doi.org/10.1080/15693430512331342602

metals.[810] Trends on use of antifungals in horticulture are not readily available, though sales and imports data have previously been used to estimate use.[811]

The use of herbicides and pesticides is common both in horticulture and in home gardens and may contribute to AMR (see section 2.3.2). However, the volume and use of these biocides is not routinely collected or reported on in Aotearoa New Zealand.

4.4.4 Antimicrobials in the environment

We lack an understanding of the amount and distribution of antimicrobials in the environment in Aotearoa New Zealand, and we don't know what impact they have on the development of AMR, nor the potential flow-on impacts for human, animal, and plant health. These knowledge gaps need to be filled.

We don't know what impact they have on the development of AMR, nor the potential flow-on impacts for human, animal, and plant health.

The existence of manmade antimicrobials in the environment is largely due to contamination from other antimicrobial uses already discussed (in human health, plants, and animals). Any reduction in antimicrobial use in humans, animals, and plants will therefore reduce presence of antimicrobials in the environment. In this way, reducing antimicrobial contamination of the environment requires coordination and sustained efforts across the human, animal, and plant sectors. The environment also contains naturally occurring antimicrobials such as those produced by soil microbes (see section 2.3.2 for more details).

Some studies have been undertaken in Aotearoa New Zealand identifying contaminants including antimicrobials:

- A study in Tāmaki Makaurau Auckland of pharmaceutical contamination in the estuarine environment identified the presence of a number of antibiotics.[812]
- A study of stockpiled sewage sludge in Kaikōura also found presence of antibiotics (specifically sulfamethoxazole and ciprofloxacin).[813]
- Testing for the presence of antimicrobial agents in freshwater in Ōtepoti Dunedin in 2019 found them below detection limits.[814]
- At the time of writing, the Parliamentary Commissioner for the Environment is working on a report exploring environmental contaminants, including the antibiotic tetracycline.

The role played by farming in environmental contamination with antimicrobials is worth exploring. The majority of antibiotics applied to livestock are excreted through urine or faeces.[815] This can then be further spread in a number of ways – use of manure for fertilisation, irrigation with wastewater,

[810] Gaw, S., Wilkins, A., Kim, N., *et al.* (2006). Trace element and ΣDDT concentrations in horticultural soils from the Tasman, Waikato and Auckland regions of New Zealand. *Science of the total environment, 355*(1-3), 31-47. https://doi.org/10.1016/j.scitotenv.2005.02.020
[811] Manktelow, D., Stevens, P., Walker, J., *et al.* (2005). *Trends in pesticide use in New Zealand: 2004*. Wellington: Ministry for the Environment.
[812] Stewart, M. (2013). *Pharmaceutical residues in the Auckland estuarine environment*. Auckland: Auckland Council. Retrieved from https://knowledgeauckland.org.nz/media/1585/tr2013-002-pharmaceutical-residues-in-the-auckland-estuarine-environment.pdf
[813] Langer, E.L., Ataria, J., Leckie, A., *et al.* (2013). *Kaikōura case study: community engagement to determine biosolids reuse*: Centre for Integrated Biowaste Research.
[814] Bernot, M.J., Bernot, R.J., & Matthaei, C.D. (2019). Emerging organic contaminants (EOCs) in freshwaters in Dunedin, New Zealand. *New Zealand Journal of Marine and Freshwater Research, 53*(1), 3-14. https://doi.org/10.1080/00288330.2018.1457062
[815] Liu, C., Tan, L., Zhang, L., *et al.* (2021). A review of the distribution of antibiotics in water in different regions of China and current antibiotic degradation pathways. *Frontiers in Environmental Science, 9*(221). https://doi.org/10.3389/fenvs.2021.692298

accidental runoffs, and even through movement of contaminated dust.[816] Dairy cattle that have been treated with antibiotics produce milk that is contaminated with antibiotics and not fit for human consumption. This milk can be applied directly to the land,[817] introducing antimicrobials into the environment. There are regulations in Aotearoa New Zealand that manage freshwater contamination risks from general farming activities under the Resource Management Act 1991 and further work is currently underway in this area under the Government's Essential Freshwater package.[818]

In addition, antimicrobial disposal should be explored. Antimicrobials that are dispensed to patients but not used may be inappropriately disposed of (i.e. down toilets, sinks or other drains). There is no clear formal guidance on how these should be disposed of, which means that people may not be aware that this is poor practice. Formal guidance for the healthcare sector on disposal and a consumer campaign to align could provide education on this issue. See section 5.5.3 for more details.

[816] Manyi-Loh, C., Mamphweli, S., Meyer, E.*, et al.* (2018). Antibiotic use in agriculture and its consequential resistance in environmental sources: Potential public health implications. *Molecules, 23*(4), 795. https://doi.org/10.3390/molecules23040795
[817] DairyNZ. (n.d.). Milk disposal. Retrieved 29 September, 2021, from https://www.dairynz.co.nz/business/adverse-events/milk-disposal/
[818] Ministry for the Environment. (2021). *Freshwater farm plan regulations: Discussion document*. Wellington: Ministry for the Environment. Retrieved from https://consult.environment.govt.nz/freshwater/freshwater-farm-plan-regulations/supporting_documents/freshwaterfarmplanregulationsdiscussiondocument.pdf

4.5 Case study: Drug-resistant skin infections are already causing significant morbidity

About one in three people have a microbe called *Staphylococcus aureus* on their skin and in their nostrils.[819] Some people always have these common bacteria present but for others they can come and go. Harbouring these bacteria (i.e. being colonised with or being a carrier of *S. aureus*) is usually harmless but can sometimes cause infections including those involving the skin and soft tissues. If *S. aureus* gets into a wound or open cut there can be serious health consequences as this can lead to bone, lung, and blood infections.

The prevalence of ***S. aureus*** infection in Aotearoa New Zealand is among the **highest reported worldwide** and rates have been increasing.

Infections caused by *S. aureus* require treatment with antibiotics, but a group of these bacteria are resistant to commonly used antibiotics, making them more difficult to treat (MRSA, as introduced in section 2.2.3 and section 4.3.1). Resistance to the antibiotic methicillin started emerging in the 1960s and has since disseminated globally, becoming a leading cause of bacterial infections in both hospital and community settings.[820] Methicillin is not available in New Zealand but resistance to methicillin also means resistance to flucloxacillin and other front-line agents like cefalexin that are among our most commonly used antibiotics.

Most MRSA infections in Aotearoa New Zealand are now acquired in the community. In a 2017 study in Aotearoa New Zealand, of the 956 patients included, nearly 90% were infected in the community and only 10% as hospital patients.[821] While MRSA used to be more commonly acquired in hospitals than in the community, IPC action led to decreases in rates in hospitals in many parts of the world, including in Aotearoa New Zealand. For more details on IPC, see section 5.3.1.

In a 2017 analysis of MRSA in Aotearoa New Zealand, most (91%) isolates were from skin and soft tissue infection. The rest were from other sites such as respiratory tract, ears, and eyes.[822]

MRSA infection causes time away from school, financial stress, health and emotional tolls, and costs for individuals, whānau and the healthcare system.[823]

4.5.1 Prevalence of *S. aureus* infection and colonisation

The prevalence of *S. aureus* infection in Aotearoa New Zealand is among the highest reported worldwide, and rates are increasing. Data from hospital and community settings found a national prevalence rate of 19.9 patients with MRSA per 100,000 population in 2017, almost double what it was in 2009 (though the 2009 figure is likely to be an underestimate).[824]

[819] Sakr, A., Brégeon, F., Mège, J.-L., *et al.* (2018). *Staphylococcus aureus* nasal colonization: An update on mechanisms, epidemiology, risk factors, and subsequent infections. *Frontiers in Microbiology, 9*. https://doi.org/10.3389/fmicb.2018.02419

[820] Lee, A.S., De Lencastre, H., Garau, J., *et al.* (2018). Methicillin-resistant *Staphylococcus aureus*. *Nature Reviews Disease Primers, 4*(1), 18033. https://doi.org/10.1038/nrdp.2018.33

[821] Heffernan, H., & Bakker, S. (2017). *2017 survey of methicillin-resistant Staphylococcus aureus (MRSA)*. Porirua, NZ: Institute of Environmental Science and Research Ltd Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/MRSA/MRSA_2017.pdf

[822] Ibid.

[823] Williamson, D.A., Roberts, S.A., Ritchie, S.R., *et al.* (2013). Clinical and molecular epidemiology of methicillin-resistant *Staphylococcus aureus* in New Zealand: Rapid emergence of sequence type 5 (ST5)-SCC mec-IV as the dominant community-associated MRSA clone. *PLOS One, 8*(4), e62020. https://doi.org/10.1371/journal.pone.0062020

[824] Heffernan, H., & Bakker, S. (2017). *2017 survey of methicillin-resistant Staphylococcus aureus (MRSA)*. Porirua, NZ: Institute of Environmental Science and Research Ltd Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/MRSA/MRSA_2017.pdf

Another study, from Tāmaki Makaurau Auckland, used laboratory-based surveillance and reported a significant increase in non-invasive *S. aureus* infections between 2001 and 2011, largely driven by community-onset MRSA infections.[825]

Around half of children in Aotearoa New Zealand have *S. aureus* present on their body, some of which is MRSA. In the Growing Up in New Zealand cohort, 2225/5126 (43.4%) of preschool children were colonised with *S. aureus.*[826] In a study of primary school children in Ōtautahi Christchurch, 53-65% of students had at least one positive test result for the presence of *S. aureus*, and the majority of these children consistently showed the presence of *S. aureus* at each round of testing.[827] Of children positive for *S. aureus,* 8.1% had MRSA (3.5% of the total cohort). Most of these were susceptible to erythromycin (83%) and all were susceptible to trimethoprim + sulfamethoxazole.[828]

4.5.2 Who is at risk?

Being colonised with *S. aureus* (having it on the body) increases the risk of infection. This includes a three- to ten-fold increased risk of SSIs.[829]

Different demographics have different risk profiles

Māori and Pacific people are more likely to get *S. aureus* infections (including MRSA) compared to those of European ethnicity.[830] A study of *S. aureus* skin and soft tissue infections in children found that Māori were twice as likely and Pacific peoples almost three times as likely to be admitted to hospital with *S. aureus* skin and soft tissue infections than European children (it is not known whether these are MSSA or MRSA isolates).[831] A more recent study found that Pacific infants had the highest risk of community-acquired invasive *S. aureus i*nfection.[832] For more details on health inequities in Aotearoa New Zealand, see section 3.4.2.

Both the young and old in our populations are more at risk. Children aged five and under have an increased likelihood of MRSA infection[833] and MRSA infections are also more prevalent among elderly New Zealand European people.[834]

People living in the more socioeconomically deprived areas are more likely to be infected with MRSA.[835] Additionally, areas with more household crowding have higher incidence of MRSA

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[825] Williamson, D.A., Lim, A., Thomas, M.G., *et al.* (2013). Incidence, trends and demographics of *Staphylococcus aureus* infections in Auckland, New Zealand, 2001–2011. *BMC Infectious Diseases, 13*(1), 569. https://doi.org/10.1186/1471-2334-13-569

[826] Hobbs, M.R., Grant, C.C., Thomas, M.G., *et al.* (2018). *Staphylococcus aureus* colonisation and its relationship with skin and soft tissue infection in New Zealand children. *European Journal of Clinical Microbiology & Infectious Diseases, 37*(10), 2001-2010. https://doi.org/10.1007/s10096-018-3336-1

[827] Scott, P., Priest, P.C., Chambers, S.T., *et al.* (2018). *Staphylococcus aureus* carriage in a New Zealand primary school: A cohort study. *The Pediatric Infectious Disease Journal, 37*(6), e172-e175. https://doi.org/10.1097/INF.0000000000001796

[828] Hobbs, M.R., Grant, C.C., Thomas, M.G., *et al.* (2018). *Staphylococcus aureus* colonisation and its relationship with skin and soft tissue infection in New Zealand children. *European Journal of Clinical Microbiology & Infectious Diseases, 37*(10), 2001-2010. https://doi.org/10.1007/s10096-018-3336-1

[829] Sakr, A., Brégeon, F., Mège, J.-L., *et al.* (2018). *Staphylococcus aureus* nasal colonization: An update on mechanisms, epidemiology, risk factors, and subsequent infections. *Frontiers in Microbiology, 9*. https://doi.org/10.3389/fmicb.2018.02419

[830] Ritchie, S.R., Fraser, J.D., Libby, E., *et al.* (2011). Demographic variation in community-based MRSA skin and soft tissue infection in Auckland, New Zealand. *The New Zealand Medical Journal, 124*(1332), 21-30. ; Blakiston, M.R., & Freeman, J.T. (2020). Population-level exposures associated with MRSA and ESBL-*E. coli* infection across district health boards in Aotearoa New Zealand: An ecological study. *The New Zealand Medical Journal, 133*(1510), 62-69.

[831] Williamson, D.A., Ritchie, S.R., Lennon, D., *et al.* (2013). Increasing incidence and sociodemographic variation in community-onset *Staphylococcus aureus* skin and soft tissue infections in New Zealand children. *The Pediatric Infectious Disease Journal, 32*(8), 923-925. https://doi.org/10.1097/INF.0b013e3182905f3d

[832] Vogel, A.M., Borland, A., Van Der Werf, B., *et al.* (2020). Community-acquired invasive *Staphylococcus aureus*: Uncovering disparities and the burden of disease in Auckland children. *Journal of Paediatrics and Child Health, 56*(2), 244-251. https://doi.org/10.1111/jpc.14573

[833] Blakiston, M.R., & Freeman, J.T. (2020). Population-level exposures associated with MRSA and ESBL-*E. coli* infection across district health boards in Aotearoa New Zealand: An ecological study. *The New Zealand Medical Journal, 133*(1510), 62-69.

[834] Ritchie, S.R., Fraser, J.D., Libby, E., *et al.* (2011). Demographic variation in community-based MRSA skin and soft tissue infection in Auckland, New Zealand. *The New Zealand Medical Journal, 124*(1332), 21-30.

[835] Blakiston, M.R., & Freeman, J.T. (2020). Population-level exposures associated with MRSA and ESBL-*E. coli* infection across district health boards in Aotearoa New Zealand: An ecological study. *The New Zealand Medical Journal, 133*(1510), 62-69.

infection.[836] There are higher rates in Northland, Counties Manukau, Lakes, Hawke's Bay, Tairāwhiti and Waitematā DHBs.[837]

People in hospital

Even though most MRSA infections in Aotearoa New Zealand are acquired in the community, being in hospital is still an important risk factor. This is because hospital patients may have wounds or open sores from invasive procedures, as well as health issues like a weakened immune system that make it harder to clear an infection. In hospitalised patients, *S. aureus* causes serious infections including bacteraemia and pneumonia. It can also cause skin and soft tissue infections particularly related to invasive procedures such as surgical wounds, vascular access sites, endotracheal tubes, and urinary catheters.[838]

Hospital workers who harbour these bacteria may be a source of infection for patients. A study in 2008 comparing the carriage rate of MRSA in 100 health workers at North Shore Hospital with the carriage rate of MRSA in the general population found a prevalence of MRSA in the health workers of 4%, but 0% in the general population group.[839]

Other risk factors

- Greater community antimicrobial use is associated with MRSA infection.[840] Aotearoa New Zealand has high community use compared with other high-income countries (see section 4.4.1 above).
- There is also a higher risk associated with injecting drugs.[841] A study from the UK has shown an increase in MRSA infection among people who inject drugs.[842]
- There is an increased risk for people who have contact with livestock.[843] Livestock-associated MRSA has been linked to localised infections in humans, such as skin and soft tissue infections (including abscesses and wound infections) and otitis media, as well as severe and invasive infections, such as bacteraemia, pneumonia, osteoarticular infections and endocarditis.[844] Meanwhile, an Aotearoa New Zealand study found no evidence of MRSA in cats and dogs attending vet

Greater community antimicrobial use is associated with MRSA infection.

[836] Blakiston, M.R., & Freeman, J.T. (2020). Population-level exposures associated with MRSA and ESBL-*E. coli* infection across district health boards in Aotearoa New Zealand: An ecological study. *Population, 133*(1510).
[837] Heffernan, H., & Bakker, S. (2017). *2017 survey of methicillin-resistant Staphylococcus aureus (MRSA)*. Porirua, NZ: Institute of Environmental Science and Research Ltd Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/MRSA/MRSA_2017.pdf
[838] Lee, A.S., De Lencastre, H., Garau, J.*, et al.* (2018). Methicillin-resistant *Staphylococcus aureus*. *Nature Reviews Disease Primers, 4*(1), 18033. https://doi.org/10.1038/nrdp.2018.33
[839] Perry, H.E., & Henderson, R.A. (2008). Comparison of methicillin-resistant Staphylococcus aureus (MRSA) carriage rate in the general population with the health-worker population. *New Zealand Journal of Medical Laboratory Science*, 4.
[840] Blakiston, M.R., & Freeman, J.T. (2020). Population-level exposures associated with MRSA and ESBL-*E. coli* infection across district health boards in Aotearoa New Zealand: An ecological study. *The New Zealand Medical Journal, 133*(1510), 62-69.
[841] Jackson, K.A., Bohm, M.K., Brooks, J.T.*, et al.* (2018). Invasive methicillin-resistant Staphylococcus aureus infections among persons who inject drugs—six sites, 2005–2016. *Morbidity and Mortality Weekly Report, 67*(22), 625. https://doi.org/10.15585/mmwr.mm6722a2
[842] Packer, S., Pichon, B., Thompson, S.*, et al.* (2019). Clonal expansion of community-associated meticillin-resistant *Staphylococcus aureus* (MRSA) in people who inject drugs (PWID): Prevalence, risk factors and molecular epidemiology, Bristol, United Kingdom, 2012 to 2017. *Eurosurveillance, 24*(13). https://doi.org/10.2807/1560-7917.Es.2019.24.13.1800124
[843] Chen, C., & Wu, F. (2020). Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) colonisation and infection among livestock workers and veterinarians: A systematic review and meta-analysis. *Occupational and Environmental Medicine, 78*(7), 530-540. https://doi.org/10.1136/oemed-2020-106418
[844] Lee, A.S., De Lencastre, H., Garau, J.*, et al.* (2018). Methicillin-resistant *Staphylococcus aureus*. *Nature Reviews Disease Primers, 4*(1), 18033. https://doi.org/10.1038/nrdp.2018.33

clinics in Tāmaki Makaurau Auckland from June 2012 to June 2013, indicating that having pets is not likely to be a major risk factor for acquiring MRSA.[845]

4.5.3 Prevalence of resistance

National surveillance of MRSA has been undertaken by ESR through periodic point-prevalence surveys (see section 4.3.1).

Testing of 751 isolates of *S. aureus* in 2014 found varying levels of resistance to a variety of antibiotics.[846] Of the isolates tested, 9% were MRSA. Additionally, there was resistance to fusidic acid (58%) and erythromycin (25%).

Recent susceptibility data collected from clinical and diagnostic laboratories around the country has included data on the resistance of MSSA and MRSA to other antibiotics (2017).[847] This data found that over 80% were not susceptible to penicillin, 50% of MRSA from skin and soft tissue were not susceptible to fusidic acid, and there were no more than 20% of isolates not susceptible to all other antibiotics tested.

4.5.4 Treatments

There are several steps that can be taken when a patient requires treatment for an MRSA infection or is colonised with MRSA. Antibiotics may be prescribed if there is an infection, but options are limited. Vancomycin has been the antibiotic of choice in hospital settings for severe infections, however dosing to achieve effective concentrations without toxicity (mainly to the kidneys) can be complicated (e.g. concentration monitoring with special software is required to support optimal dosing).

4.5.5 Actions and solutions

IPC is integral to reducing potential harm. In hospitals, this might involve screening and active surveillance for colonisation (e.g. swabbing patients on admission and discharge to see if they are carrying MRSA, see section 4.3.1). A better understanding of the *S. aureus* colonisation in hospitals and the community across all age and ethnic groups is required to better inform prevention strategies.

There are ways to prevent development of infection in carriers, such as using topical antimicrobials applied to nostrils. But use of these agents may contribute to AMR, so non-antibiotic prevention measures should be considered. Decolonisation may be attempted, which includes a large number of steps that include various personal hygiene measures, washing and house cleaning, use of antiseptics on the skin and hair, and nose decontamination.[848]

There are many ways to prevent or reduce transmission between patients, people, and surfaces. This includes adherence to standard and transmission-based precautions such as practising hand hygiene, being aware of mobile phones as a key source of transmission,[849] using personal protective equipment, isolation and other contact precautions, and possibly surface treatments or probiotic

[845] Karkaba, A., Benschop, J., Hill, K., *et al.* (2017). Characterisation of methicillin-resistant *Staphylococcus aureus* clinical isolates from animals in New Zealand, 2012–2013, and subclinical colonisation in dogs and cats in Auckland. *New Zealand Veterinary Journal, 65*(2), 78-83. https://doi.org/10.1080/00480169.2016.1222919

[846] Heffernan, H., Bakker, S., Woodhouse, R., *et al.* (2015). *Demographics, antimicrobial susceptibility and molecular epidemiology of Staphylococcus aureus in New Zealand, 2014*. Porirua, NZ: Institute of Environmental Science and Research Ltd.

[847] Institute of Environmental Science and Research Limited (ESR). (2017). *Antimicrobial susceptibility data from hospital and community laboratories, 2017*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/AR/National_AR_2017.pdf

[848] Canterbury District Health Board. (2021). Skin decolonisation. Retrieved 15 October, 2021, from https://www.healthinfo.org.nz/index.htm?Skin-decolonisation.htm

[849] Chang, C.-H., Chen, S.-Y., Lu, J.-J., *et al.* (2017). Nasal colonization and bacterial contamination of mobile phones carried by medical staff in the operating room. *PLOS One, 12*(5), e0175811. https://doi.org/10.1371/journal.pone.0175811

cleaners.[850] There is research underway for development of a vaccine against *S. aureus*, however this is not yet available, [851] and previous attempts to develop a vaccine for *S. aureus* have been unsuccessful.[852]

In healthcare settings the most obvious areas to target include the practices of inserting and maintaining vascular access devices and reducing skin colonisation with *S. aureus* prior to any surgery.[853] There is an example of a national quality improvement programme in Aotearoa New Zealand for SSI Improvement for orthopaedic SSIs.[854] Data from this programme found introduction of the programme resulted in an increase in compliance with expected best practice and an associated reduction in incidence of SSI from the baseline median of 1.4% in 2013-2014 to 0.9% in 2015-2017. Infection prevention and control is discussed further in section 5.3.1.

[850] Steeman, M. (2020, 20 December). NZ-developed nanoparticle technology to fight Covid-19 and other powerful bugs, *Stuff*. Retrieved from https://www.stuff.co.nz/business/123737541/nzdeveloped-nanoparticle-technology-to-fight-covid19-and-other-powerful-bugs
[851] GlaxoSmithKline. (2020). Safety, immunogenicity and efficacy of GSK *S. Aureus* candidate vaccine (GSK3878858A) when administered to healthy adults (dose-escalation) and to adults 18 to 50 years of age with a recent *S. Aureus* skin and soft tissue infection (SSTI). [Clinical trial]. Retrieved from https://ClinicalTrials.gov/show/NCT04420221
[852] Clegg, J., Soldaini, E., McLoughlin, R.M.*, et al.* (2021). *Staphylococcus aureus* vaccine research and development: The past, present and future, including novel therapeutic strategies. *Frontiers in Immunology, 12*(2693). https://doi.org/10.3389/fimmu.2021.705360
[853] Roberts, S., Grae, N., Muttaiyah, S.*, et al.* (2020). Healthcare-associated *Staphylococcus aureus* bacteraemia: Time to reduce the harm caused by a largely preventable event. *The New Zealand Medical Journal, 133*(1509), 58-64.
[854] Morris, A.J., Roberts, S.A., Grae, N.*, et al.* (2018). The New Zealand Surgical Site Infection Improvement (SSII) programme: A national quality improvement programme reducing orthopaedic surgical site infections. *The New Zealand Medical Journal, 131*(1479), 45-56.

4.6 Case study: Antimicrobial-resistant UTIs

UTIs are very common, particularly in women, with 50-60% of adult women experiencing one or more in their lifetime.[855] UTIs are usually caused by bacteria living on or in our bodies, such as those found in the digestive system (e.g. *E. coli*). For most healthy people UTIs just involve the bladder ('cystitis') and can be resolved with a short course of oral antibiotics. Some UTIs may be more serious, with spread of infection to one or both kidneys. This causes more pain and illness, sometimes leading to sepsis, hospitalisation, IV antimicrobial therapy, and even death. Animals are also able to get UTIs. One study estimated that 14% of dogs will experience a UTI in their lifetime.[856]

Pathogens that can cause UTIs include *K. pneumoniae*, *P. aeruginosa*, and *Enterococcus* spp.[857] although *E. coli* is the most frequently detected urinary pathogen. These UTI-causing bacteria are developing resistance to the antibiotics that we rely on for treatment.[858] A lack of effective oral treatments may mean that once-simple infections managed in the community will instead require use of IV antimicrobials in hospital settings. In turn, this could increase the risk of more serious infections.

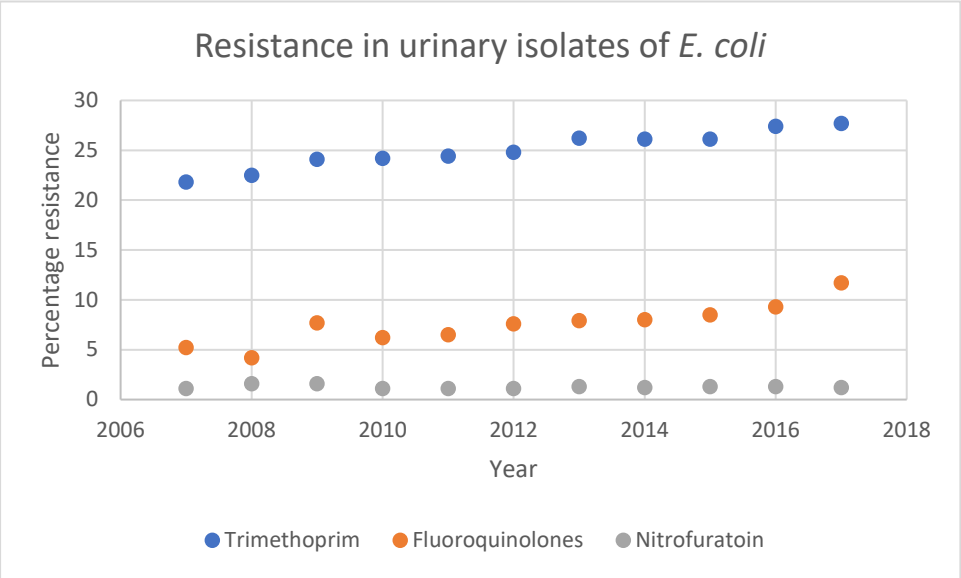

Figure 35: Resistance among urinary isolates of *E. coli* to trimethoprim, fluoroquinolones and nitrofurantoin over time. Data from ESR.

Among urinary *E. coli* isolates, resistance to trimethoprim has increased (Figure 35). This level of resistance may warrant a reconsideration of empiric treatment for UTIs and in many settings with prescribing guidelines, nitrofurantoin is now the first choice antibiotic for UTIs.[859] Data collated by ESR over 2016 and 2017 was further broken down into ESBL and non-ESBL *E. coli*, revealing that ESBL *E. coli* isolates also harbour greater resistance (or non-susceptibility) to trimethoprim and fluoroquinolones such as ciprofloxacin compared with non-ESBL isolates (Table 12).[860]

[855] Medina, M., & Castillo-Pino, E. (2019). An introduction to the epidemiology and burden of urinary tract infections. *Therapeutic Advances in Urology, 11*, 175628721983217. https://doi.org/10.1177/1756287219832172
[856] Bartges, J.W. (2004). Diagnosis of urinary tract infections. *Veterinary Clinics: Small Animal Practice, 34*(4), 923-933.
[857] Flores-Mireles, A.L., Walker, J.N., Caparon, M., *et al.* (2015). Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. *Nature Reviews Microbiology, 13*(5), 269-284. https://doi.org/10.1038/nrmicro3432
[858] Wagenlehner, F., Tandogdu, Z., Bartoletti, R., *et al.* (2016). The Global Prevalence of Infections in Urology Study: A Long-Term, Worldwide Surveillance Study on Urological Infections. *Pathogens, 5*(1), 10. https://doi.org/10.3390/pathogens5010010
[859] bpac nz. (2021, March). Antibiotic guide: Urinary tract infection – cystitis adult. Retrieved 13 December, 2021, from https://bpac.org.nz/antibiotics/guide.aspx#uti-adult
[860] Institute of Environmental Science and Research Limited (ESR). (2016). *Antimicrobial susceptibility data from hospital and community laboratories, 2016*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/AR/National_AR_2016.pdf;

Table 12: Resistance profiles of urinary *E. coli* isolates, split into ESBLs and non-ESBLs. Data from ESR.

Year	Resistance (%)					
	Trimethoprim		Fluoroquinolones		Nitrofurantoin	
	non-ESBL	ESBL	non-ESBL	ESBL	non-ESBL	ESBL
2017	25.9	69.8	9.2	67.3	1.1	3.3
2016	25.7	70.6	7	62.6	1.2	4.6

Additionally, a study in Tāmaki Makaurau Auckland found that the prevalence of AmpC β-lactamase-producing *E. coli* (which are resistant to most β-lactam antimicrobials except fourth-generation cephalosporins and carbapenems) isolated from UTIs was relatively low in the Tāmaki Makaurau Auckland community but has increased in recent years.[861]

AMR has been observed in companion animal UTIs too. In dogs in Aotearoa New Zealand, between 2005 and 2012 there was an increase in resistance to some antimicrobials commonly used to treat UTIs, including amoxicillin + clavulanic acid and enrofloxacin (a quinolone antibiotic), but there was no change in resistance to trimethoprim + sulphonamide.[862]

4.6.1 People most at risk of acquiring drug-resistant UTIs

Studies have identified individual risk factors and predisposing factors that increase the chances of someone acquiring UTIs and drug-resistant UTIs.[863]

Factors that increase an individual's risk for UTIs and multidrug-resistant UTIs include:[864]

- **Being a woman.** Across all ages, UTIs are four times more common in women than in men. Consistently, a local study suggested that elderly women are three times as likely as elderly men to have an MDRO as the cause of their UTI.
- **Being elderly.** The rates of UTIs including those due to MDROs get higher with age.
- **Having recurrent UTIs.** In a local study of elderly people, those suffering from recurrent UTIs (three or more in a 12-month period) were 2.2 times more likely to acquire a multidrug-resistant UTI. Recurrent UTIs might also signal need for more thinking about preventative measures.
- **Having diabetes.** In a local study of elderly people, those who had diabetes were 2.4 times more likely to acquire a multidrug-resistant UTI.
- **Being sexually active.** Sexual intercourse, spermicide use, and having a new sexual partner are all important risk factors.[865]

Healthcare-associated factors that predispose someone to UTIs and multidrug-resistant UTIs include:[866]

Institute of Environmental Science and Research Limited (ESR). (2017). *Antimicrobial susceptibility data from hospital and community laboratories, 2017*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/AR/National_AR_2017.pdf

[861] Drinkovic, D., Morris, A.J., Dyet, K.*, et al.* (2015). Plasmid-mediated AmpC beta-lactamase-producing Escherichia coli causing urinary tract infection in the Auckland community likely to be resistant to commonly prescribed antimicrobials. *The New Zealand Medical Journal, 128*(1410), 50-59.

[862] McMeekin, C., Hill, K., Gibson, I.*, et al.* (2017). Antimicrobial resistance patterns of bacteria isolated from canine urinary samples submitted to a New Zealand veterinary diagnostic laboratory between 2005–2012. *New Zealand Veterinary Journal, 65*(2), 99-104. https://doi.org/10.1080/00480169.2016.1259594

[863] Tenney, J., Hudson, N., Alnifaidy, H.*, et al.* (2018). Risk factors for aquiring multidrug-resistant organisms in urinary tract infections: A systematic literature review. *Saudi Pharmaceutical Journal, 26*(5), 678-684. https://doi.org/https://doi.org/10.1016/j.jsps.2018.02.023

[864] Ikram, R., Psutka, R., Carter, A.*, et al.* (2015). An outbreak of multi-drug resistant *Escherichia coli* urinary tract infection in an elderly population: A case-control study of risk factors. *BMC Infectious Diseases, 15*(1). https://doi.org/10.1186/s12879-015-0974-0
Health Quality & Safety Commission. (2020). Community use of antibiotics. Retrieved 5 October, 2021, from https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/community-use-of-antibiotics/

[865] Cai, T. (2021). Recurrent uncomplicated urinary tract infections: definitions and risk factors. *GMS Infectious Diseases, 9*. https://doi.org/10.3205/id000072

[866] Ikram, R., Psutka, R., Carter, A.*, et al.* (2015). An outbreak of multi-drug resistant *Escherichia coli* urinary tract infection in an elderly population: A case-control study of risk factors. *BMC Infectious Diseases, 15*(1). https://doi.org/10.1186/s12879-015-0974-0; Health

- **Living in ARC facilities, particularly with high dependency needs.** In a local study of elderly people, residing in aged care facilities increased the likelihood of acquiring a multidrug-resistant UTI by 2.3 times. For those in high dependency care, it increased to 7.5 times. According to the Atlas of Healthcare Variation, for people aged 65–74, antimicrobial prescriptions for a UTI in people in aged care were three times higher than for those living in the community (18% vs 6%).
- **Taking antibiotics previously.** In a local study of elderly people, those who had been prescribed particular antimicrobials in hospital were 5.6 times more likely to have a multidrug-resistant UTI.
- **Having a catheter in your bladder.**[867] Catheterisation, and length of catheterisation, are risk factors for developing a UTI.
- **Recent travel.**[868] Recent travel can be predictive of resistance based on the country that a patient has recently visited. For example, recent travel to countries in Asia is reported to have a particularly high risk for resistance.[869]

4.6.2 Actions and solutions

Appropriate prescribing must be supported, especially in the aged care sector

In Aotearoa New Zealand, a specific workstream focusing on UTIs is underway by the HQSC and the ARC sector to improve the quality of antimicrobial use. Asymptomatic bacteriuria (bacteria growing in the urine without causing symptoms of a UTI) is common, especially among the elderly and people with catheters or incontinence.[870] Most of the time it should not be treated as it will self-resolve. Nonetheless, urine samples are often sent to the lab and antibiotics inappropriately given because bacteria are detected. This may cause harm to patients via development of AMR or side effects from the antibiotics.[871] A Cochrane review found that there is no clinical benefit from treating asymptomatic bacteriuria, but significantly more adverse events.[872]

Prior to initiation of the HQSC project, rates of antimicrobial prescribing were decreasing based on data from 2015-2017: 24% of aged care residents were dispensed an antibiotic specifically indicated for UTIs in 2017 down from 30% in 2015. The biggest decrease was seen in Māori patients (from 34% down to 22%).[873] Data beyond 2018 is not available on the HQSC Atlas of Healthcare Variation.

Studies overseas have also shown high levels of inappropriate prescribing for UTIs.[874] There has recently been significant work undertaken in the United Kingdom in relation to improving the management of UTIs in older people. Their research suggests that urine cultures should only be sent

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Quality & Safety Commission. (2020). Community use of antibiotics. Retrieved 5 October, 2021, from https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/community-use-of-antibiotics/

[867] Kranz, J., Schmidt, S., Wagenlehner, F., *et al.* (2020). Catheter-associated urinary tract infections in adult patients - preventive strategies and treatment options. *Deutsches Ärzteblatt International, 117*, 83-88. https://doi.org/10.3238/arztebl.2020.0083

[868] Søraas, A., Sundsfjord, A., Sandven, I., *et al.* (2013). Risk factors for community-acquired urinary tract infections caused by ESBL-producing enterobacteriaceae–a case–control study in a low prevalence country. *PLOS One, 8*(7), e69581. https://doi.org/10.1371/journal.pone.0069581

[869] Osthoff, M., McGuinness, S.L., Wagen, A.Z., *et al.* (2015). Urinary tract infections due to extended-spectrum beta-lactamase-producing Gram-negative bacteria: Identification of risk factors and outcome predictors in an Australian tertiary referral hospital. *International Journal of Infectious Diseases, 34*, 79-83. https://doi.org/10.1016/j.ijid.2015.03.006

[870] Grae, N. (2021). Personal communication.

[871] Health Quality & Safety Commission. (2020). *Appropriate medication use in aged residential care: Optimising the use of antibiotics, antipsychotics and fentanyl*. Wellington, New Zealand: Retrieved from https://www.hqsc.govt.nz/assets/ARC/PR/ARC_polypharmacy_final_April2020.pdf

[872] Zalmanovici Trestioreanu, A., Lador, A., Sauerbrun-Cutler, M.T., *et al.* (2015). Antibiotics for asymptomatic bacteriuria. *Cochrane Database of Systematic Reviews, 4*. https://doi.org/10.1002/14651858.CD009534.pub2

[873] Health Quality & Safety Commission. (2021). Atlas of Healthcare Variation. Retrieved 15 April, 2021, from https://public.tableau.com/profile/hqi2803#!/vizhome/Communityantibioticusesinglemap/AtlasofHealthcareVariationCommunityantibioticuse

[874] Clark, A.W., Durkin, M.J., Olsen, M.A., *et al.* (2021). Rural–urban differences in antibiotic prescribing for uncomplicated urinary tract infection. *Infection Control & Hospital Epidemiology*, 1-8. https://doi.org/10.1017/ice.2021.21

when UTIs are suspected based on clinical symptoms and that uncomplicated UTIs should be treated with a short course of an oral antibiotic.[875]

After low rates of adherence to antimicrobial guidelines for UTIs were found at Auckland City Hospital, a mobile app ('SCRIPT') was trialled to provide on-the-go access to antibiotic guidelines to hospital prescribers. Evaluation found that there was no change in guideline adherence among prescribers caring for patients with UTIs with use of the app.[876] During the baseline period, 98/209 (47%) patients were prescribed guideline-adherent treatment and during the intervention period 106/211 (50%) patients were prescribed guideline-adherent treatment.

New technology for diagnosis is desperately needed

Accurate diagnosis is needed, however there are currently no good rapid tests which can accurately detect UTI or differentiate it from asymptomatic bacteriuria. Emerging technology in this area includes an algorithm to predict AMR in UTIs and guide treatment.[877]

Over-the-counter trimethoprim to treat some UTI cases

In Aotearoa New Zealand, an antibiotic (trimethoprim) used for treatment of UTIs is available to be purchased from accredited pharmacists without a prescription if certain conditions are met. This approach was introduced in 2012 and is only available to women who are experiencing uncomplicated cystitis.[878] While this approach may enhance access for some women, there is little oversight of this dispensing and it is unknown how well pharmacists adhere to guidelines for providing trimethoprim for UTIs.[879] It would be beneficial to collect and analyse data on the quantity and nature of trimethoprim purchased, and whether this treatment is effective.

An audit performed from June 2016 to August 2018 found that around one quarter of *E. coli* isolates causing cystitis in women were not susceptible to trimethoprim, a level of non-susceptibility sufficiently high to suggest that use of trimethoprim as the empiric treatment should be reconsidered.[880] Further, as discussed above, there is growing resistance to trimethoprim and some prescribing guidance now recommends nitrofurantoin as the first-line treatment for UTIs. This suggests that over-the-counter provision of trimethoprim should be reconsidered.

… around one quarter of ***E. coli*** isolates causing cystitis in women were not susceptible to trimethoprim, a level of non-susceptibility sufficiently high to suggest that use of trimethoprim as the empiric treatment should be reconsidered.

[875] Grimwade, K. (2021). Personal communication.
[876] Yoon, C.H., Ritchie, S.R., Duffy, E.J., *et al.* (2019). Impact of a smartphone app on prescriber adherence to antibiotic guidelines in adult patients with community acquired pneumonia or urinary tract infections. *PLOS One, 14*(1), e0211157. https://doi.org/10.1371/journal.pone.0211157
[877] Yelin, I., Snitser, O., Novich, G., *et al.* (2019). Personal clinical history predicts antibiotic resistance of urinary tract infections. *Nature Medicine, 25*(7), 1143-1152. https://doi.org/10.1038/s41591-019-0503-6
[878] Gauld, N.J., Zeng, I.S., Ikram, R.B., *et al.* (2017). Antibiotic treatment of women with uncomplicated cystitis before and after allowing pharmacist-supply of trimethoprim. *International Journal of Clinical Pharmacy, 39*(1), 165-172. https://doi.org/10.1007/s11096-016-0415-1
[879] Gauld, N.J., Zeng, I.S., Ikram, R.B., *et al.* (2016). Treatment of uncomplicated cystitis: Analysis of prescribing in New Zealand. *New Zealand Medical Journal, 129*(1437), 55-63.
[880] Ussher, J.E., McAuliffe, G.N., Elvy, J.A., *et al.* (2020). Appropriateness of trimethoprim as empiric treatment for cystitis in 15-55 year-old women: An audit. *New Zealand Medical Journal, 133*(1519), 62-69.

4.7 Case study: Treating tuberculosis is a growing challenge – what this means for Aotearoa New Zealand

Globally, TB is the most common bacterial infectious disease leading to death. It is caused by the bacterium *Mycobacterium tuberculosis*. Despite being both curable and preventable, an estimated 10 million people fell ill with TB in 2019, with 1.4 million people dying from this infection in the same year.[881] The COVID-19 pandemic has contributed to disrupted TB diagnosis and treatment: 2020 saw an increase in TB deaths for the first time in a decade, with approximately 1.5 million deaths.[882]

The rise of multi- and extensively drug-resistant TB poses a **significant threat** to all countries.

TB mainly affects the lungs, with symptoms including persistent coughing (including coughing up blood and mucous), chest pain, weight loss, fever, and fatigue. TB symptoms may not present until months or years after initial exposure. TB can be spread between people while the infection is active.

Some countries face a very high burden of TB, with over 95% of cases occurring in developing countries. While Aotearoa New Zealand is not one of those countries, TB still causes significant morbidity to some people in our country. Around 7-10 per 100,000 people are diagnosed with TB each year in Aotearoa New Zealand (320 cases were notified in 2020) and most cases are acquired overseas. Historically, TB was a significant cause of death: cases became notifiable in 1940 and peaked at 2,600 cases in 1943 (i.e. 159 cases per 100,000 people).[883] Following World War II, the Tuberculosis Act 1948 was enacted to assist with prevention and treatment of TB.

The rise of multi- and extensively drug-resistant TB poses a significant threat to all countries. While global prevalence of TB is decreasing, the proportion of cases that are resistant to drugs is increasing – WHO reported a 10% increase in multidrug- or rifampicin-resistant TB between 2018 and 2019. Most Pacific Islands have national TB management programmes, where incidence, prevalence, and mortality generally remained stable or declined between 2000-2013.[884] Modelling estimates suggest that additional interventions are likely needed to achieve meaningful reductions in TB morbidity and mortality in Pacific Island countries between 2020-2030, such as new transformational tools (e.g. vaccines, new diagnostic tools, shorter treatment).[885]

4.7.1 Data on resistance

TB is typically treated using combination antibiotic therapy, with four antibiotics used to target the bacteria. Even fully susceptible TB is difficult to treat on account of the bacteria's structure and metabolism and ability to withstand drug treatment and immune attack. Combination therapy was

[881] World Health Organization. (2020). Tuberculosis. Retrieved 14 October 2021, from https://www.who.int/news-room/fact-sheets/detail/tuberculosis

[882] World Health Organization. (2021, 14 October). *Tuberculosis deaths rise for the first time in more than a decade due to the COVID-19 pandemic* [Press release]. Retrieved from https://www.who.int/news/item/14-10-2021-tuberculosis-deaths-rise-for-the-first-time-in-more-than-a-decade-due-to-the-covid-19-pandemic

[883] Ministry of Health. (2002). *Guidelines for tuberculosis control in New Zealand 2003*. Wellington, NZ: Ministry of Health. Retrieved from https://www.tbonline.info/media/uploads/documents/guidelines_for_tuberculosis_control_in_new_zealand_%282003%29.pdf

[884] Viney, K., Hoy, D., Roth, A.*, et al.* (2015). The epidemiology of tuberculosis in the Pacific, 2000 to 2013. *Western Pacific Surveillance and Response journal: WPSAR, 6*(3), 59. https://doi.org/10.5365/WPSAR.2015.6.3-059

[885] Estill, J., Islam, T., Houben, R.M.*, et al.* (2021). Tuberculosis in the Western Pacific Region: Estimating the burden of disease and return on investment 2020–2030 in four countries. *The Lancet Regional Health-Western Pacific, 11*, 100147. https://doi.org/10.1016/j.lanwpc.2021.100147

developed in response to this, as well as being strategy to reduce the emergence of AMR. Despite this, resistance to various antibiotics used in combination therapy has been observed.[886]

Testing between 2007 and 2017 shows increasing resistance to streptomycin and decreasing resistance to pyrazinamide in Aotearoa New Zealand.[887] In the ten years to 2017, there were 34 cases of multidrug-resistant TB. All but one were acquired overseas before arriving or returning here. For TB, multidrug resistance is refers to an isolate that is resistant to the two most important first-line TB drugs (isoniazid and rifampicin).

In the ten years to 2017, there were 34 cases of multidrug-resistant TB.

An average of 1.3% of TB cases each year were multidrug resistant. ESR reported on 230 isolates from TB cases in 2016[888] and found resistance to a number of antimicrobials: isoniazid (6.5%); rifampicin (1.7%); ethambutol (0.9%); streptomycin (8.3%); and pyrazinamide (0.9%).

In 2014, MoH established the Tuberculosis Clinical Network, which provides advice and assists with developing management plans for patients with multidrug-resistant cases. All multidrug-resistant cases must be treated in consultation with the Network, which helps ensure that sufficient drugs are used initially to avoid further resistance developing.[889]

WHO recently released its first catalogue of mutations in the TB genome complex, providing a list of mutations, their frequency, and whether they are associated with resistance.[890]

4.7.2 Who is most affected in Aotearoa New Zealand?

There are a number of factors that are associated with an increased risk of TB infection. Many of these factors may be associated and additive. For example, people who have recently migrated to Aotearoa New Zealand from a country with high incidence of TB may also be more likely to experience overcrowding in housing.[891]

- **Overseas travel and being born overseas**. Most cases are people who acquired the infection overseas. Because there is a lag between catching TB and diagnosis, they are often not diagnosed until they are in Aotearoa New Zealand. Country of birth is a major risk factor: 246 of the 295 new cases in 2017 were in people who were born overseas.[892] For those born

[886] Kerantzas, C.A., Jacobs, W.R., Rubin, E.J., *et al.* (2017). Origins of combination therapy for tuberculosis: Lessons for future antimicrobial development and application. *mBio, 8*(2), e01586-01516. https://doi.org/10.1128/mBio.01586-16
[887] Institute of Environmental Science and Research Limited (ESR). (2019). *Tuberculosis in New Zealand annual report 2016*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/AnnTBReports/TBannualreport2016.pdf
[888] Ibid.
[889] Ministry of Health. (2019). *Guidelines for tuberculosis control in New Zealand, 2019*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/system/files/documents/publications/guidelines-tuberculosis-control-new-zealand-2019-august2019-final.pdf
[890] World Health Organization. (2021). *Catalogue of mutations in Mycobacterium tuberculosis complex and their association with drug resistance*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.who.int/publications/i/item/9789240028173
[891] Baker, M., Das, D., Venugopal, K., *et al.* (2008). Tuberculosis associated with household crowding in a developed country. *Journal of Epidemiology & Community Health, 62*(8), 715-721. https://doi.org/10.1136/jech.2007.063610
[892] Institute of Environmental Science and Research Limited (ESR). (2021). *Tuberculosis in New Zealand: Annual report 2017*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/AnnTBReports/TBAnnualReport2017.pdf

overseas, the time between date of arrival and date of diagnosis varied between 0 and 59 years in 2017, though almost 20% were notified in the first year after arrival.[893]

- **Ethnicity**. People of Asian ethnicity have the highest rates (and accounted for almost 70% of the notified cases in 2020).[894] Māori and Pacific people also have higher burden of disease. For Māori the rate is approximately six times higher than for Europeans,[895] with Pacific people experiencing even higher rates. Ethnicity is also reported to be associated with different strains of TB – a unique strain known as the Rangipo strain is strongly associated with Māori.[896] WGS suggests that there has been ongoing transmission of this strain over almost thirty years.[897]
- **Weakened immune system, particularly HIV infection.** TB occurs in about 2% of people with HIV infection in Aotearoa New Zealand.[898] MoH recommends that people diagnosed with TB should be offered HIV testing on an opt-out basis given that it is a major risk factor for developing active TB.[899] Due to this association, there is reportedly stigma associated with TB in some communities, which should be considered when developing strategies to address TB.[900] People prescribed tumour necrosis factor inhibitors (medicines to help stop inflammation) are also at increased risk of TB.[901] Among this patient group, there is a necessity to screen for and treat latent TB,[902] but no ability to detect resistant TB. Treating for latent TB with a single drug may therefore lead to multidrug-resistant TB.
- **Crowded housing.** Living in a crowded house may be associated with a higher risk of TB infection.[903] This also includes institutions that may be crowded including ARC facilities, prisons, and long-stay hospitals.

…a unique strain known as the Rangipo strain is strongly associated with Māori. Whole genome sequencing suggests that there has been ongoing transmission of this strain over almost thirty years.

[893] Ibid.
[894] 220 of 321 cases in 2020. New Zealand notifiable disease statistics for 2020, ESR.
[895] Aung, H.L., & Devine, T.J. (2019). Reducing the burden of tuberculosis in the Māori, the Indigenous people of New Zealand. *The Lancet Global Health, 7*(7), e845. https://doi.org/10.1016/S2214-109X(19)30236-0
[896] Aung, H.L., Devine, T.J., Mulholland, C.V*., et al.* (2019). Tackling tuberculosis in the indigenous people of New Zealand. *The Lancet Public Health, 4*(10), e496. https://doi.org/10.1016/S2468-2667(19)30180-X
[897] Ibid.
[898] Immunisation Advisory Centre. (2017). Tuberculosis. Retrieved 14 October, 2021, from https://www.immune.org.nz/diseases/tuberculosis
[899] Ministry of Health. (2019). *Guidelines for tuberculosis control in New Zealand, 2019*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/system/files/documents/publications/guidelines-tuberculosis-control-new-zealand-2019-august2019-final.pdf
[900] Badu, E., Mpofu, C., & Farvid, P. (2018). Towards TB elimination in Aotearoa/New Zealand: Key informant insights on the determinants of TB among African migrants. *Tropical medicine and infectious disease, 3*(2), 44. https://doi.org/10.3390/tropicalmed3020044
[901] Harris, J., & Keane, J. (2010). How tumour necrosis factor blockers interfere with tuberculosis immunity. *Clinical & Experimental Immunology, 161*(1), 1-9. https://doi.org/10.1111/j.1365-2249.2010.04146.x; Solovic, I., Sester, M., Gomez-Reino, J.J*., et al.* (2010). The risk of tuberculosis related to tumour necrosis factor antagonist therapies: A TBNET consensus statement. *European Respiratory Journal, 36*(5), 1185. https://doi.org/10.1183/09031936.00028510
[902] Lee, H., Park, H.Y., Jeon, K*., et al.* (2015). QuantiFERON-TB Gold in-tube assay for screening arthritis patients for latent tuberculosis infection before starting anti-tumor necrosis factor treatment. *PLOS One, 10*(3), e0119260. https://doi.org/10.1371/journal.pone.0119260
[903] Baker, M., Das, D., Venugopal, K*., et al.* (2008). Tuberculosis associated with household crowding in a developed country. *Journal of Epidemiology & Community Health, 62*(8), 715-721. https://doi.org/10.1136/jech.2007.063610

4.7.3 Actions and solutions

Better diagnostics

There is a need for better diagnostics, particularly for screening of latent TB. TB is typically diagnosed by bacterial culture, acid fast staining or PCR. Each method has pros and cons:

- **Bacterial culture** is the gold standard. It has high accuracy but takes weeks to complete.
- **Microscopy (acid fast/auramine staining)** is easy and cheap but is not available in all laboratories and only detects about half of all cases. This leaves opportunity for more transmission of the infection between people, and for more serious infection to develop that then requires more difficult treatment. In turn, this can lead to greater drug resistance.
- **PCR testing** may be deployed when diagnosis needs to be made with certainty and quickly[904] – for example to diagnose TB meningitis by testing cerebrospinal fluid. It is more sensitive than microscopy but less sensitive than culture.

Other methods of testing include interferon gamma release assays, such as the QuantiFERON Gold blood test. This detects whether a person has even been infected with TB but it cannot differentiate between latent and active infections. X-ray and CT scans are also used for diagnosis purposes, but they are not specific so usually need to be coupled with symptoms or signs compatible with active TB in order to make a probable diagnosis. Probable cases may be determined using histology that is strongly suggestive of *M. tuberculosis*, which requires a biopsy. In addition, there are new highly sensitive blood tests that can find traces of the bacteria that causes TB in infants a year before they develop the disease.[905] Research efforts in Aotearoa New Zealand have been undertaken to develop a rapid molecular diagnostic approach that can be used to identify the Rangipo TB strain.[906]

Samples that test positive undergo further testing to obtain information on drug resistance.[907] For example, resistance to rifampicin can be tested for using GeneXpert® MTB/RIF. Access to this test near the point of care coupled with WGS nationally would improve clinical and public health management through early identification of drug resistance and outbreaks.

TB screening and immigration

To attain a visa or permit to live in Aotearoa New Zealand, applicants may be required to undergo TB testing to demonstrate that they don't have an active TB infection. Currently, Immigration New Zealand screens for TB among individuals intending to stay for more than 12 months, requiring them to undergo a medical examination and a

There is a risk that, out of concern for their immigration status, migrants avoid engaging with the health system upon experiencing TB symptoms. **This has negative implications for their own health and wellbeing and for Aotearoa New Zealand's ability to curb TB spread.**

[904] Prakash, A.K., Datta, B., Goyal, P., *et al.* (2016). GENE-XPERT gives early diagnosis in early tuberculosis. *European Respiratory Journal, 48*(suppl 60), PA2775. https://doi.org/10.1183/13993003.congress-2016.PA2775

[905] Mao, L., LaCourse, S.M., Kim, S., *et al.* (2021). Evaluation of a serum-based antigen test for tuberculosis in HIV-exposed infants: a diagnostic accuracy study. *BMC Medicine, 19*(1), 113. https://doi.org/10.1186/s12916-021-01983-w

[906] Mulholland, C.V., Ruthe, A., Cursons, R.T., *et al.* (2017). Rapid molecular diagnosis of the *Mycobacterium tuberculosis* Rangipo strain responsible for the largest recurring TB cluster in New Zealand. *Diagnostic Microbiology and Infectious Disease, 88*(2), 138-140. https://doi.org/10.1016/j.diagmicrobio.2017.03.012

[907] Ministry of Health. (2019). *Guidelines for tuberculosis control in New Zealand, 2019*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/system/files/documents/publications/guidelines-tuberculosis-control-new-zealand-2019-august2019-final.pdf

chest X-ray.[908] Those intending to stay more than six months but less than 12 who are assessed as having certain risk factors for TB are also required to undergo this screening.

Aotearoa New Zealand doesn't have a program for identifying latent TB infection, so migrants with TB may not be detected through current practices, and a latent TB infection could subsequently become active. There is a risk that, out of concern for their immigration status, migrants avoid engaging with the health system upon experiencing TB symptoms. This has negative implications both for their own health and wellbeing and for Aotearoa New Zealand's ability to curb TB spread.[909]

Better management of treatment

WGS can be more widely utilised to inform treatment of TB, and overseas research has found using WGS leads to lower mortality.[910] WGS can inform tailored treatment for multidrug-resistant TB in the first week after diagnosis – much faster than traditional susceptibility testing which can take several weeks.[911] High-income countries overseas have steadily moved away from culture-based diagnostics to WGS for identifying the species, molecular strain typing, and resistance.[912] In Aotearoa New Zealand, WGS is available but is not routinely used to characterise all samples and is not utilised for routine susceptibility testing either.

Support of global TB prevention, care and control will benefit Aotearoa New Zealand by reducing imported cases.

There have also been local management approaches that have shown benefits to TB management. For example, Capital & Coast DHB has streamlined the management of latent TB in a fortnightly registrar-led clinic.[913] Patients can start treatment at their first (and usually only) clinic visit with follow-up by scheduled telephone visits. This combined with shorter treatment regimens mean the non-attendance rate has fallen from 45% to 16%, and more patients can be treated with the same staff resource. Similar approaches may be possible in other regions.

An elimination strategy?

While Aotearoa New Zealand has a number of measures in place, additional improvements could potentially be achieved through a TB elimination strategy.[914] An elimination strategy could target the most vulnerable and hard to reach groups, and ensure there is continued surveillance, programme monitoring and evaluation, and case-based data management. Additionally, support of global TB prevention, care and control will benefit Aotearoa New Zealand by reducing imported cases. No

[908] Ibid.
[909] Badu, E., Mpofu, C., & Farvid, P. (2018). Is New Zealand immigration policy a barrier to TB elimination? *New Zealand Medical Journal, 131*(1477), 120-122.
[910] Zürcher, K., Reichmuth, M.L., Ballif, M., *et al.* (2021). Mortality from drug-resistant tuberculosis in high-burden countries comparing routine drug susceptibility testing with whole-genome sequencing: a multicentre cohort study. *The Lancet Microbe*. https://doi.org/10.1016/S2666-5247(21)00044-6
[911] Grobbel, H.-P., Merker, M., Köhler, N., *et al.* (2021). Design of multidrug-resistant tuberculosis treatment regimens based on DNA sequencing. *Clinical Infectious Diseases, 73*(7), 1194-1202. https://doi.org/10.1093/cid/ciab359
[912] Basu, I., Bower, J.E., Roberts, S.A., *et al.* (2018). Utility of whole genome sequencing for multidrug resistant *Mycobacterium tuberculosis* isolates in a reference TB laboratory in New Zealand. *New Zealand Medical Journal, 131*(1487), 15-22.
[913] Verrall, A.J., Hill, P.C., Thorburn, D., *et al.* (2020). Towards elimination of tuberculosis in New Zealand. *The New Zealand Medical Journal, 133*(1513), 89-96.
[914] Ibid.

country has managed to eliminate TB, although many have low incidence.[915] The WHO has a 2035 goal of TB elimination, defined as less than one incident case per million worldwide.[916]

[915] Matteelli, A., Rendon, A., Tiberi, S*., et al.* (2018). Tuberculosis elimination: Where are we now? *European Respiratory Review, 27*(148), 180035. https://doi.org/10.1183/16000617.0035-2018

[916] World Health Organization. (n.d.). The End TB strategy. Retrieved 23 November, 2021, from https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy

4.8 Case study: Super-gonorrhoea and the impending threat of drug-resistant STIs

Gonorrhoea is an STI caused by a bacterium called *Neisseria gonorrhoeae*. It can affect the urethra, reproductive tract and organs, anus, throat, and eyes. Left untreated, the infection can cause pelvic inflammatory disease and pregnancy complications and infertility (in women), inflammation of the epididymis and sterility (in men), and eye infections (due to contact during drug delivery in neonates and contact with sexual fluids in adults).[917]

N. gonorrhoeae has developed resistance to a wide range of antibiotics.

N. gonorrhoeae has developed resistance to a wide range of antibiotics (Figure 36). Dual therapy with ceftriaxone plus azithromycin is now recommended as the first-line treatment for gonorrhoea in the *New Zealand Sexual Health Society Gonorrhoea Guideline*.[918] Prescribing occurs in the absence of AST results.

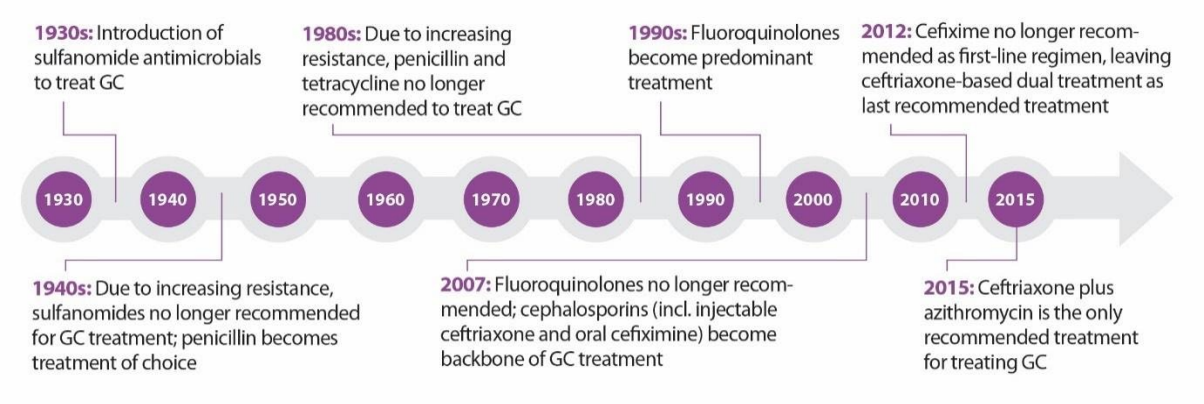

Figure 36: History of the gonorrhoea bacterium developing resistance to every antibiotic used to treat it. Note that cefiximine and cefixime are not used in Aotearoa New Zealand. GC is an alternative name for gonorrhoea. Image credit: CDC.

4.8.1 Reducing infections is essential to prevent spread of drug-resistant strains

The number of people becoming infected with gonorrhoea is increasing every year. Based on ESR surveillance data, the prevalence of infection has nearly doubled between 2013 and 2019 – from 77 cases per 100,000 people to 146 cases per 100,000 people.[919] However, it should be noted that more testing and the use of more sensitive testing technology has contributed to higher reported cases. Infections are often asymptomatic, which means that infections can often be missed. There

[917] Lee, J.S., Choi, H.Y., Lee, J.E., *et al.* (2002). Gonococcal keratoconjunctivitis in adults. *Eye, 16*(5), 646-649. https://doi.org/10.1038/sj.eye.6700112

[918] Gonorrhoea Guideline Writing Group on behalf of the New Zealand Sexual Health Society. (2014). *New Zealand Guideline for the Management of Gonorrhoea, 2014, and Response to the Threat of Antimicrobial Resistance*. New Zealand Sexual Health Society. 4

[919] Institute of Environmental Science and Research Limited (ESR). (2021). Sexually transmitted infection (STI) surveillance (dashboard). Retrieved 1 October, 2021, from https://www.esr.cri.nz/our-services/consultancy/public-health/sti/; Institute of Environmental Science and Research Limited (ESR). (2019). *Sexually transmitted infections in New Zealand annual surveillance report 2016*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2016/FINAL_2016_STI_AnnualReport.pdf

are also ongoing barriers to testing which mean that reported cases almost certainly underrepresent actual cases.[920] These barriers include:

- Personal barriers: underestimating risk and perceiving STIs as not serious, self-consciousness associated with genital examinations, fear of invasive procedures, and being too busy.
- Structural barriers: financial cost and clinician attributes and attitude, lack of funded sexual health clinics in many DHBs/regions, clinic accessibility.
- Social barriers: concern of being stigmatised or about being asked to disclose sexual partners to allow contact tracing and treatment.

There's an uneven burden of gonorrhoea in Aotearoa New Zealand depending on age, sex, ethnicity and location. Younger people have higher rates of gonorrhoea. Most cases in men are aged 20-29 and most cases in women are 15-29 years old.[921] However, less than 10% of men and 22-35% of women in the highest risk age groups had at least one annual STI test.[922]

In 2019, men had 174 cases per 100,000 people whereas women had 116 cases per 100,000 people.

While men are less likely to be tested, gonorrhoea is more prevalent in this group – particularly among men who have sex with men.[923] In 2019, men had 174 cases per 100,000 people whereas women had 116 cases per 100,000 people. The rate of increase was greater in men in recent years, but this reversed in 2019. There is also regional variability in how rates differ by sex – most regions have higher rates for men and this is strongest in Tāmaki Makaurau Auckland and Te Whanganui-a-Tara Wellington. Some regions have the opposite, with Te Tai Tokerau Northland and Te Matau-a-Māui Hawke's Bay reporting higher rates in women.[924]

…most of the disease burden still sits with Māori and Pacific women, but for men the highest rates are among Middle Eastern, Latin American and African men and these rates have increased rapidly to over 400 cases per 100,000 people.

Overall, gonorrhoea is more prevalent among Māori and Pacific peoples. Māori and Pacific peoples had a greater increase in prevalence in recent years compared with other ethnic groups. Prevalence among Māori increased from 165 to 289 cases per 100,000 people between 2014 and 2019. For Pacific peoples, the increase over the same period was from 143 to 323 cases per 100,000 people. In contrast, people who identified as European/Other had a rate of 83 cases per 100,000 in 2019, and for Asian people it was 103 per 100,000. Looking at both sex and ethnicity, most of the disease burden still sits with Māori and

[920] Denison, H.J., Bromhead, C., Grainger, R., *et al.* (2017). Barriers to sexually transmitted infection testing in New Zealand: a qualitative study. *Australian and New Zealand Journal of Public Health, 41*(4), 432-437. https://doi.org/10.1111/1753-6405.12680
[921] Institute of Environmental Science and Research Limited (ESR). (2021). Sexually transmitted infection (STI) surveillance (dashboard). Retrieved 1 October, 2021, from https://www.esr.cri.nz/our-services/consultancy/public-health/sti/
[922] Institute of Environmental Science and Research Limited (ESR). (2019). *Sexually transmitted infections in New Zealand annual surveillance report 2016*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2016/FINAL_2016_STI_AnnualReport.pdf
[923] Institute of Environmental Science and Research Limited (ESR). (2019). *STI epidemiology update*. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2019/STIsurvupdateDEC2019.pdf?m=1581887236&
[924]Institute of Environmental Science and Research Limited (ESR). (2021). Sexually transmitted infection (STI) surveillance (dashboard). Retrieved 1 October, 2021, from https://www.esr.cri.nz/our-services/consultancy/public-health/sti/
Institute of Environmental Science and Research Limited (ESR). (2019). *Sexually transmitted infections in New Zealand annual surveillance report 2016*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2016/FINAL_2016_STI_AnnualReport.pdf

Pacific women, but for men the highest rates are among Middle Eastern, Latin American and African men and these rates have increased rapidly to over 400 cases per 100,000 people.[925]

The Auckland region had the **highest rates** reported at 231 per 100,000 people and these rates had been steadily increasing.

There is also disparity in prevalence by regions. The Tāmaki Makaurau Auckland region had the highest rates reported at 231 per 100,000 people and these rates had been steadily increasing. Some other regions, including Te Matau-a-Māui Hawke's Bay and Taranaki, had reported a marked increase recently. In contrast, rates of infection in Tairāwhiti decreased significantly, from 394 cases per 100,000 in 2013 to 82 cases per 100,000 in 2019.[926] However, this may have been due to an outbreak in younger people observed in 2013.

These increases are concerning because the more cases of gonorrhoea locally, the more likely we will start to see untreatable infections in Aotearoa New Zealand.

Disease patterns differ by sexual behaviour, however, there is limited data to understand the details of these differences. A study of disease clusters found isolates from both sexes in each cluster[927] and a questionnaire in 2019 found that heterosexual women (27%) and men who have sex with men (26%) accounted for the greatest proportion of cases.[928]

4.8.2 Resistance to antimicrobials is prevalent in *N. gonorrhoeae* in Aotearoa New Zealand

AMR and molecular epidemiology of *N. gonorrhoeae* has been surveyed and reported on in detail in Aotearoa New Zealand in 2014-15 and 2018-19.[929] Current circulating strains are resistant to some but not all antimicrobials. No multi- or extensively drug-resistant strains were identified in a population survey of antimicrobial susceptibility for samples from 2014 and 2015, nor between 2018 and 2019, but 'pre-multidrug-resistant' strains were – that is, where there was either decreased susceptibility to extended-spectrum cephalosporins (a 'category I' drug), plus resistance to two or more 'category II' drugs.[930]

Current circulating strains are resistant to some but not all antimicrobials.

The proportion of *N. gonorrhoeae* samples displaying resistance to the current first-line treatments in Aotearoa New Zealand of ceftriaxone and azithromycin was low in 2014-15 and in 2018-19.[931]

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[925] ESR. (2019). STI epidemiology update. Retrieved 1 October 2021, from https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2019/STIsurvupdateDEC2019.pdf?m=1581887236&

[926] Institute of Environmental Science and Research Limited (ESR). (2021). Sexually transmitted infection (STI) surveillance (dashboard). Retrieved 1 October, 2021, from https://www.esr.cri.nz/our-services/consultancy/public-health/sti/

[927] Lee, R.S., Seemann, T., Heffernan, H., *et al.* (2018). Genomic epidemiology and antimicrobial resistance of *Neisseria gonorrhoeae* in New Zealand. *Journal of Antimicrobial Chemotherapy, 73*(2), 353-364. https://doi.org/10.1093/jac/dkx405

[928] Institute of Environmental Science and Research Limited (ESR). (2021). Sexually transmitted infection (STI) surveillance (dashboard). Retrieved 1 October, 2021, from https://www.esr.cri.nz/our-services/consultancy/public-health/sti/

[929] Straub, C., Thirkell, C., & Dyet, K. (2021). *Antimicrobial resistance and molecular epidemiology of Neisseria gonorrhoeae in New Zealand, 2018-2019*. Porirua, New Zealand: Institute of Environmental Science and Research Ltd. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/Gono/NgonoSurvey2019_FINAL.pdf

[930] Lee, R.S., Seemann, T., Heffernan, H., *et al.* (2018). Genomic epidemiology and antimicrobial resistance of *Neisseria gonorrhoeae* in New Zealand. *Journal of Antimicrobial Chemotherapy, 73*(2), 353-364. https://doi.org/10.1093/jac/dkx405

[931] Heffernan, H., Woodhouse, R., & Williamson, D. (2015). *Antimicrobial resistance and molecular epidemiology of Neisseria gonorrhoeae in New Zealand, 2014-15*. Porirua, NZ: Institute of Environmental Science and Research Ltd.

Meanwhile, resistance to previously relied on treatments is common in most of Aotearoa New Zealand.[932] Penicillin resistance was reported in 12% (51/425) of isolates tested in 2014-15 and in 8% (28/344) isolates tested in 2018-19. This is lower than the 22% resistance to penicillin observed in Australia in 2019. In a Tāmaki Makaurau Auckland-specific sample, the vast of majority of isolates (n=2,256, 98%) were resistant to penicillin.[933]

According to the national data collated by ESR in 2018-19, resistance to various antibiotics in *N. gonorrhoeae* has remained stable or decreased since 2014-15 – with the exception of azithromycin and tetracycline.[934]

Trend data is available from a study of 2,301 isolates from Auckland Regional Sexual Health Service and Auckland City Hospital from 2008 to 2016.[935] The proportion of samples displaying resistance to all antimicrobials declined from 2013-2016 (see Figure 37). The biggest decreases are in the antibiotics that are not used as first-line treatments. Resistance rates to ciprofloxacin (22%), penicillin (21%), and tetracycline (42%) remained consistently above the WHO-recommended 5% threshold for the use of these agents as empiric therapy for gonorrhoea infections. This does not include samples from GP practices, where the majority of diagnoses are made.[936]

Overseas trends suggest '**super gonorrhoea**' will develop here, so its spread needs to be detected, mitigated and prevented.

The move to DNA-based diagnosis of gonorrhoea means that fewer isolates are available for susceptibility testing and sequencing at ESR. Nearly 80% of notified cases over 2018-19 did not have a culturable isolate referred to ESR, meaning only around 20% of cases are captured in this analysis.[937] The retention of culturing capability is essential for monitoring of *N. gonorrhoeae* in the absence of widely accessible molecular assays that can identify resistance profiles.

There is limited information on the demographics and behaviours of people with resistant infections. The trend data from Tāmaki Makaurau Auckland showed that isolates from men, and those from extragenital sites, were overall more likely to be resistant to an antibiotic, which likely reflects the fact that these sites are more likely to be sampled in men who have sex with men.[938] There's no ethnicity data on who has drug-resistant gonorrhoeal infections.

Institute of Environmental Science and Research Limited (ESR). (2019). *Sexually transmitted infections in New Zealand annual surveillance report 2016*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2016/FINAL_2016_STI_AnnualReport.pdf

[932] Heffernan, H., Woodhouse, R., & Williamson, D. (2015). *Antimicrobial resistance and molecular epidemiology of Neisseria gonorrhoeae in New Zealand, 2014-15*. Porirua, NZ: Institute of Environmental Science and Research Ltd.

Institute of Environmental Science and Research Limited (ESR). (2019). *Sexually transmitted infections in New Zealand annual surveillance report 2016*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2016/FINAL_2016_STI_AnnualReport.pdf

[933] McAuliffe, G., Smith, M., Brokenshire, M., *et al.* (2018). Keeping track of antimicrobial resistance for *Neisseria gonorrhoeae* in Auckland, New Zealand: Past, present and future considerations. *The New Zealand Medical Journal, 131*, 71-77.

[934] Heffernan, H., Woodhouse, R., & Williamson, D. (2015). *Antimicrobial resistance and molecular epidemiology of Neisseria gonorrhoeae in New Zealand, 2014-15*. Porirua, NZ: Institute of Environmental Science and Research Ltd.

[935] McAuliffe, G., Smith, M., Brokenshire, M., *et al.* (2018). Keeping track of antimicrobial resistance for *Neisseria gonorrhoeae* in Auckland, New Zealand: Past, present and future considerations. *The New Zealand Medical Journal, 131*, 71-77.

[936] Institute of Environmental Science and Research Limited (ESR). (2019). *Sexually transmitted infections in New Zealand annual surveillance report 2016*. Porirua, NZ: ESR. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2016/FINAL_2016_STI_AnnualReport.pdf

[937] Heffernan, H., Woodhouse, R., & Williamson, D. (2015). *Antimicrobial resistance and molecular epidemiology of Neisseria gonorrhoeae in New Zealand, 2014-15*. Porirua, NZ: Institute of Environmental Science and Research Ltd.

[938] McAuliffe, G., Smith, M., Brokenshire, M., *et al.* (2018). Keeping track of antimicrobial resistance for *Neisseria gonorrhoeae* in Auckland, New Zealand: Past, present and future considerations. *The New Zealand Medical Journal, 131*, 71-77.

Overseas trends suggest 'super gonorrhoea' will develop here, so its spread needs to be mitigated and prevented. Worldwide there are increasing reports of people being infected with strains of *N. gonorrhoeae* that are resistant to either or both of ceftriaxone and high-level azithromycin, which are the current first-line antibiotics.[939] Some studies have looked at whether there has been a change in the minimum antimicrobial concentrations needed to suppress growth of *N. gonorrhoeae* over time.[940] Such data is not publicly available for Aotearoa New Zealand, however we have heard anecdotally of increasing minimum inhibitory concentrations being observed.

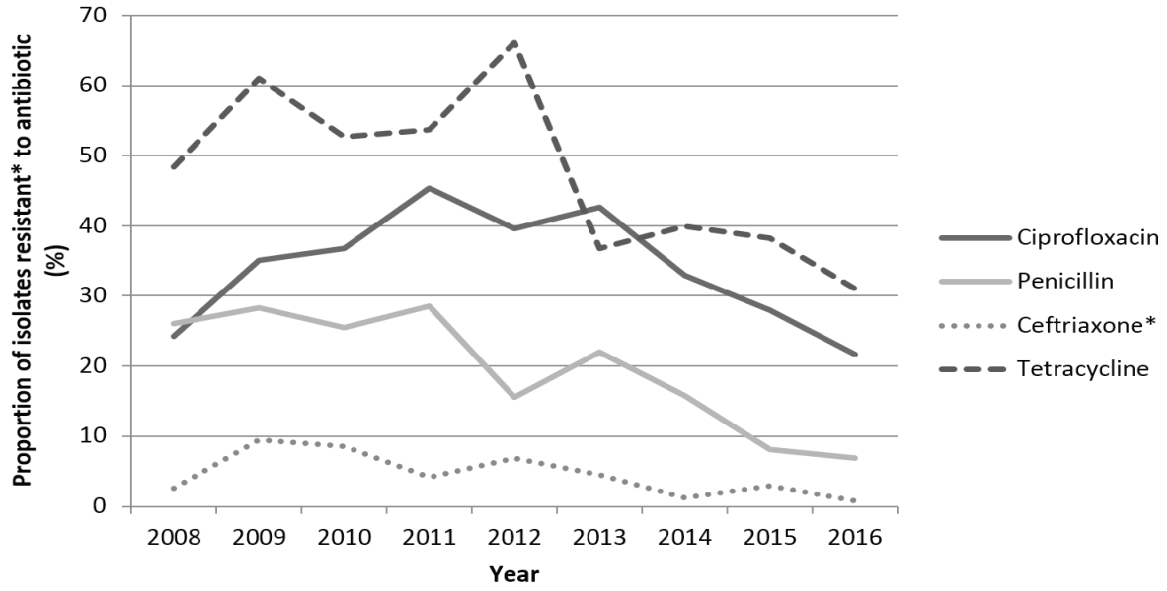


*Figure 37: Trends in antibiotic resistance for Neisseria gonorrhoeae isolates, LabPlus 2008–2016.[1] * For ceftriaxone, decreased susceptibility (MIC ≥0.06 mg/L) is represented.*

4.8.3 Notification, testing, and surveillance

Gonorrhoea has been notifiable in Aotearoa New Zealand since 4 January 2017 and data is collated by ESR. Not all laboratory-confirmed cases appear to be notified.[941] GP and sexual health clinics had the highest number of notifications, while family planning clinics were the lowest.

Testing and diagnosis methods have changed over the years. Since 2008, nucleic acid amplification tests have become the primary method of diagnosing *N. gonorrhoeae* here. Throat swab testing can be less sensitive for culture-based tests, while testing the DNA can be better but can also lead to false positives.[942]

[939] Jennison, A.V., Whiley, D., Lahra, M.M., *et al.* (2019). Genetic relatedness of ceftriaxone-resistant and high-level azithromycin resistant *Neisseria gonorrhoeae* cases, United Kingdom and Australia, February to April 2018. *Eurosurveillance, 24*(8). https://doi.org/10.2807/1560-7917.es.2019.24.8.1900118; Golparian, D., Rose, L., Lynam, A., *et al.* (2018). Multidrug-resistant *Neisseria gonorrhoeae* isolate, belonging to the internationally spreading Japanese FC428 clone, with ceftriaxone resistance and intermediate resistance to azithromycin, Ireland, August 2018. *Eurosurveillance, 23*(47), 1800617. https://doi.org/10.2807/1560-7917.ES.2018.23.47.1800617; Derbie, A., Mekonnen, D., Woldeamanuel, Y., *et al.* (2020). Azithromycin resistant gonococci: A literature review. *Antimicrobial Resistance & Infection Control, 9*(1). https://doi.org/10.1186/s13756-020-00805-7; Yin, Y.-P., Han, Y., Dai, X.-Q., *et al.* (2018). Susceptibility of *Neisseria gonorrhoeae* to azithromycin and ceftriaxone in China: A retrospective study of national surveillance data from 2013 to 2016. *PLOS Medicine, 15*(2), e1002499. https://doi.org/10.1371/journal.pmed.1002499

[940] Lee, R.S., Seemann, T., Heffernan, H., *et al.* (2018). Genomic epidemiology and antimicrobial resistance of *Neisseria gonorrhoeae* in New Zealand. *Journal of Antimicrobial Chemotherapy, 73*(2), 353-364. https://doi.org/10.1093/jac/dkx405"

[941] Institute of Environmental Science and Research Limited (ESR). (2019). *STI epidemiology update*. Retrieved from https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2019/STIsurvupdateDEC2019.pdf?m=1581887236&

[942] Lewis, D.A. (2015). Will targeting oropharyngeal gonorrhoea delay the further emergence of drug-resistant *Neisseria gonorrhoeae* strains? *Sexually Transmitted Infections, 91*(4), 234-237. https://doi.org/10.1136/sextrans-2014-051731; Upton, A., Bromhead, C., &

Gonorrhoea is targeted for enhanced surveillance by ESR, including reporting *N. gonorrhoeae* with decreased susceptibility to ceftriaxone or high-level azithromycin resistance (≥ 16 mg/L). Auckland DHB/sexual health clinics now perform real-time susceptibility testing of *N. gonorrhoeae* isolates so that patients infected with resistant strains can be identified earlier.[943] Currently, surveillance of antibiotic resistance in *N. gonorrhoeae* in Aotearoa New Zealand relies on the availability of culture to undertake AST.

4.8.4 Actions and solutions

AMS interventions are needed: we need to use the remaining effective drugs wisely throughout the healthcare system. We could also address potential sources of unnecessary administration of antimicrobials elsewhere; in sexual health this includes considering encouraging the use of a seven-day doxycycline regimen for chlamydia, as recommended in recent updates to national guidelines, rather than use of single-dose azithromycin.[944] Rationalisation of azithromycin, ceftriaxone, and ciprofloxacin use for other indications should be considered (e.g. use of azithromycin for anti-inflammatory effects in general practice, ceftriaxone for outpatient management of cellulitis, and unrestricted use of ciprofloxacin in the community – see section 5.5.1).

Better surveillance and diagnostics are needed. *N. gonorrhoeae* infections, particularly in the throat, are often asymptomatic and therefore often not detected or treated. These infections tend to be transient. But the throat provides an enabling environment for horizontal transfer of genetic material from *Neisseria* spp., and other bacterial species to *N. gonorrhoeae.*[945] There is a need to think about testing and treating throat infections (and the effectiveness of the treatments for the throat).

The WHO has classified ***N. gonorrhoeae*** as **a high-priority pathogen for the development of new antibiotics** as there are no obvious antimicrobials left to use against gonorrhoea when the current recommended treatments start to fail.

Faster susceptibility testing could potentially enable use of old antibiotics by providing clinicians with insight into which antibiotics are likely to work for a given infection.[946] Some of the antimicrobials (e.g. penicillin, ciprofloxacin) used previously would be effective in some cases, but susceptibility would need to be known before the treatment was administered. It is estimated that rapid susceptibility testing could reduce the number of ceftriaxone courses by more than 66% as most people could be given either penicillin or ciprofloxacin.[947] PCR-based susceptibility tests exist, and their utilisation could support more carefully tailored antibiotic prescribing. In addition, WGS offers a powerful surveillance tool for both genotypic resistance and epidemiological surveillance,[948] but systems would need to be established to enable this in the

Whiley, D.M. (2013). *Neisseria gonorrhoeae* false-positive result obtained from a pharyngeal swab by using the Roche cobas 4800 CT/NG assay in New Zealand in 2012. *Journal of Clinical Microbiology, 51*(5), 1609-1610. https://doi.org/10.1128/JCM.00485-13

[943] McAuliffe, G., Smith, M., Brokenshire, M., *et al.* (2018). Keeping track of antimicrobial resistance for *Neisseria gonorrhoeae* in Auckland, New Zealand: Past, present and future considerations. *The New Zealand Medical Journal, 131*, 71-77.

[944] Ibid.

[945] Lewis, D.A. (2015). Will targeting oropharyngeal gonorrhoea delay the further emergence of drug-resistant *Neisseria gonorrhoeae* strains? *Sexually Transmitted Infections, 91*(4), 234-237. https://doi.org/10.1136/sextrans-2014-051731

[946] O'Neill, J. (2016). *Tackling drug-resistant infections globally: Final report and recommendations*. UK: HM Government and Wellcome Trust. Retrieved from https://amr-review.org/

[947] Ibid.

[948] Lee, R.S., Seemann, T., Heffernan, H., *et al.* (2018). Genomic epidemiology and antimicrobial resistance of *Neisseria gonorrhoeae* in New Zealand. *Journal of Antimicrobial Chemotherapy, 73*(2), 353-364. https://doi.org/10.1093/jac/dkx405"

clinical setting. WGS requires a culture isolate, highlighting the need to continue obtaining culture isolates alongside nucleic acid amplification tests.

Developing new treatments is critical. WHO has classified *N. gonorrhoeae* as a high-priority pathogen for the development of new antibiotics as there are no obvious antimicrobials left to use against gonorrhoea when the current recommended treatments start to fail. A new antibiotic, zoliflodacin, is currently being trialled as a potential treatment for gonorrhoea.[949] In addition to calling for the development of new antibiotics, in November 2021 WHO released a technical document describing its preferred product characteristics for a potential *N. gonnorrhoeae* vaccine, with WHO considering a vaccine to be feasible and important, with need partially justified by increasing prevalence of AMR.[950]

Supporting people to get tested and treated is important. There are opportunities to encourage more STI health-seeking behaviour among New Zealanders to improve the rates of people getting tested and treated, though further studies are needed to understand how to achieve this for different groups.[951] Overseas experience suggests that payment, competitions or vouchers can be a useful tool to modify health behaviour and incentivise STI testing, but it is unknown how this would be received in Aotearoa New Zealand.[952] People need to be encouraged to be tested and not feel judged. Educating healthcare providers about ensuring a compassionate and non-judgemental environment, and recommending routine provision of patient advice about retesting and strategies to promote timely and equitable access to testing could help to address this.[953] To address inequities in access to testing and treatment, out-of-facility approaches to improve STI testing (e.g. mail-out services or street outreach) have been trialled in other countries with positive effects, particularly in populations that are usually underserved. These methods could easily be adopted in New Zealand.

There are opportunities to **encourage more STI health-seeking behaviour in New Zealanders** to improve the rates of people getting tested and treated, though further studies are needed to understand how to achieve this for different groups.

[949] National Institutes of Health. (2021). Zoliflodacin in uncomplicated gonorrhoea. Retrieved 1 October 2021, from https://www.clinicaltrials.gov/ct2/show/NCT03959527
[950] World Health Organization. (2021). *WHO preferred product characteristics for gonococcal vaccines*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.who.int/publications/i/item/9789240039827
[951] Smith, A.J., & Wilby, K.J. (2020). Health services for sexually transmitted infections: Where are we at in New Zealand? A narrative literature review. *Journal of Primary Health Care, 12*(4), 335-344. https://doi.org/https://doi.org/10.1071/HC20039
[952] Ibid.
[953] Ibid.

4.9 Summary and progress

Part four has outlined what is known about the presence of antimicrobial-resistant microbes and genes in Aotearoa New Zealand across humans, animals, plants and the wider environment. It has also discussed the use of antimicrobials across the human health and agricultural sectors, and presence in the environment. This body of evidence leads to three key messages:

- In human health, infections caused by drug-resistant microbes are less common in Aotearoa New Zealand than most other countries. However, we need to act now to prevent an increase in AMR and drug-resistant infections locally and build our resilience.
- Multidrug-resistant microbes from overseas regularly enter Aotearoa New Zealand, and these incursions continue to threaten our health and wellbeing.
- Aotearoa New Zealand is behind other developed countries in taking action to address AMR – we have a national AMR action plan but there has been limited action and the plan itself should be strengthened.

Part four has highlighted that there is ample room for improvement in our national approach to AMR. Below we analyse some recent progress on tackling AMR in Aotearoa New Zealand, before diving into the detail of solutions in part five. This final part outlines approaches, actions and innovations that we can implement or scale up in Aotearoa New Zealand to tackle the twin challenges of infectious disease and AMR.

4.9.1 How we are progressing

In Aotearoa New Zealand, there has been much discussed about AMR over several decades, but only limited and sporadic action.

The *New Zealand AMR Action Plan* has yet to spur action

Both MoH and MPI have convened expert panels on AMR since at least the late 1990s. In 2017, the two ministries published the *New Zealand AMR Action Plan* which included objectives and priorities for the subsequent five years. In a 2019 update, the plan was re-evaluated, and actions prioritised to account for resource limitations.[954] The expert group involved in the plan's initial formation was not consulted on this update. Despite this re-evaluation, there has still been minimal progress on implementation. See the foreword for the OPMCSA's evaluation of progress against the *AMR Action Plan's* objectives and priorities and appendix 7.5 for Aotearoa New Zealand's self-assessments for regular reporting to the Tripartite AMR survey.

Government-led initiatives have lacked staying power

An AMR Governance Group brings together stakeholders from the ministries. This group has been active in recent months, but little accessible information is provided about this group.[955] MoH has convened a Human Antimicrobial Resistance Committee but this stopped being active prior to the COVID-19 pandemic. This was preceded by an Antibiotic Resistance Advisory Group in the early 2000s. We have heard anecdotally that previous members of such committees are frustrated by the lack of support provided, and that significant time invested does not translate into impact.

There are some government workstreams that have made progress, such as HQSC's Atlas of Healthcare Variation and SSI Improvement Programme, and ACC's scoping exercise for developing antimicrobial prescribing guidance. These are discussed in more detail in section 5.5.1. Other

[954] Ministry of Health, & Ministry for Primary Industries. (2019). *New Zealand antimicrobial resistance action plan: Year two and beyond*. Ministry of Health. Wellington, NZ.
[955] Ministry of Health. (n.d., 23 September 2019). New Zealand Antimicrobial Resistance Action Plan Governance Group. Retrieved 29 October, 2021, from https://www.health.govt.nz/our-work/diseases-and-conditions/antimicrobial-resistance/new-zealand-antimicrobial-resistance-action-plan/new-zealand-antimicrobial-resistance-action-plan-governance-group

projects are ongoing including an internal stocktake of AMR action in MoH and a project on CPEs in the MoH public health team.

There have been various communications campaigns over the years aimed at reducing unnecessary prescribing. These have included the 'Kick the Bug: Wise use of antibiotics' campaign from 2007 and the 'Choosing Wisely' campaign initiated in 2016. There is no current communications campaign focused on antimicrobial prescribing aimed at the public or healthcare workforce.

There has been more action in the animal health sector than in human health

Compared with human health, there has been more action in the animal health space from the New Zealand Veterinary Association (NZVA), MPI, and industry (see scorecard accompanying the foreword and appendix 7.5). The NZVA published a statement in 2015 outlining its commitment to phase out blanket prophylactic use of antibiotics, and this has been supported by communications campaigns to encourage AMS.[956] MPI has been progressing a reassessment of antibiotics and has undertaken sampling in the poultry and pork industries.

[956] New Zealand Veterinary Association. (n.d.). Antimicrobial resistance (AMR). Retrieved October 29, 2021, from https://www.nzva.org.nz/resource/general/amr/

5 Part five: Prevention and solutions

Figure 38: Some of the first COVID-19 vaccine doses to arrive in Aotearoa New Zealand in February 2021. Image credit: Damian Christie/Ministry of Health.

5.1 Overview

While the preceding parts of this report have focused on the challenges posed by infectious disease and AMR globally and in Aotearoa New Zealand, this section of the report explores a range of solutions. Examples of good practice at home and abroad are included to highlight initiatives we could draw on or expand to secure better health for all New Zealanders.

This section is structured around four overarching themes: prevention, detection, treatment, and people and capability. In the prevention section, we focus on IPC interventions and vaccines, both measures that can prevent or curb the spread of infections. We are conscious that tackling the wider social determinants of health such as poverty and housing quality is key to addressing infectious disease and AMR in Aotearoa New Zealand and supporting greater equity in health outcomes, as described in section 3.4.2. While largely beyond the scope of this project, we endorse efforts taken to tackle these problems.

Change for the better is dependent on good information about the problem.

The detection section covers surveillance and reporting of data on drug-resistant microorganisms, infectious diseases, and outbreaks. Change for the better is dependent on good information about the problem. Data needs to be in a standardised, accessible format so we can make cross-sector connections and extract insights across human, animal, plant, and environmental health. We also discuss how technologies such as genomics and rapid diagnostics can support detection and surveillance.

The treatments section focuses on AMS as an essential approach to conserve the effectiveness of existing antimicrobials, so they are available for future generations. We discuss the need to elevate and expand AMS, supported by national antimicrobial prescribing guidance and useful data collection that is leveraged to drive change. This section also outlines the opportunities and challenges of antimicrobial development, as well as alternative approaches to treatment that are being explored.

We need evidence-based communication and behavioural science to help us enhance health literacy.

The final section is about people. We need to use evidence-based approaches to communication and education to help us enhance health literacy across the public and professionals in relevant sectors.

5.2 Key messages

- Our approach to tackling infectious diseases and AMR must be carried out within a cross-sector, unified framework that recognises the interdependence of human, animal, plant, and environmental health. Kotahitanga must be at the heart of our efforts to tackle AMR and infectious disease.

- Aotearoa New Zealand needs to elevate and expand IPC with national leadership and governance. Increased connectivity between human, animal, plant, and environmental health would enable transfer and application of lessons learned into new contexts.

- We can do more to increase uptake of vaccines in both the human and animal health sectors. In addition, development of new vaccines has scope to further contribute to disease prevention and reduce the need for antimicrobial use. Aotearoa New Zealand has a role to play in this effort.

- Detection of infectious diseases and drug-resistant pathogens can be supported by greater utilisation of existing tools, sharing of data and samples, and the use of rapid diagnostics and genomics. Detection alone is not enough – data needs to be relevant, accessible and usable. We would benefit from integrated, real-time surveillance of drug-resistant organisms, genes, and infectious diseases in centralised, accessible platforms, across human, animal, plant, and environmental health.

- Aotearoa New Zealand is lagging when it comes to AMS. We need national leadership and governance structures, coupled with targets for reducing inappropriate antimicrobial use. To achieve this, we need to gather data on the quantity of antimicrobials used and the quality of that use, and target interventions accordingly.

- We need an honest appraisal of the infectious disease, AMS, and IPC workforces across the country. This includes considering overall numbers, distribution of staff, workforce diversity, and training and education. A strong and well-resourced workforce is required to combat infectious disease and AMR.

- In addition to working to prevent and reduce the spread of disease and preserve the effectiveness of existing antimicrobials, new antimicrobials and other innovative treatment and management approaches are needed. Research, investment, and horizon scanning is key.

- Enhancing health literacy and building trust can empower all New Zealanders to play a role in combatting infectious disease and AMR.

5.3 Prevention is better than a cure

Preventing infections before they occur and stopping spread in its tracks are the best ways to tackle both infectious diseases and AMR. This section focuses on IPC and vaccination as key disease control and prevention measures. We also note that tackling wider determinants of health – such as poverty, crowding and damp/mouldy housing – would help to prevent infection, but in-depth discussion of solutions in these areas is beyond the scope of this report.

5.3.1 Infection prevention and control

IPC refers to measures taken to reduce the occurrence and spread of infections, encompassing interventions like hand hygiene, cleaning, equipment decontamination, the use of PPE, and managing the built environment.[957] IPC primarily focuses on measures taken in human health facilities but can be applied in settings like schools, prisons, beauty parlours, and households. The exact IPC measures employed depend on the infectious disease in question (including its mode of transmission) and the context (including the setting and people involved). For example, given the extra risks posed by drug-resistant microbes, stepped up IPC measures may be implemented in situations where resistant pathogens are known to be present.[958] In addition, special precautions may be taken when working with highly infectious pathogens (e.g. SARS-CoV-2), or with people at higher risk of infection or adverse outcomes (e.g. immunocompromised patients).

As well as reducing illness and suffering, preventing infections can save money. For example, seven separate studies looking at the economics of preventing drug-resistant HAIs found that evidence-based IPC practices invariably paid off.[959]

Improving IPC measures in Aotearoa New Zealand was among the actions recommended in the *2017 New Zealand AMR Action Plan*. Objective three of the plan called for evidence-based IPC strategies and vaccination programmes across all sectors and settings,[960] but little action has been taken.

… seven separate studies looking at the economics of preventing drug-resistant healthcare-associated infections found that **evidence-based IPC practices invariably paid off.**

IPC in human health

This section focuses on IPC measures in healthcare settings. Within hospitals, there are five core areas under the IPC umbrella:

- **The built environment** and healthcare design – i.e. how everything is set up. This includes things like ventilation, taps that don't splash water (which can spread microbes), thoughtful placement of hand hygiene stations, and rooms or wards that can be isolated.
- **Environmental management** – including day-to-day cleaning, waste management, and laundry.

[957] Health Quality & Safety Commission. (n.d., 17 May 2021). About us. Retrieved 15 November, 2021, from https://www.hqsc.govt.nz/our-programmes/infection-prevention-and-control/about-us/; World Health Organization. (n.d.). About us. Retrieved 15 November, 2021, from https://www.who.int/teams/integrated-health-services/infection-prevention-control/about

[958] Tomczyk, S., Zanichelli, V., Grayson, M.L., *et al.* (2019). Control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* in healthcare facilities: A systematic review and reanalysis of quasi-experimental studies. *Clinical Infectious Diseases, 68*(5), 873-884. https://doi.org/10.1093/cid/ciy752

[959] Tchouaket Nguemeleu, E., Beogo, I., Sia, D., *et al.* (2020). Economic analysis of healthcare-associated infection prevention and control interventions in medical and surgical units: Systematic review using a discounting approach. *Journal of Hospital Infection, 106*(1), 134-154. https://doi.org/10.1016/j.jhin.2020.07.004

[960] Ministry of Health and Ministry for Primary Industries. (2017). *New Zealand Antimicrobial Resistance Action Plan*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/publication/new-zealand-antimicrobial-resistance-action-plan

- **Reprocessing of medical devices** – i.e. cleaning, disinfection, and sterilisation of items such as hoists, toilet chairs, endoscopes, and surgical instruments.
- **Surveillance** – including triage, alerts about antimicrobial-resistant organisms and real-time results from microbiology labs.
- **Education** – including for all healthcare workers and support staff such as cleaners, delivered through formal education (including in undergraduate and postgraduate courses) and ongoing on-the-job training and education.

It should be noted that IPC in healthcare settings isn't just about protecting patients and the public from infection – it is also about protecting the healthcare workers who expose themselves to risks while working to protect others.

A strong, educated, diverse IPC workforce is key

While there are no current surveys describing our IPC workforce, available evidence suggests it is likely underpowered relative to international guidelines.[961] In addition, IPC expertise lies mostly with nurses. A 2014 Australasian survey of healthcare professionals working in IPC found that 93% of respondents were nurses[962] and a recent survey in Aotearoa New Zealand also supports the finding that IPC FTE is largely nurse-led.[963] Further, this workforce is ageing, raising workforce sustainability concerns.[964] Elevating IPC and making it a multidisciplinary responsibility that is part of organisational culture may help to achieve IPC objectives.[965] In addition, capacity building and education in the IPC workforce is important for improving IPC practices, with healthcare workers who have an IPC qualification likely to undertake research more frequently, contributing to IPC evaluation and improvement.[966]

Elevating IPC and making it a multidisciplinary responsibility that is part of organisational culture may help to achieve IPC objectives.

[961] Roberts, S. (2013). The provision of infection prevention and control services in the public health sector in New Zealand. *Healthcare Infection, 18*(3), 91-93. https://doi.org/10.1071/HI13017; van den Broek, P.J., Kluytmans, J.A.J.W., Ummels, L.C*., et al.* (2007). How many infection control staff do we need in hospitals? *Journal of Hospital Infection, 65*(2), 108-111. https://doi.org/10.1016/j.jhin.2006.10.003; World Health Organization. (2019). *Minimum requirements for infection prevention and control programmes*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.who.int/publications/i/item/9789241516945

[962] Hall, L., Halton, K., Macbeth, D*., et al.* (2015). Roles, responsibilities and scope of practice: Describing the 'state of play' for infection control professionals in Australia and New Zealand. *Healthcare Infection, 20*(1), 29-35. https://doi.org/10.1071/HI14037

[963] Health Quality & Safety Commission. (2020). *Learning from COVID-19: Summary of feedback from the hospital and aged residential care (ARC) surveys during the COVID-19 response to identify gaps and opportunities for improvement* Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/PR/Summary_of_feedback_from_COVID_surveys_FINAL.pdf

[964] Hall, L., Halton, K., Macbeth, D*., et al.* (2015). Roles, responsibilities and scope of practice: Describing the 'state of play' for infection control professionals in Australia and New Zealand. *Healthcare Infection, 20*(1), 29-35. https://doi.org/10.1071/HI14037

[965] Resar, R., Griffin, F.A., Haraden, C*., et al.* (2012). *Using care bundles to improve health care quality*. Cambridge, MA: Institute for Healthcare Improvement. Retrieved from http://www.ihi.org/resources/Pages/IHIWhitePapers/UsingCareBundles.aspx; Stodart, J. (2017). *Infection prevention and control clinical governance in New Zealand District Health Boards.* (Master of Public Health), University of Otago, Dunedin, NZ. Retrieved from https://www.nzno.org.nz/Portals/0/Files/Documents/Services/Library/2017-08%20STODART_Jo%20-%20Infection%20Prevention%20and%20Control%20Clinical%20Governance%20in%20NZ%20DHBs.pdf

[966] Hall, L., Halton, K., Macbeth, D*., et al.* (2015). Roles, responsibilities and scope of practice: Describing the 'state of play' for infection control professionals in Australia and New Zealand. *Healthcare Infection, 20*(1), 29-35. https://doi.org/10.1071/HI14037

Beyond the IPC specialist workforce, there is scope to elevate education and training in IPC for health professionals and other workers in the health system across the sector. Even training in IPC fundamentals like the use of PPE could be enhanced. A 2020 Australasian survey found that, while most healthcare worker orientation programmes in Australia and Aotearoa New Zealand covered PPE use, less than half of respondents received annual training updates and one-third didn't receive any hands-on training.[967] In a hospital survey conducted by the HQSC, more than 75% of respondents felt there was a resource gap in information about PPE use during early planning for COVID-19.[968]

A 2020 Australasian survey found that, while most healthcare worker orientation programmes in Australia and Aotearoa New Zealand covered PPE use, less than half of respondents received annual training updates and **one-third didn't receive any hands-on training**.

When hospitals get busy, aspects of IPC can suffer. COVID-19-related hospital pressure saw reduced focus on non-COVID-19 IPC in a New Jersey, US, hospital, leading to increased incidence of drug-resistant HAIs. Workforce strain and PPE rationing both played a role, highlighting the importance of staffing IPC appropriately and making sure the workforce has the resources it needs, including during times of increased pressure and global supply chain stresses.[969]

IPC in Aotearoa New Zealand needs to be elevated, expanded, and prioritised

The majority of IPC work in Aotearoa New Zealand occurs in healthcare facilities, with IPC requirements under the Health and Disability Services Standard (updated in 2021)[970] only compulsorily applying to services listed under the Health and Disability Services (Safety) Act 2001 (which also includes ARC settings).[971] This leaves out places like schools, beauty and tattoo parlours, prisons, and sheltered living, all of which could benefit from evidence-based IPC practices.[972] With COVID-19 leading to the introduction of IPC guidelines and rules for workplaces, schools, and other venues, the importance of IPC beyond the health sector has become clear. Making IPC expertise accessible across this range of settings is an important area for development.

[967] Barratt, R., Shaban, R.Z., & Gilbert, G.L. (2020). Characteristics of personal protective equipment training programs in Australia and New Zealand hospitals: A survey. *Infection, Disease & Health, 25*(4), 253-261. https://doi.org/https://doi.org/10.1016/j.idh.2020.05.005
[968] Health Quality & Safety Commission. (2020). *Learning from COVID-19: Summary of feedback from the hospital and aged residential care (ARC) surveys during the COVID-19 response to identify gaps and opportunities for improvement* Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/PR/Summary_of_feedback_from_COVID_surveys_FINAL.pdf
[969] Perez, S., Innes, G.K., Walters, M.S.*, et al.* (2020). Increase in hospital-acquired carbapenem-resistant *Acinetobacter baumannii* infection and colonization in an acute care hospital during a surge in COVID-19 admissions - New Jersey, February-July 2020. *Morbidity and Mortality Weekly Report, 69*(48), 1827-1831. https://doi.org/10.15585/mmwr.mm6948e1
[970] Standards New Zealand. (2021). NZS 8134:2021: Ngā paerewa Health and disability services standard. Retrieved from https://www.standards.govt.nz/shop/nzs-81342021/
[971] New Zealand Government. (2020). *Health and Disability Services (Safety) Act 2001*. Retrieved from https://www.legislation.govt.nz/act/public/2001/0093/latest/DLM119975.html
[972] Boyack, N. (2019). Calls for safety regulations governing tattooists, body piercing outfits and nail bars. *Stuff*. Retrieved from https://www.stuff.co.nz/national/health/111093069/calls-for-safety-regulations-governing-tattooists-body-piercing-outfits-and-nail-bars

The HQSC, a Crown entity established in 2010, plays a central role in IPC in healthcare facilities.[973] Its IPC work is evidence-based, guided by the cross-sector Strategic IPC Advisory Group (SIPCAG).[974] HQSC produces guidelines, manuals, and promotional materials on IPC, as well as working to reduce rates of SSIs and bloodstream infections caused by IV lines.

With the advent of COVID-19, the MoH established a national expert body designed to advise on IPC in the context of COVID-19, the National IPC Expert Group (NIPCEG). NIPCEG's mandate has since been expanded to set a national IPC strategy, beyond COVID-19.[975] This will help ensure expert advice is embedded in our approach to IPC and much needed national guidelines are available.[976]

There is further scope to elevate and prioritise the importance of IPC by embedding it in the new nationwide and regional structures with the health reforms.

In 2012, MoH convened the Healthcare Associated Infections Governance Group (HAIGG). The group's objective was:

> "…to provide national leadership and set direction for the Ministry of Health on the clinical, scientific, and strategic aspects of surveillance, infection prevention and control, antimicrobial resistance, and new and emerging threats to the health of New Zealanders, with the aim of reducing harm and cost to society from infections associated with healthcare exposure."[977]

The HAIGG was required to meet quarterly and minutes are available online up to 2016.[978] Useful online resources are available (see p. 230).

There is further scope to elevate and prioritise the importance of IPC by embedding it in the new nationwide and regional structures with the health reforms. In an offshore example, all registered National Health Service (NHS) care providers in England are required to have a Director of IPC with authority and responsibility for implementation strategies to prevent avoidable HAIs.[979] This approach, which works to embed expertise and responsibility for IPC throughout the health system, could be explored in the Aotearoa New Zealand context.

IPC saves lives and money in Aotearoa New Zealand

To test the effectiveness of IPC interventions in healthcare facilities, Aotearoa New Zealand needs to build up an understanding of how, why, and where HAIs are occurring. We currently don't have a

[973] Health Quality & Safety Commission. (n.d., 17 May 2021). About us. Retrieved 15 November, 2021, from https://www.hqsc.govt.nz/our-programmes/infection-prevention-and-control/about-us/
[974] Health Quality & Safety Commission. (2021, 18 August). Infection prevention and control leadership. Retrieved 15 November, 2021, from https://www.hqsc.govt.nz/our-programmes/infection-prevention-and-control/infection-prevention-and-control-leadership/
[975] Health Quality & Safety Commission. (2020). Minutes of the 28th meeting of the Strategic Infection Prevention and Control Advisory Group. Wellington, NZ: Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/Surgical-Site-Infection-Surveillance/SIPCAG-minutes-29-Sept-20.pdf
[976] Health Quality & Safety Commission. (2020). *Learning from COVID-19: Summary of feedback from the hospital and aged residential care (ARC) surveys during the COVID-19 response to identify gaps and opportunities for improvement* Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/PR/Summary_of_feedback_from_COVID_surveys_FINAL.pdf
[977] Ministry of Health. (2016, 15 March). Terms of reference for the Healthcare Associated Infections Governance Group. Retrieved 7 October, 2021, from https://www.health.govt.nz/about-ministry/leadership-ministry/expert-groups/healthcare-associated-infections-governance-group/terms-reference-healthcare-associated-infections-governance-group
[978] Ministry of Health. (2016, 10 August). Meeting minutes for the Healthcare Associated Infections Governance Group. Retrieved 10 October, 2021, from https://www.health.govt.nz/about-ministry/leadership-ministry/expert-groups/healthcare-associated-infections-governance-group/meeting-minutes-healthcare-associated-infections-governance-group
[979] National Health Service. (2015). *Director of Infection Prevention and Control role profile* Retrieved from https://www.nlg.nhs.uk/content/uploads/2015/05/NLG15276-The-Role-of-Director-of-Infection-Prevent-and-Control-DIPC.pdf

clear picture of the overall prevalence and burden of HAIs. Until recently, Aotearoa New Zealand had not conducted a survey to gather this data, instead looking only at a select few categories of HAIs and SSIs. This failure to conduct systematic HAI surveys makes Aotearoa New Zealand anomalous among countries with complex healthcare systems. For example, the EU has been conducting surveillance and reporting since 2010.[980] Australia, also a laggard, has just completed its first HAI point prevalence survey in 34 years.[981] To fill our domestic data gap, HQSC has recently completed the first ever national HAI point prevalence survey across all DHBs and is currently analysing the data gathered. HQSC intends to use that data to inform its future work plan.[982] If this survey becomes routine, we will be better placed to evaluate the effectiveness of IPC practices and target areas for interventions.

… failure to conduct systematic HAI surveys makes Aotearoa New Zealand anomalous among countries with complex healthcare systems.

Data limitations aside, HQSC has previously appraised its major IPC programmes on hand hygiene, bloodstream infections caused by IV lines, and SSIs. Through these programme reviews, it is clear that central leadership, resourcing, and commitment to evidence-based IPC in Aotearoa New Zealand can improve patient outcomes and save money.

- **Hand hygiene**: HQSC has made a concerted effort to lift compliance with international best practice for hand hygiene across DHBs. Compliance increased from 62% in 2012 to 85% in 2019. A 2014 review found that the programme, which at the time cost around NZ$3 million per year, generated upwards of NZ$13 million in annual savings. Factors that have been key to this success include a strong evidence base, drawing on Australian expertise and experience, standardised auditing and reporting, an effective communication strategy, introduction of accountability measures, and workforce capability building.[983]
- **CLAB campaign**: Central line catheters are used to deliver treatments into a patient's bloodstream and monitor their health. However, these catheters create a potential point of entry for pathogens, which can lead to central line-associated bacteraemia (CLAB), a type of bloodstream infection with a 10-50% mortality rate. A campaign from October 2011 to March 2013 reduced CLAB rates to less than one infection for every 1,000 line days by implementing a series of evidence-based IPC interventions across all DHBs. While the baseline had to be estimated due to lack of CLAB surveillance prior to the campaign, CLAB incidence in ICUs across the country was cut to one-tenth of its previous level, reducing patient harm and saving about NZ$1.8 million. The programme's success was supported by nationwide collaboration, the use of international evidence modified for the local context, a good communication plan, and national and regional training sessions.[984]

[980] European Centre for Disease Prevention and Control. (2012). Point prevalence survey database (HAI-Net). Retrieved from https://www.ecdc.europa.eu/en/healthcare-associated-infections-acute-care-hospitals/surveillance-disease-data/database
[981] Russo, P.L., Stewardson, A.J., Cheng, A.C., *et al.* (2019). The prevalence of healthcare associated infections among adult inpatients at nineteen large Australian acute-care public hospitals: A point prevalence survey. *Antimicrobial Resistance & Infection Control, 8*(1), 114. https://doi.org/10.1186/s13756-019-0570-y
[982] Roberts, S., Morris, A., & Grae, N. (2021). *Establishing the prevalence of health associated infections in New Zealand hospitals (HAINZ): National point prevalence survey methodology*. Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/PR/PPS_METHODOLOGY_V2.0.pdf
[983] Freeman, J.T., Dawson, L., Jowitt, D.M., *et al.* (2016). The impact of the Hand Hygiene New Zealand programme on hand hygiene practices in New Zealand's public hospitals. *New Zealand Medical Journal, 129*(1443), 67-76. ; Roberts, S.A., & Grae, N. (2019). *New Zealand hand hygiene programme: Requirements to sustain improvement in a changing environment*. Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/Hand-Hygiene/PR/Hand-hygiene-poster-Oct-2019-PRINT.pdf
[984] Gray, J., Proudfoot, S., Power, M., *et al.* (2015). Target CLAB Zero: A national improvement collaborative to reduce central line-associated bacteraemia in New Zealand intensive care units. *New Zealand Medical Journal, 128*(1421), 13-21. ; Proudfoot, S., Aimer, M., &

- **SSI reduction**: HQSC ran a programme to reduce SSIs associated with orthopaedic and cardiac surgeries from 2012 to 2017. IPC interventions were introduced across DHBs, with around 95% compliance by 2017. Orthopaedic SSIs reduced from 1.18 per 100 procedures in the first half of the programme to 0.93 in the second half. As well as improving patient wellbeing, the orthopaedic arm of the programme delivered up to a three-fold return on investment. A lack of baseline data meant the success of the cardiac arm of the programme couldn't be evaluated.[985]

Achieving success with IPC requires collecting and using good evidence

Many IPC interventions have a long history. For example:

- The face masks that have become so familiar during the COVID-19 pandemic are not markedly different from those used in the 1910-1911 Manchurian plague.[986]
- The utility of hand hygiene in healthcare settings was clearly demonstrated in the mid-1800s when Ignaz Semmelweis observed that maternal mortality rates were heightened when medical staff didn't disinfect their hands between autopsies and births.[987]
- Tikanga Māori places emphasis on safe food handling practices, such as not sitting on surfaces or tables used for food preparation or eating, keeping food prep separate from other areas (especially toilet facilities), and controlling human contamination and waste in food collection areas.[988]
- In 1859, Florence Nightingale wrote about the benefits of ventilation in hospitals.[989] Her advocacy for high ceilings, adequate natural light, and sufficient ventilation remains relevant in hospital ward design today.[990]
- Quarantine has been used since at least the 14th century as a way to keep potentially infectious people away from those they might infect.[991]

As well as having a long history, many IPC measures also have strong evidence bases. For example, since Semmelweis' observations in the mid-1800s, the evidence for hand hygiene has ballooned – WHO's evidence synthesis on the topic spans 270 pages.[992] Similarly, over 150 years on from Nightingale's advocacy, the evidence for ventilation has grown,[993] including in the context of COVID-

Sturland, S. (2013). *Target CLAB Zero: National collaborative to prevent central line associated bacteraemia – Final report*. Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/Catheter-Related-Bloodstream-Infections/CLAB-final-report-June-2013.pdf

[985] Artus, J., Blick, G., & Ryan, M. (2018). *Evaluation of the surgical site infection improvement programme: Final (summative) report*. Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/Surgical-Site-Infection-Surveillance/SSIIP-evaluation-report-27Aug2018-FINAL.pdf

[986] Lynteris, C. (2018). Plague masks: The visual emergence of anti-epidemic personal protection equipment. *Medical Anthropology, 37*(6), 442-457. https://doi.org/10.1080/01459740.2017.1423072

[987] World Health Organization, & World Alliance for Patient Safety. (2009). *WHO guidelines on hand hygiene in health care*. Geneva, Switzerland: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/44102/9789241597906_eng.pdf

[988] Wilson, M. (1998). *Traditional Māori food preparation*. Wellington, NZ: Ministry of Health. Retrieved from https://www.moh.govt.nz/notebook/nbbooks.nsf/0/84BCB0807976AFF5CC256BF2007160E7/$file/traditional-maori-food-preparation.pdf; bpac nz. (2008). Tikanga relating to food. *Best Practice Journal, 15*, 46-47.

[989] Nightingale, F. (1859). *Notes on nursing: What it is and what it is not*. London, UK: Harrison.

[990] Burridge, H.C., Bhagat, R.K., Stettler, M.E.J., *et al.* (2021). The ventilation of buildings and other mitigating measures for COVID-19: A focus on wintertime. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences, 477*(2247), 20200855. https://doi.org/10.1098/rspa.2020.0855

[991] Tognotti, E. (2013). Lessons from the history of quarantine, from plague to influenza A. *Emerging Infectious Diseases, 19*(2), 254. https://doi.org/10.3201/eid1902.120312

[992] World Health Organization, & World Alliance for Patient Safety. (2009). *WHO guidelines on hand hygiene in health care*. Geneva, Switzerland: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/44102/9789241597906_eng.pdf

[993] Atkinson, J., Chartier, Y., Otaiza, F., *et al.* (2009). *Natural ventilation for infection control in health-care settings*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.who.int/water_sanitation_health/publications/natural_ventilation.pdf

19.[994] In Aotearoa New Zealand, NIWA has recently leveraged its existing air quality research to advise on classroom ventilation to reduce COVID-19 infection risk.[995]

In addition, more recent IPC practices are underpinned by strong evidence. For example, a 2012 paper published by the Institute for Healthcare Improvement demonstrated that rolling out bundles of targeted IPC interventions can vastly reduce HAIs and improve ICU outcomes.[996] The bundle approach (i.e. groups of specific IPC interventions) is utilised in healthcare facilities around the world, including in Aotearoa New Zealand.

Useful resources for IPC

1. National surgical site infection improvement programme dashboards -
   - **Orthopaedic** - https://public.tableau.com/app/profile/hqi2803/viz/SSIorthopaedicdashboardpublic/SSIIPorthopaedicsurgery?publish=yes
   - **Cardiac** - https://public.tableau.com/app/profile/hqi2803/viz/SSIcardiacdashboardpublic/SSIIPcardiacsurgery?publish=yes
2. National hand hygiene reports - https://www.hqsc.govt.nz/our-work/infection-prevention-and-control/our-programmes/hand-hygiene/compliance-reports-and-qsms/
3. Atlas for healthcare variation antimicrobial use atlases - https://www.hqsc.govt.nz/our-data/atlas-of-healthcare-variation/infection-and-antibiotic-use-following-major-surgery/
4. Point prevalence survey report - https://www.hqsc.govt.nz/our-work/infection-prevention-and-control/our-programmes/point-prevalence-survey/

It can take time and hard work to establish evidence on which to base IPC interventions. This was clearly seen with the changing public health recommendations on mask use at the start of the COVID-19 pandemic, with a research paper commissioned by WHO half a year into the pandemic eventually bringing clarity to the matter by concluding that "face mask use could result in a large reduction in risk of infection".[997] Evidence demonstrating the utility of masks against COVID-19 has since grown.[998]

Sometimes research reveals that IPC measures that seem intuitive don't have the intended effect, highlighting the importance of continually appraising interventions. For example, Public Health

[994] Burridge, H.C., Bhagat, R.K., Stettler, M.E.J., *et al.* (2021). The ventilation of buildings and other mitigating measures for COVID-19: A focus on wintertime. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences, 477*(2247), 20200855. https://doi.org/10.1098/rspa.2020.0855

[995] NIWA. (2021, 21 October). *Opening windows and doors "one of the best ways" to remove Covid-19 from classroom air* [Press release]. Retrieved from https://niwa.co.nz/news/opening-classroom-windows-and-doors-one-of-the-best-ways-to-remove-covid-19-from-air

[996] Resar, R., Griffin, F.A., Haraden, C., *et al.* (2012). *Using care bundles to improve health care quality*. Cambridge, MA: Institute for Healthcare Improvement. Retrieved from http://www.ihi.org/resources/Pages/IHIWhitePapers/UsingCareBundles.aspx

[997] Chu, D.K., Akl, E.A., Duda, S., *et al.* (2020). Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: A systematic review and meta-analysis. *The Lancet, 395*(10242), 1973-1987. https://doi.org/10.1016/S0140-6736(20)31142-9

[998] Howard, J., Huang, A., Li, Z., *et al.* (2021). An evidence review of face masks against COVID-19. *Proceedings of the National Academy of Sciences, 118*(4), e2014564118. https://doi.org/10.1073/pnas.2014564118

England recommended the use of long-sleeved gowns for healthcare workers in high-risk COVID-19 areas, but a hospital-led study found that the sleeves stopped healthcare workers from washing their hands properly, having an overall negative impact on IPC.[999] And in an ongoing debate,[1000] researchers are trying to work out the conditions under which plastic barriers reduce COVID-19 spread. In some settings, they appear to do more harm than good by obstructing airflow.[1001]

IPC interventions only work if they are implemented and products are used by staff. A range of factors can support compliance with IPC practices, including involvement and feedback from frontline healthcare workers in IPC decision making. Ensuring that practitioners understand why measures are used by making sure they are underpinned by clear evidence is helpful. Central leadership, clear communication, ongoing evaluation and adaptation, accountability measures, capability building, and resourcing are also key.[1002]

COVID-19 has shown that the public may be more willing to adopt IPC measures than previously thought. A *COVID-19 lessons learned* report published by the UK House of Commons in September 2021 found that one of the UK's biggest mistakes at the start of the pandemic was assuming that the public wouldn't accept lockdowns or contact tracing to prevent virus spread.[1003] Two years into the pandemic, it is clear the assumption was unfounded. COVID-19 represents an opportunity to explore how to encourage the population to adopt IPC measures across other areas of human health, including AMR and infectious disease prevention and management more broadly.[1004]

COVID-19 represents an opportunity to explore how to encourage the population to adopt IPC measures across other areas of human health, including AMR and infectious disease prevention and management more broadly.

[999] Meda, M., Gentry, V., Reidy, P.*, et al.* (2020). Unintended consequences of long-sleeved gowns in a critical care setting during the COVID-19 pandemic. *Journal of Hospital Infection, 106*(3), 605-609. https://doi.org/10.1016/j.jhin.2020.07.036
[1000] Parker-Pope, T. (2021, 19 August). Those anti-Covid plastic barriers probably don't help and may make things worse, *The New York Times*. Retrieved from https://www.nytimes.com/2021/08/19/well/live/coronavirus-restaurants-classrooms-salons.html
[1001] Burridge, H.C., Bhagat, R.K., Stettler, M.E.J.*, et al.* (2021). The ventilation of buildings and other mitigating measures for COVID-19: A focus on wintertime. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences, 477*(2247), 20200855. https://doi.org/10.1098/rspa.2020.0855; Lessler, J., Grabowski, M.K., Grantz Kyra, H.*, et al.* (2021). Household COVID-19 risk and in-person schooling. *Science, 372*(6546), 1092-1097. https://doi.org/10.1126/science.abh2939
[1002] Artus, J., Blick, G., & Ryan, M. (2018). *Evaluation of the surgical site infection improvement programme: Final (summative) report*. Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/Surgical-Site-Infection-Surveillance/SSIIP-evaluation-report-27Aug2018-FINAL.pdf; Freeman, J.T., Dawson, L., Jowitt, D.M.*, et al.* (2016). The impact of the Hand Hygiene New Zealand programme on hand hygiene practices in New Zealand's public hospitals. *New Zealand Medical Journal, 129*(1443), 67-76. ; Gray, J., Proudfoot, S., Power, M.*, et al.* (2015). Target CLAB Zero: A national improvement collaborative to reduce central line-associated bacteraemia in New Zealand intensive care units. *New Zealand Medical Journal, 128*(1421), 13-21. ; Proudfoot, S., Aimer, M., & Sturland, S. (2013). *Target CLAB Zero: National collaborative to prevent central line associated bacteraemia – Final report*. Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/assets/Infection-Prevention/Catheter-Related-Bloodstream-Infections/CLAB-final-report-June-2013.pdf; Resar, R., Griffin, F.A., Haraden, C.*, et al.* (2012). *Using care bundles to improve health care quality*. Cambridge, MA: Institute for Healthcare Improvement. Retrieved from http://www.ihi.org/resources/Pages/IHIWhitePapers/UsingCareBundles.aspx
[1003] Health and Social Care Committee, & Science and Technology Committee. (2021). *Coronavirus: Lessons learned to date*. London, UK: House of Commons. Retrieved from https://committees.parliament.uk/publications/7496/documents/78687/default/
[1004] Shaw, J.A., Sethi, N., & Cassel, C.K. (2020). Social license for the use of big data in the COVID-19 era. *npj Digital Medicine, 3*(1), 128. https://doi.org/10.1038/s41746-020-00342-y

Technology can enhance IPC

While many IPC practices involve simple, long-established interventions like handwashing and face masks, IPC can be supported by innovation. For example, while ideally buildings would be designed with ventilation and airflow principles in mind, for those buildings that don't support these aspects of IPC, technological interventions could be implemented to reduce the odds of infection with airborne pathogens in high-risk environments like hospitals and aged care settings. Two examples of remedial solutions include UV-C lamps and high efficiency particulate air (HEPA) filters.[1005]

- **UV-C lamps** emit UV-C light into the upper, unoccupied zone of a room where the light rapidly kills airborne microbes. Under experimental test conditions, SARS-CoV-2 has been demonstrated to be highly susceptible to inactivation by UV-C light.[1006] UV-C lamps are also being investigated for inactivation of other microbes, including *E. coli*, while far-UV-C radiation may be able to inactivate microbes without causing harm to exposed skin.[1007]
- **HEPA filters**, capable of removing particles smaller than 0.01 micrometres from the air,[1008] are also effective against SARS-CoV-2, although their effectiveness depends on their placement and the size of the room, among other factors.[1009]

However, chemical and physical interventions such as disinfectants and UV radiation can also select microorganisms that develop higher levels of tolerance to antibiotics. For example, *E. coli* with a gene that confers resistance to the antibiotic bleomycin is also more resistant to UV.[1010]

Antimicrobial surface and device coatings can complement traditional IPC strategies.[1011] These coatings can be found on surfaces in food preparation, construction and healthcare, that people may touch and contaminate. Antimicrobial coatings can also be found on surgical or implantable devices like catheters. Active ingredients of these coatings include copper, silver particles, titanium dioxide, quaternary ammonium compounds, and triclosan.[1012] However, the relative effectiveness of these approaches is debated, [1013] and while laboratory studies show promising results, these results are not routinely replicated in real life situations.[1014]

[1005] Burridge, H.C., Bhagat, R.K., Stettler, M.E.J., *et al.* (2021). The ventilation of buildings and other mitigating measures for COVID-19: A focus on wintertime. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences, 477*(2247), 20200855. https://doi.org/10.1098/rspa.2020.0855; Arnold, B. (2021). Personal communication.

[1006] Biasin, M., Bianco, A., Pareschi, G., *et al.* (2021). UV-C irradiation is highly effective in inactivating SARS-CoV-2 replication. *Scientific Reports, 11*(1), 6260. https://doi.org/10.1038/s41598-021-85425-w

[1007] Beck, S.E., Ryu, H., Boczek, L.A., *et al.* (2017). Evaluating UV-C LED disinfection performance and investigating potential dual-wavelength synergy. *Water Research, 109*, 207-216. https://doi.org/10.1016/j.watres.2016.11.024; Buonanno, M., Welch, D., Shuryak, I., *et al.* (2020). Far-UVC light (222 nm) efficiently and safely inactivates airborne human coronaviruses. *Scientific Reports, 10*(1), 10285. https://doi.org/10.1038/s41598-020-67211-2; Welch, D., Buonanno, M., Grilj, V., *et al.* (2018). Far-UVC light: A new tool to control the spread of airborne-mediated microbial diseases. *Scientific Reports, 8*(1), 2752. https://doi.org/10.1038/s41598-018-21058-w; Zakaria, F., Harelimana, B., Ćurko, J., *et al.* (2016). Effectiveness of UV-C light irradiation on disinfection of an eSOS® smart toilet evaluated in a temporary settlement in the Philippines. *International Journal of Environmental Health Research, 26*(5-6), 536-553. https://doi.org/10.1080/09603123.2016.1217313

[1008] Perry, J.L., Agui, J.H., & Vijayakimar, R. (2016). *Submicron and nanoparticulate matter removal by HEPA-rated media filters and packed beds of granular materials*. NASA. Retrieved from https://ntrs.nasa.gov/citations/20170005166

[1009] Heffernan, T. (2020). Can HEPA air purifiers capture the coronavirus? Retrieved from https://www.nytimes.com/wirecutter/blog/can-hepa-air-purifiers-capture-coronavirus/

[1010] Heinemann, J.A., Ankenbauer, R.G., & Amábile-Cuevas, C.F. (2000). Do antibiotics maintain antibiotic resistance? *Drug Discovery Today, 5*(5), 195-204. https://doi.org/10.1016/s1359-6446(00)01483-5

[1011] Ellingson, K.D., Pogreba-Brown, K., Gerba, C.P., *et al.* (2020). Impact of a novel antimicrobial surface coating on health care-associated infections and environmental bioburden at 2 urban hospitals. *Clinical Infectious Diseases, 71*(8), 1807-1813. https://doi.org/10.1093/cid/ciz1077

[1012] Wasa, A., Land, J.G., Gorthy, R., *et al.* (2021). Antimicrobial and biofilm-disrupting nanostructured TiO2 coating demonstrating photoactivity and dark activity. *FEMS Microbiology Letters, 368*(7). https://doi.org/10.1093/femsle/fnab039

[1013] Dunne, S.S., Ahonen, M., Modic, M., *et al.* (2018). Specialized cleaning associated with antimicrobial coatings for reduction of hospital-acquired infection: Opinion of the COST Action Network AMiCI (CA15114). *Journal of Hospital Infection, 99*(3), 250-255. https://doi.org/10.1016/j.jhin.2018.03.006

[1014] Ibid.

It should be noted that, like antimicrobial drugs and surface cleaners, microbes can develop resistance to antimicrobial coatings:[1015] there is evidence of microbes becoming resistant to silver,[1016] copper,[1017] and quaternary ammonium compounds.[1018] Moreover, resistance to the materials used in the coating can also reduce the effectiveness of antibiotics used in human medicine.[1019] There may also be some leaching of the antimicrobial from the surface into the environment over time, which can also lead to the development of AMR.

There are several antimicrobial coating research and development projects underway in Aotearoa New Zealand:

- Resene paints, which markets a silver-based antimicrobial paint,[1020] in collaboration with Victoria University of Wellington, has demonstrated high efficacy of antimicrobial paints to sterilise surfaces experimentally loaded with multidrug resistant bacteria. Evaluation of these paints in clinical settings is underway.
- Inhibit Coating is developing a silver-based antimicrobial coating that retains silver nanoparticles within the coating polymer matrix, preventing leaching to improve the life of the coating and reduce environmental contamination.[1021]
- Coatings containing titanium dioxide particles generate microbe-damaging reactive oxygen species in the presence of light.[1022] This has been proposed as an attractive solution in areas of high ambient light because titanium dioxide is relatively cheap and non-toxic. A research group at the University of Canterbury[1023] is investigating the attachment of titanium dioxide nanoparticles to metal surfaces.[1024]

Digital solutions can also support IPC. Software such as ICNET's hospital infection prevention module can help to streamline IPC management across the whole organisation. It is a surveillance and data system that provides near-real-time alerts on organisms of interest, allowing for better patient management. Data on events such as SSIs is collated in ICNET, bypassing the need for point prevalence surveys and reducing time spent on manual data collection. Canterbury DHB, which has used ICNET since 2012, have found evidence of ICNET contributing to decreased frequency and shorter duration of norovirus outbreaks.[1025] The scope for digital technologies to help combat infectious disease and AMR goes beyond IPC, with benefits for AMR surveillance, broader disease surveillance, and antimicrobial use data collection, explored in section 5.4 and section 5.5.

A holistic approach to IPC involves resilient infrastructure

The way hospitals, homes, and other buildings are designed can support IPC. There is room to improve building design and maintenance to support IPC.

[1015] Pietsch, F., O'Neill, A.J., Ivask, A., *et al.* (2020). Selection of resistance by antimicrobial coatings in the healthcare setting. *Journal of Hospital Infection, 106*(1), 115-125. https://doi.org/10.1016/j.jhin.2020.06.006

[1016] Hosny, A.E.M., Rasmy, S.A., Aboul-Magd, D.S., *et al.* (2019). The increasing threat of silver-resistance in clinical isolates from wounds and burns. *Infection and Drug Resistance, 12*, 1985-2001. https://doi.org/10.2147/idr.S209881

[1017] Staehlin, B.M., Gibbons, J.G., Rokas, A., *et al.* (2016). Evolution of a heavy metal homeostasis/resistance island reflects increasing copper stress in Enterobacteria. *Genome Biology and Evolution, 8*(3), 811-826. https://doi.org/10.1093/gbe/evw031

[1018] Bragg, R., Jansen, A., Coetzee, M., *et al.* (2014). *Bacterial resistance to quaternary ammonium compounds (QAC) disinfectants.* Paper presented at the Infectious Diseases and Nanomedicine II, New Delhi.

[1019] Jun, H., Kurenbach, B., Aitken, J., *et al.* (2019). Effects of sub-lethal concentrations of copper ammonium acetate, pyrethrins and atrazine on the response of Escherichia coli to antibiotics. *F1000Research, 8*(32). https://doi.org/10.12688/f1000research.17652.1

[1020] Resene. (2011). Wall protection. Retrieved 15 November, 2021, from https://www.resene.co.nz/comn/whtsnew/wall_protection.htm

[1021] Inhibit Coatings. (n.d.). Inhibit Coatings. Retrieved 15 November, 2021, from https://www.inhibitcoatings.com/

[1022] Foster, H.A., Ditta, I.B., Varghese, S., *et al.* (2011). Photocatalytic disinfection using titanium dioxide: spectrum and mechanism of antimicrobial activity. *Applied Microbiology and Biotechnology, 90*(6), 1847-1868. https://doi.org/10.1007/s00253-011-3213-7

[1023] University of Canterbury. (2019, 20 February). *Shape-changing element holds key to anti-bacterial coating* [Press release]. Retrieved from https://www.canterbury.ac.nz/news/2019/shape-changing-element-holds-key-to-anti-bacterial-coating.html

[1024] Krumdieck, S.P., Boichot, R., Gorthy, R., *et al.* (2019). Nanostructured TiO_2 anatase-rutile-carbon solid coating with visible light antimicrobial activity. *Scientific Reports, 9*(1), 1883. https://doi.org/10.1038/s41598-018-38291-y

[1025] Taylor, M. (2021). Personal communication. [Research in press]

- Internationally, principles underpinning hospital design (including high ceilings, adequate natural lighting, and sufficient ventilation) aren't always applied in other settings that could benefit from them, such as offices, schools, and ARC facilities.[1026]
- In households, crowding, inadequate heating and insulation, cold, mould, and dampness contribute to negative health outcomes and pathogen spread.[1027] Aotearoa New Zealand's new healthy homes standards look set to make a positive contribution to the health of people living in rental properties.[1028] The impact of housing on infectious disease is also discussed in section 3.4.

In addition to buildings, the design and maintenance of other kinds of infrastructure can support IPC. One of Aotearoa New Zealand's biggest challenges in this regard is our ageing water infrastructure.[1029] Making sure the Three Waters[1030] initiative elevates the importance of combatting waterborne diseases is essential (see section 3.6.2 for information on a waterborne outbreak).

There is room to improve building design and maintenance to support IPC.

IPC in animal and plant health

Many of the principles that apply to IPC in human health can also be transferred to animal and plant health – and vice versa. Recognising these connections and enabling knowledge transfer between these sectors can support disease management across human, animal, and plant health in Aotearoa New Zealand. In addition, IPC measures can help reduce the spread of zoonotic diseases between animals and humans.

Vets in Aotearoa New Zealand aren't required to observe IPC practices in the same way that healthcare workers in the human health sector are – their obligations come under the Health and Safety at Work Act 2015, which requires them to keep their staff and customers safe, including from infections.[1031] However, the NZVA has developed a set of IPC guidelines aimed at preventing and controlling the transmission of microbes between animals and from animals to humans. Many of the guidelines have parallels with human health IPC practices. For example, they are encouraged to factor IPC into facility design, practice good hand hygiene, use PPE appropriately, sterilise equipment, isolate infected animals, and ensure staff are trained in IPC. [1032]

[1026] Burridge, H.C., Bhagat, R.K., Stettler, M.E.J., *et al.* (2021). The ventilation of buildings and other mitigating measures for COVID-19: A focus on wintertime. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences, 477*(2247), 20200855. https://doi.org/10.1098/rspa.2020.0855

[1027] See section 6.2 of the OPMCSA evidence summary on Group A *Streptococcus* and acute rheumatic fever in Aotearoa New Zealand.

[1028] Ministry of Housing and Urban Development. (2021, 13 October). Healthy homes standards. Retrieved 15 November, 2021, from https://www.hud.govt.nz/residential-housing/renting/healthy-homes-standards/

[1029] Mandow, N. (2021, 1 March). Wellington tip of iceberg for country's water woes, *Newsroom*. Retrieved from https://www.newsroom.co.nz/under-the-surface-of-our-ageing-water-infrastructure

[1030] New Zealand Government. (n.d.). Three waters reform programme. Retrieved 15 November, 2021, from https://threewaters.govt.nz/

[1031] New Zealand Government. (2015). *Health and Safety at Work Act 2015*. Retrieved from https://www.legislation.govt.nz/act/public/2015/0070/latest/DLM5976660.html

[1032] New Zealand Veterinary Association. (2016). *Guideline for infection control: Reducing the risk of infectious disease transmission for veterinarians*. New Zealand Veterinary Association. Retrieved from https://www.nzva.org.nz/assets/Policies-Guidelines-Resources/Guideline-infection-control_.pdf

The agricultural community has a role to play in IPC in Aotearoa New Zealand. Biosecurity measures taken on our farms and orchards can reduce the chances of animals and plants getting infected and infections spreading, thereby promoting animal welfare and plant health, reducing economic losses, and reducing the need for farmers to use antimicrobial treatments.

The NZVA has developed a set of IPC guidelines aimed at preventing and controlling the transmission of microbes between animals and from animals to humans. Many of the guidelines have parallels with human health IPC practices.

Animal husbandry practices play a significant role in infection spread. For example, the denser the animal population, the more readily infections can spread. While our cows, sheep, and deer aren't closely packed together,[1033] high density chicken and pig farming is the norm in most countries, including Aotearoa New Zealand – for example, approximately 3% of pigs in Aotearoa New Zealand are free range.[1034] It should be noted, however, that even if animals are given more space, they won't always utilise it[1035] and disease spread remains possible, so free ranging isn't a complete IPC fix on its own (see also section 4.4.2).

Managing animal movements is another IPC measure used in the agricultural industry. One of the central components of IPC in cattle and deer farming is the National Animal Identification and Tracing programme, which identifies individual animals and records where they are in the supply chain so that animal health, disease outbreaks, food safety, and biosecurity risks can be managed. Compliance with the programme has lifted over the last five years, supported by education delivered to the farming community and targeted communications, aligned with key events on the farming calendar. Technological innovations – such as the rollout of an app to make it easier for farmers to complete Animal Status Declaration forms – support compliance too.[1036]

In some situations, preventing disease spread may require animal movements to be halted altogether. Restricting cattle movements is a key component of the *Mycoplasma bovis* management strategy – farms with infected animals are placed on Restricted Place Notices under the Biosecurity Act 1993 to prevent animals and other risk goods moving on and off the property until the animals test negative or are culled (for more on *M. bovis*, see section 3.5.1).[1037] The foot-and-mouth disease response and recovery plan calls for an immediate nationwide livestock movement standstill if this potentially economically catastrophic virus is detected in the country.[1038]

[1033] Hipgrave, P. (2020). Number and density of livestock in New Zealand. In Zealand (Ed.). Wellington, NZ: Massey University. Retrieved from https://ehinz.ac.nz/assets/Factsheets/Released_2020/Livestock-Numbers-Density.pdf; Ministry for Primary Industries. (2012). *Pastoral input trends in New Zealand: A snapshot*. Wellington, NZ: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/4168/direct; Stats NZ. (2021, 15 April). Livestock numbers. Retrieved 15 November, 2021, from https://www.stats.govt.nz/indicators/livestock-numbers

[1034] NZ Pork. (n.d.). Farming styles in New Zealand. Retrieved 7 December, 2021, from https://www.nzpork.co.nz/farmers/pork-farming-styles-in-new-zealand

[1035] Pettersson, I.C., Freire, R., & Nicol, C.J. (2016). Factors affecting ranging behaviour in commercial free-range hens. *World's Poultry Science Journal, 72*(1), 137-150. https://doi.org/10.1017/S0043933915002664

[1036] OSPRI Ltd. (2021). *Annual report 2020–2021*. Retrieved from https://www.ospri.co.nz/assets/ResourcePDFs/OSPRI-Annual-Report-2020-2021.pdf

[1037] Ministry for Primary Industries. (n.d., 15 July 2021). *Mycoplasma bovis* disease eradication programme. Retrieved 4 August, 2021, from https://www.mpi.govt.nz/biosecurity/mycoplasma-bovis/; Ministry for Primary Industries. (2021, 11 November). *M. bovis programme review identifies key lessons to strengthen biosecurity* [Press release]. Retrieved from https://www.mpi.govt.nz/news/media-releases/m-bovis-programme-review-identifies-key-lessons-to-strengthen-biosecurity-2/

[1038] Biosecurity New Zealand. (2018). *Foot and mouth disease response and recovery plan*. Wellington, NZ: Ministry for Primary Industries. Retrieved from https://www.mpi.govt.nz/dmsdocument/32386-The-New-Zealand-Government-Foot-and-Mouth-Disease-Response-and-Recovery-Plan

Innovative solutions can also support IPC in plants and animals. For example:

- As discussed in section 4.4.2, teat sealants can reduce infection risks on dairy farms, providing a non-antimicrobial alternative to antimicrobial prophylaxis.[1039]
- Interventions like good animal and plant nutrition and the use of probiotics and other biological control agents can also promote resilience to disease. For example, biological controls like yeast and bacteriophages have been explored to control Psa (for more on Psa, see section 3.5.1).[1040]
- While there is no government-mandated biosecurity standard for pig farming, NZ Pork promotes the implementation of good biosecurity practices to the commercial industry through development of industry good practice guidelines, under the leadership of pig veterinarians. The PigCare industry standards facilitated by NZ Pork cover about 95% of commercial pig farmers and include measures for the management of health and injury, and the requirement to have a biosecurity programme developed in consultation with a veterinarian.[1041]
- Plant and Food Research includes Psa tolerance among its selection traits when breeding new kiwifruit cultivars (for more on selective breeding, see section 5.5.5). [1042]
- Extensive testing of different decontaminants was conducted to inform the design of hygiene stations to curb the spread of the microbe responsible for kauri dieback, although more research is needed to find a way to deactivate dormant pathogens.[1043]

When it comes to plants, integrated pest management is a holistic way of approaching IPC (see section 5.5.5). This may involve use of disease-resistant crop varieties, pathogen monitoring to ensure antimicrobials are only used when needed, exclusionary practices to prevent the introduction of pathogens onto a crop, and soil improvement and crop rotation to prevent pathogen build-up.[1044]

For kauri dieback, identifying the main modes of transmission was one of the first fundamental research questions to be addressed.

As with IPC in human health, forming a strong evidence base to guide interventions is key. For kauri dieback, identifying the main modes of transmission was one of the first fundamental research questions to be addressed. The conclusion – that spread is primarily driven by human activities leading to the movement of soil on people, equipment, and vehicles – allowed for the development of evidence-based interventions including creation of exclusion zones, hygiene stations, track management, and event management protocols for running and mountain biking races. Devising these interventions is only half the battle: the challenge is to encourage compliance, just like IPC

[1039] Dufour, S., Wellemans, V., Roy, J.P., *et al.* (2019). Non-antimicrobial approaches at drying-off for treating and preventing intramammary infections in dairy cows. Part 1. Meta-analyses of efficacy of using an internal teat sealant without a concomitant antimicrobial treatment. *Animal Health Research Reviews, 20*(1), 86-97. https://doi.org/10.1017/s1466252319000070; Rabiee, A.R., & Lean, I.J. (2013). The effect of internal teat sealant products (Teatseal and Orbeseal) on intramammary infection, clinical mastitis, and somatic cell counts in lactating dairy cows: A meta-analysis. *Journal of Dairy Science, 96*(11), 6915-6931. https://doi.org/10.3168/jds.2013-6544

[1040] Woodcock, S.D. (2016). *A review of research and development undertaken on Psa*. Tauranga: Kiwifruit Vine Health. Retrieved from http://www.kvh.org.nz/vdb/document/103504

[1041] NZ Pork. (2021). Personal communication.

[1042] Woodcock, S.D. (2016). *A review of research and development undertaken on Psa*. Tauranga: Kiwifruit Vine Health. Retrieved from http://www.kvh.org.nz/vdb/document/103504

[1043] Froud, K.J. (2020). *Kauri dieback building knowledge review*. Kauri Dieback Programme and the Ministry for Primary Industries. Retrieved from https://www.kauriprotection.co.nz/media/2096/kauri-dieback-building-knowledge.pdf

[1044] Food and Agriculture Organization Antimicrobial Resistance Working Group. (2018). *Antimicrobial resistance and foods of plant origin: Summary report of an FAO meeting of experts*. Retrieved from http://www.fao.org/3/BU657en/bu657en.pdf

measures in human health need to be put into practice to have an effect. Part of the kauri dieback research programme has involved work by social scientists to understand what kinds of signage encourage compliance with IPC measures.[1045]

Stopping microbes at the border is a first line of defence

For pathogens that aren't in the country, the most effective infection prevention strategy is to stop them from entering the country altogether. Biosecurity measures at our borders help to stop exotic plant and animal pathogens from entering the country (as well as pests and weeds). Being an isolated island nation plays to our advantage – our borders aren't very porous which means we have more visibility over what comes into the country than those nations with land borders or close neighbours.[1046]

Our COVID-19 border restrictions[1047] and the medical examination requirements we place on some visa applicants[1048] (e.g. chest x-rays to screen for TB) demonstrate that we are also willing to use this geographic advantage to prevent the introduction of certain human pathogens too. See section 3.3 for more details about the unique infectious diseases landscape in Aotearoa New Zealand as it relates to our physical isolation and border control.

This ability to stop pathogens at the border is a privilege not afforded to many others around the world. We have a responsibility to engage with global efforts to combat AMR and infectious disease offshore (see section 2.4.3 and section 5.6.2) which in turn will help to reduce cases arriving at our borders.

5.3.2 Vaccines

Vaccination in humans and animals can be used to reduce the prevalence of many bacterial and viral diseases, including infections caused by drug-resistant pathogens.[1049] Additionally, vaccination has the potential to reduce the need for antimicrobials, thereby helping to slow the development of AMR.[1050] For example, *H. influenzae* b and *S. pnuemoniae* vaccines have resulted in reductions in disease burden in human health as well as decreased incidence of resistant strains.[1051]Additionally, the economic benefits associated with disease prevention through vaccination can be considerable. For example, between 2011 and 2020, vaccines against ten different antigens in 73 lower-income countries saved an average of US$28.50 in health costs for every dollar invested in purchasing and rollout.[1052]

[1045] Froud, K.J. (2020). *Kauri dieback building knowledge review*. Kauri Dieback Programme and the Ministry for Primary Industries. Retrieved from https://www.kauriprotection.co.nz/media/2096/kauri-dieback-building-knowledge.pdf
[1046] Crump, J.A., Murdoch, D.R., & Baker, M.G. (2001). Emerging infectious diseases in an island ecosystem: The New Zealand perspective. *Emerging Infectious Diseases, 7*(5), 767-772. https://doi.org/10.3201/eid0705.017501
[1047] New Zealand Government. (n.d.). You want to enter New Zealand. Retrieved 15 November, 2021, from https://www.immigration.govt.nz/about-us/covid-19/border-closures-and-exceptions
[1048] New Zealand Government. (n.d.). Who needs an x-ray or medical examination. Retrieved 15 November, 2021, from https://www.immigration.govt.nz/new-zealand-visas/apply-for-a-visa/tools-and-information/medical-info/when-you-need-an-x-ray-or-medical-examination
[1049] Ginsburg, A.S., & Klugman, K.P. (2017). Vaccination to reduce antimicrobial resistance. *The Lancet Global Health, 5*(12), e1176-e1177. https://doi.org/10.1016/S2214-109X(17)30364-9
[1050] Bloom, D.E., Black, S., Salisbury, D.*, et al.* (2018). Antimicrobial resistance and the role of vaccines. *Proceedings of the National Academy of Sciences, 115*(51), 12868-12871. https://doi.org/10.1073/pnas.1717157115
[1051] Wellcome Trust, & The Boston Consulting Group. (2018). *Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities*. Retrieved from https://vaccinesforamr.org/wp-content/uploads/2018/09/Vaccines_for_AMR.pdf
[1052] International Vaccine Access Center. (n.d.). The value of vaccine porgrams. Retrieved 15 November, 2021, from https://vaccineroi.org/

Enhancing vaccination is two-pronged, involving both increased uptake of existing vaccinations and development of new vaccines. Researchers internationally highlight diseases such as TB, influenza, RSV and gonorrhoea as priority areas for continued development of vaccines in human health.[1053]

Uptake of vaccines in human health could be improved

Aotearoa New Zealand has a National Immunisation Schedule, which is the series of vaccines that are available for free at pre-specified ages for babies, children, adolescents, and adults, including pregnant people.[1054] The schedule includes vaccines targeting infections caused by bacteria such as *Streptococcus pneumoniae* (which can cause meningitis, pneumonia, septicaemia, and other infections), toxin-producing strains of *Corynebacterium* spp. (which can cause diptheria), *Haemophilus influenzae* type b (which can cause meningitis and epiglottitis), and *Clostridium tetani* (which can cause tetanus). It also includes vaccines to prevent viral infections, such as the human papillomavirus (HPV) vaccine.

… low (and declining) uptake of childhood immunisation signals **a need for national leadership** and renewed focus in the immunisation space.

For children aged two years, immunisation schedule uptake is approximately 88% (July 2020 - June 2021).[1055] However, uptake varies widely by ethnicity: it is very high for Asian people (96%), lower for NZ Europeans (90%) and Pacific peoples (88%), and much lower for Māori (79%). For the last ten years, immunisation uptake for this age has varied between 91% and 93%, with decreases between 2016 and 2018 triggering an evidence review to improve childhood immunisation rates.[1056] The steep drop to 88% for the period July 2020 - June 2021 may be in part due to COVID-19-related restrictions. Even at coverage levels seen in years prior to 2020, Aotearoa New Zealand has low uptake compared with international standards.

Any renewed focus needs to be sustained and focused on **equity**.

This low (and declining) uptake of childhood immunisation signals a need for national leadership and renewed focus on vaccination. There may also be benefits to increasing community-led immunisation services to reach underserved communities, such as Māori and people living in remote areas. Any renewed focus needs to be sustained and focused on equity. In 2014, immunisation inequities between Māori and non-Māori were essentially eliminated as the result of concerted efforts and resourcing, but when that focus drifted, the equity gains were lost.[1057]

Improving uptake of vaccines is complex and there are many factors that can impact rates. For childhood vaccinations these include improving access (e.g. costs, distance to travel, clinic time

[1053] Clift, C., & Salisbury, D.M. (2017). Enhancing the role of vaccines in combatting antimicrobial resistance. *Vaccine, 35*(48, Part B), 6591-6593. https://doi.org/10.1016/j.vaccine.2017.09.053
[1054] Ministry of Health. (2020). New Zealand Immunisation Schedule. Retrieved 28 October, 2021, from https://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/new-zealand-immunisation-schedule
[1055] Ministry of Health. (2021). National and DHB immunisation data. Retrieved 28 October, 2021, from https://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/immunisation-coverage/national-and-dhb-immunisation-data
[1056] Allen + Clarke. (2019). *Improving New Zealand's childhood immunisation rates: Evidence review*. Retrieved from https://www.health.govt.nz/system/files/documents/publications/improving-new-zealands-childhood-immunisation-rates-sep19.pdf
[1057] Health Quality & Safety Commission. (2019). *A window on the quality of Aotearoa New Zealand's health care 2019 – A view on Māori health equity*. Wellington, New Zealand: Health Quality & Safety Commission. Retrieved from https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/publications-and-resources/publication/3721/

availability, cultural acceptability, and enrolment), incentivising parents and doctors, and mandatory immunisation (mandatory childhood vaccination policies are in place in many countries, which may allow individuals to opt out for a variety of reasons).[1058]

One study in Aotearoa New Zealand investigated the public's confidence in the safety of childhood vaccinations between 2013 and 2017.[1059] The study found that attitudes were becoming increasingly polarised with around 30% of participants becoming more concerned about vaccine safety over time and 10% displaying increased confidence in vaccines. The remaining participants showed consistent high vaccine confidence.

Increasing our vaccination numbers would be supported by improvements to:

- Primary care, including follow up regarding vaccine hesitancy,
- Understanding of cultural differences and effective interventions,
- Data collection and reporting to support targeted interventions, and
- Outreach in communities and delivery of flexible services.

In particular, efforts should not focus solely on delivering facts, but on building trust and positive relationships,[1060] and drawing on the collective value of social networks within communities to enhance trust.[1061] In 2017, the WHO released a publication titled *Vaccination and trust*, which outlines what research can tell us about vaccine hesitancy and how communication can help, alongside some guidelines to build trust.[1062] A recent systematic review canvassed the literature for interventions to address vaccine hesitancy, finding that the most successful interventions were multi-component with a variety of media, incorporated dialogue, and were personalised and tailored to the target audience's specific concerns, historical experiences, socioeconomic status, and trusted messengers for information.[1063] Health literacy and communication is further explored in section 5.6.1.

Efforts should not focus solely on delivering facts, but on **building trust and positive relationships**, and drawing on the collective value of social networks within communities to enhance trust.

Beyond the immunisation schedule, there is also public funding for vaccines for children and adults who are at increased risk of certain diseases due to other medical conditions. These include vaccines for hepatitis A, hepatitis B, *H. influenzae* type b, HPV, influenza, meningococcal disease, pertussis (whooping cough), pneumococcal disease, TB, and chicken pox.

[1058] Allen + Clarke. (2019). *Improving New Zealand's childhood immunisation rates: Evidence review*. Retrieved from https://www.health.govt.nz/system/files/documents/publications/improving-new-zealands-childhood-immunisation-rates-sep19.pdf
[1059] Lee, C.H., & Sibley, C.G. (2020). Attitudes toward vaccinations are becoming more polarized in New Zealand: Findings from a longitudinal survey. *EClinicalMedicine, 23*, 100387. https://doi.org/10.1016/j.eclinm.2020.100387
[1060] Benin, A.L., Wisler-Scher, D.J., Colson, E., *et al.* (2006). Qualitative analysis of mothers' decision-making about vaccines for infants: The importance of trust. *Pediatrics, 117*(5), 1532-1541. https://doi.org/10.1542/peds.2005-1728
[1061] Ozawa, S., Paina, L., & Qiu, M. (2016). Exploring pathways for building trust in vaccination and strengthening health system resilience. *BMC Health Services Research, 16*(7), 639. https://doi.org/10.1186/s12913-016-1867-7
[1062] World Health Organization. (2017). *Vaccination and trust: How concerns arise and the role of communication in mitigating crises*. Geneva, Switzerland: World Health Organization. Retrieved from https://apps.who.int/iris/handle/10665/343299
[1063] Olson, O., Berry, C., & Kumar, N. (2020). Addressing parental vaccine hesitancy towards childhood vaccines in the United States: A systematic literature review of communication interventions and strategies. *Vaccines, 8*(4), 590.

… looking at the evidence showed us that expanding the immunisation schedule could get more benefits from an existing vaccine.

There are also other vaccinations available in Aotearoa New Zealand, though not necessarily part of the immunisation schedule, that could have wider benefits than originally anticipated. For example, surveillance data found that exposure to the meningococcal group B vaccine (against *Neisseria meningitidis*) was associated with reduced rates of gonorrhoea diagnosis (caused by *Neisseria gonorrhoeae*).[1064] In the late 1990s there was a large increase in cases of meningitis associated with a particular strain of the meningococcal B bacterium and this led to development of a vaccine and was offered free for specific age groups over a short period of time. Cases decreased significantly and the vaccine is no longer needed to control this specific strain. At the same time, there was an associated reduced rate of gonorrhoea diagnosis; the organisms that cause each disease are similar and this is likely why there was cross protection seen.[1065] There is greater AMR being seen in gonorrhoea, which means that vaccine development for this disease is increasing in priority.

A further example is the extension of funding for the human papillomavirus (HPV) vaccine, which was initially funded for girls in 2008 before being funded for boys as well from 2017 (in addition to expanded age eligibility).[1066] This expansion was in response to recognition of growing prevalence of oral and throat cancers in men[1067] – looking at the evidence showed us that expanding the immunisation schedule could get more benefits from an existing vaccine.

Leveraging the COVID-19 experience for vaccine development

The COVID-19 pandemic has shown how quickly vaccines can be developed when prioritisation, resourcing, and suitable clinical trial environments are no barrier and existing research is leveraged. The standard timeline for a vaccine to reach the market from the clinical trial stage has historically been around ten years.[1068] In contrast, three different COVID-19 vaccines were able to reach the market in less than one year. Achieving development on a short timeline required massive financial investment, expedited but robust regulatory processes, a large number of researchers focused on the disease and sharing knowledge freely, a higher appetite for financial risk, availability of suitable environments to run clinical trials, and utilisation of innovative technologies.

The COVID-19 pandemic has shown how quickly vaccines can be developed when unprecedented resources are applied to research.

[1064] Petousis-Harris, H., Paynter, J., Morgan, J*., et al.* (2017). Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. *Lancet, 390*(10102), 1603-1610. https://doi.org/10.1016/s0140-6736(17)31449-6

[1065] Semchenko, E.A., Tan, A., Borrow, R*., et al.* (2018). The Serogroup B Meningococcal Vaccine Bexsero Elicits Antibodies to Neisseria gonorrhoeae. *Clinical Infectious Diseases, 69*(7), 1101-1111. https://doi.org/10.1093/cid/ciy1061

[1066] Health Central. (2016). HPV vaccinations: Don't forget the boys. Retrieved 29 November, 2021, from https://healthcentral.nz/hpv-vaccinations-dont-forget-the-boys-2/

[1067] Schmeler, K.M., & Sturgis, E.M. (2016). Expanding the benefits of HPV vaccination to boys and men. *The Lancet, 387*(10030), 1798-1799. https://doi.org/10.1016/S0140-6736(16)30314-2

[1068] Agrawal, G., Hermann, R., Poetes, R*., et al.* (2021). Fast-forward: Will the speed of COVID-19 vaccine development reset industry norms? Retrieved 5 November, 2021, from https://www.mckinsey.com/industries/life-sciences/our-insights/fast-forward-will-the-speed-of-covid-19-vaccine-development-reset-industry-norms

Several authorised COVID-19 vaccines are based on technology platforms that had previously never or rarely been used for human vaccines. These platforms – namely, mRNA and viral vector platforms – had been developed in the years prior to COVID-19 and were deployed to rapidly develop vaccine candidates specific to SARS-CoV-2.[1069] There are opportunities to build on the research and development of COVID-19 vaccines to inform development of vaccines for other diseases, particularly those that are hard to prevent or hard to treat.

There are opportunities to build on the research and development of COVID-19 vaccines to **inform development of vaccines for other diseases**, particularly those that are hard to prevent or hard to treat

There are ongoing challenges with developing new vaccines that are relevant in the fight against AMR, key among these is the high cost of development.[1070] While many vaccinations in the past have had a very clear-cut and direct cost-benefit analysis, this calculation may be more nuanced for development of vaccines for infections caused by drug-resistant pathogens. In addition, vaccine development can be technically challenging, with unique challenges associated with different pathogens depending on their properties and mechanisms of action.

Due to the small size of our market, the majority of vaccines used in Aotearoa New Zealand are supplied by overseas manufacturers, although we do manufacture some animal vaccines commercially.[1071] Any cost-benefit analysis exploring investment in manufacturing capabilities will need to consider the value of this capability in the event of supply chain disruption or global emergency. Onshore vaccine manufacturing for human health may help Aotearoa New Zealand play a role in supplying vaccines to the Pacific region. However, supply chain disruption of raw materials needed to manufacture vaccines onshore may still eventuate. In addition, making vaccines onshore would require considerable investment in infrastructure and human resources.

Vaccinating animals can help prevent the spread of zoonoses and reduce the need for antimicrobials

Vaccinations in animals are important for maintaining both animal and human health, through preventing diseases that can spread from animals to humans. An example of work in this area is the NZVA and Society of Dairy Cattle Vets national risk management programme to reduce risk of human leptospirosis infection on dairy farms. The programme, known as Leptosure, is a working plan that includes a vaccination programme and farm management practices. It is estimated that more than 90% of dairy cattle are

It is estimated that more than 90% of dairy cattle are vaccinated against leptospirosis.

[1069] Dolgin, E. (2021). The tangled history of mRNA vaccines. *Nature, 597*(7876), 318-324. https://doi.org/doi.org/10.1038/d41586-021-02483-w

[1070] O'Neill, J. (2016). *Tackling drug-resistant infections globally: Final report and recommendations*. UK: HM Government and Wellcome Trust. Retrieved from https://amr-review.org/

[1071] E.g. Biocell Corporation. (n.d.). Vaccine manufacture. Retrieved 9 December, 2021, from https://biocellcorp.co.nz/vaccine-manufacture/

vaccinated against leptospirosis.[1072] However, any increase in leptospirosis strains not included in the vaccine will necessitate continued development of vaccines and other management techniques.

Other farm animals also transmit leptospirosis, including cattle and sheep, though vaccination numbers are much lower compared with dairy cows. The commercial pig industry reportedly manages leptospirosis by a sow vaccination programme.[1073] Boosting vaccination in these animals would improve both animal and human health. Similarly, wider uptake of the *Salmonella* vaccine would help to prevent outbreaks of salmonellosis among herds and flocks, while also reducing the risk for people.[1074]

Wider use of vaccines in animals is also important to reduce antimicrobial use – because vaccines can prevent the infections that may require antimicrobial treatment (e.g. bovine mastitis). As detailed in section 4.4.2, most antimicrobial use in dairy cows is for the prevention and treatment of mastitis. There is a vaccine available in Aotearoa New Zealand that can reduce the incidence and severity of mastitis caused by *Staphylococcus aureus*, coliforms and coagulase-negative staphylococci.[1075] Further, there are other vaccines not yet registered in Aotearoa New Zealand, such as Ubac that can reduce clinical mastitis caused by *Streptococcus uberis.*[1076] Testing of bacterial isolates that cause bovine mastitis has shown resistance to several different antibiotics (see section 4.3.2) so registration and greater uptake of vaccination may have positive impacts. However, to be economical and effective, vaccination needs to be combined with other infection control procedures.[1077]

Wider uptake of the ***Salmonella*** vaccine would **help to prevent outbreaks** of salmonellosis among herds and flocks, while also reducing the risk for people.

Overseas, pig and poultry industries use autogenous vaccines.[1078] These vaccines are made from bacterial or viral isolates taken from the infected herd or flock, and are used to stimulate immunity to that isolate in other herds or flocks. Autogenous vaccines can be useful when there are barriers to importation of commercial vaccines but can also be difficult to manufacture and use. An autogenous vaccine has been developed for zoonotic *Yersinia* spp. (and tested with inconclusive results),[1079] but most autogenous vaccines are helpful for simply protecting animal health and reducing the need for antimicrobials.

[1072] New Zealand Veterinary Association. (2019). Leptosure: Leptospirosis in New Zealand. Retrieved 5 November 2021, from https://www.nzva.org.nz/resource/general/specific/leptosure/
[1073] NZ Pork. (2021). Personal communication.
[1074] DairyNZ. (n.d.). Salmonella. Retrieved 10 September, 2021, from https://www.dairynz.co.nz/animal/cow-health/salmonella/
[1075] Agilis. (n.d.). Startvac + diagnostic kits. Retrieved 9 December, 2021, from https://www.agilis.nz/products/startvac-mastitis-vaccine/ Bryan, M., & Hea, S. (2015). *Evaluation of Staphylococcus Aureus vaccine in dairy cattle in New Zealand* (Vol. Pan Pacific (NZVA and AVA) Veterinary Conference 2015): Australian Veterinary Association.
[1076] European Medicines Agency. (2021). Ubac Retrieved 9 December 2021, from https://www.ema.europa.eu/en/medicines/veterinary/EPAR/ubac
[1077] Ismail, Z.B. (2017). Mastitis vaccines in dairy cows: Recent developments and recommendations of application. *Veterinary World, 10*(9), 1057-1062. https://doi.org/10.14202/vetworld.2017.1057-1062
[1078] Esco Lifesciences Group. (n.d.). Autogenous vaccines. Retrieved 9 December, 2021, from https://escovaccixcell.com/applications/animal-health/Autogenous-Vaccines
[1079] Stanger, K.J., McGregor, H., Marenda, M.*, et al.* (2019). Assessment of the efficacy of an autogenous vaccine against Yersinia pseudotuberculosis in young Merino sheep. *New Zealand Veterinary Journal, 67*(1), 27-35. https://doi.org/10.1080/00480169.2018.1523758

Vaccinations are routine best practice in companion animals.[1080] A dog (working or pet) in Aotearoa New Zealand may be vaccinated against leptospirosis (with boosters required for ongoing effectiveness),[1081] parovirus, distemper, hepatitis, parainfluenza, and kennel cough. Cats may be vaccinated against flu viruses and feline immunodeficiency virus. In horses, tetanus and strangles are the most common and highly recommended vaccines, with equine vaccination guidelines available.[1082]

Other vaccines developed for animal diseases (and zoonoses) are covered in section 3.5.1. While there are some vaccines available for food and companion animals, there is still scope for further vaccine development. For example, a *Campylobacter* vaccine for poultry would make a huge difference to both animal and human health.[1083]

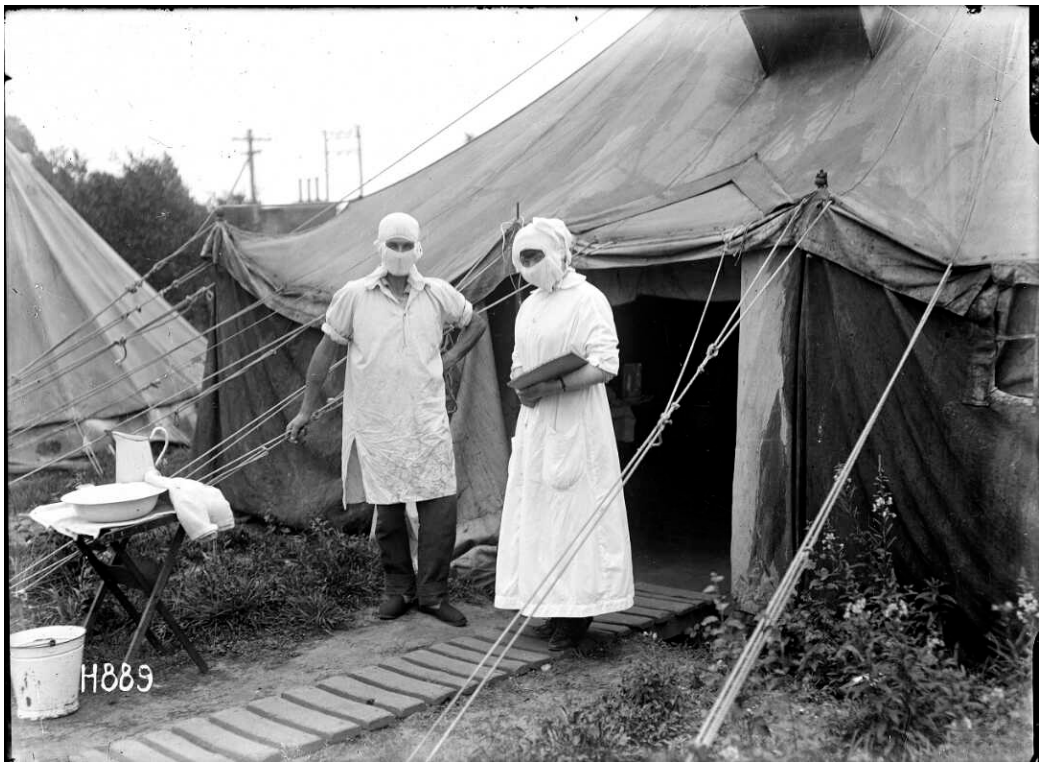


Figure 39: A New Zealand nurse and orderly outside the diphtheria ward, New Zealand Stationary Hospital, France. Royal New Zealand Returned and Services' Association: New Zealand official negatives, World War 1914-1918. Alexander Turnbull Library / Ref: 1/2-013466-G.

[1080] New Zealand Veterinary Association. (2017). *Vaccine use in New Zealand cats and dogs*. Retrieved from https://cdn.ymaws.com/www.nzva.org.nz/resource/resmgr/docs/policies_and_guidelines/170720_Vaccine_use_cats_dogs.pdf
[1081] WorkSafe NZ. (2017). Leptospirosis: Working with farm dogs and other pets in rural areas. Retrieved 9 December 2021, from https://www.worksafe.govt.nz/topic-and-industry/agriculture/working-with-animals/prevention-and-control-of-leptospirosis/working-with-farm-dogs/
[1082] O'Flaherty, J., Australian Equine Infectious Diseases Advisory Board, & New Zealand Equine Veterinary Association. (2014). *Equine vaccination guidelines for New Zealand.* Retrieved from https://www.zoetis.co.nz/tools/equine-vaccination-guidelines/assets/pdf/guidelines.pdf
[1083] Meunier, M., Guyard-Nicodème, M., Vigouroux, E.*, et al.* (2017). Promising new vaccine candidates against *Campylobacter* in broilers. *PLOS One, 12*(11), e0188472. https://doi.org/10.1371/journal.pone.0188472

5.4 Detection

Early detection of infectious diseases, antimicrobial-resistant microbes, and resistance genes across the One Health landscape facilitates timely treatment of infected organisms and implementation of measures to curb spread within and between the human, animal, and plant spheres.

This section explores the theme of detection, looking at drug-resistant pathogens specifically and diseases and outbreaks more generally, and considering data management and surveillance systems as well as diagnostic and susceptibility testing techniques.

Surveillance is information for action. It is not enough to simply amass lots of data; we must ensure that we are collecting the right data in useable formats in order to harness it for insights and knowledge that then inform evidence-based action.

5.4.1 Detecting drug-resistant pathogens

We need a centralised, cross-sector platform for AMR data

We need a centralised, accessible platform that collates standardised and useable susceptibility and resistance data from across the human, animal, plant, food and environmental sectors. This will allow risks and transmission routes at the in human, animal, plant, and environment interfaces to be identified and better understood. For example, if we are finding AMR genes in wastewater, are these also appearing in samples from patients? Are resistant strains of *Campylobacter* spp. isolated from poultry sheds also found in people? Integrating data from different sources is key to answering these questions and helping us design effective interventions.

Integrating data from different sources is key to answering these questions and helping us design effective interventions.

There are elements to our systems that would allow us to quickly position Aotearoa New Zealand well in terms of establishing a national AMR database for humans, though more work would be required to also incorporate animal, plant, and environmental testing. For humans, there is some foundation data (see section 4.3.1) we have unique health identification due to the National Health Index (NHI) number, and the population is relatively small. We can build on the Early Aberration Reporting System (EARS) which applies aberration detection algorithms to notifiable disease surveillance data and flags anomalies.[1084] In addition, the government's investment in health sector digital infrastructure and capability, announced in the 2021 budget,[1085] and the current health sector reform present a good opportunity to explore the development of a comprehensive AMR data system for human health. Being able to access comprehensive digital data easily will be a key factor in building AMR knowledge and strategy by identifying issues rapidly and monitoring the effectiveness of targeted interventions.

[1084] Institute of Environmental Science and Research Limited (ESR). (n.d.). Early Aberration Reporting System (EARS). Retrieved 9 December, 2021, from https://surv.esr.cri.nz/EARS/background.php

[1085] Ministry of Health. (n.d., 17 November 2021). Hira (National health information platform). Retrieved 9 December, 2021, from https://www.health.govt.nz/our-work/digital-health/other-digital-health-initiatives/hira-national-health-information-platform

In human health, data collection, collation, and utilisation could be improved

The way we currently gather and analyse data about AMR in human health in Aotearoa New Zealand makes it difficult to draw national insights. The *New Zealand AMR Action Plan* calls for ongoing efforts to "strengthen the knowledge and evidence base about AMR through surveillance and research."[1086] However, Aotearoa New Zealand does not have central mechanisms to harness AMR data to inform nationally-led decision making for human health.[1087] This means our national guidelines for managing drug-resistant pathogens are often outdated. MoH's *Guidelines for the control of multidrug-resistant organisms in New Zealand* were published in 2007[1088] and the *Guidelines for the control of methicillin-resistant Staphylococcus aureus in New Zealand* are from 2002.[1089] Given the wealth of knowledge generated since these publications – not to mention the emergence and spread of new resistance mechanisms – these guidelines would benefit from a refresh, informed by good data.

… our national guidelines for managing drug-resistant pathogens are often outdated.

ESR is Aotearoa New Zealand's national reference laboratory for human pathogens and carries out testing for a wide variety of microorganisms, collates laboratory and notification data generated by laboratories around the country, and leads the country's surveillance programme for AMR in human pathogens.[1090] As detailed in section 4.3.1, the surveillance programme would benefit greatly from more timely, regular and prioritised reporting, as well as a central, accessible database to collate national data and thus facilitate research and understanding of AMR patterns.

Stepped up screening?

Screening criteria for MDROs could be reviewed to better capture cases (see section 4.3). We need to ensure we have robust systems in place to ensure screening guidelines keep pace with international developments. This requires keeping track of AMR threats – especially new resistance mechanisms – that are emerging abroad. For example, outbreaks of a drug-resistant fungus, *Candida*

Outbreaks of a drug-resistant fungus, ***Candida auris***, are occurring in the US with person-to-person transmission, but **we are not consistently screening for this organism**.

[1086] Ministry of Health and Ministry for Primary Industries. (2017). *New Zealand Antimicrobial Resistance Action Plan*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/publication/new-zealand-antimicrobial-resistance-action-plan
[1087] World Health Organization. (2020). Global database for the tripartite antimicrobial resistance (AMR) country self-assessment survey (TrACSS). Retrieved 4 August 2021 https://amrcountryprogress.org/
[1088] Ministry of Health. (2007). *Guidelines for the control of multidrug-resistant organisms in New Zealand*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/system/files/documents/publications/guidelines-for-control-of-multidrug-resistant-organisms-dec07.pdf
[1089] Ministry of Health. (2002). *Guidelines for the control of methicillin-resistant Staphylococcus aureus in New Zealand*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/system/files/documents/publications/mrsa.pdf
[1090] Institute of Environmental Science and Research Limited (ESR). (n.d.). Specialist testing. Retrieved 16 November, 2021, from https://www.esr.cri.nz/home/specialist-testing?DepartmentTitle=&start=60

auris, are occurring in the US with person-to-person transmission,[1091] but we are not consistently screening for this organism.

Aotearoa New Zealand's diagnostic laboratories are relatively fragmented, comprising a mix of both public and community/private labs. There is a basic level of linking up through the New Zealand Microbiology Network, which connects clinical laboratories to provide timely and consistent responses to issues relating to laboratory testing and to ensure regular communication between microbiology laboratories in Aotearoa New Zealand.

… the lab network has a number of issues that impede transformation of data into action. The primary issue is **a lack of standardisation**.

However, the lab network has a number of issues that impede transformation of data into action. The primary issue is a lack of standardisation. With no standard approach to testing and data management, it is difficult to collate data and draw national insights. When it comes to testing, different labs may use different AST methods, have different standards for interpreting AST results, use different PCR panels (see example below), or have different levels of access to the technologies and capabilities needed for specific techniques. When it comes to data management, different systems and reporting styles make it difficult to bring data together into a national dataset. Standardisation of testing and data management would help considerably. There is scope to consider expanding this standardisation to animal, plant, and environmental health as well.

Legionellosis detection as an example of variable lab practices

Some labs use urinary antigen testing to detect legionellosis while others use PCR. Among the increasing number that use PCR, the PCR panels differ, with some only designed to indicate the presence of a *Legionella* spp. generally, and others able to discriminate between different species such as *L. longbeachae* or *L. pneumophila*. This results in inconsistent surveillance of legionellosis, further complicated by the fact that labs do not always refer their positive samples to ESR.[1092]

There is a need to better coordinate, standardise, connect and upskill diagnostic labs to ensure that complete, accurate, and high-quality data is collected and assessed at the national level. The New Zealand National Antimicrobial Susceptibility Testing Committee (see section 4.3.1) has undertaken some work to improve diagnostic labs' capabilities and make antibiograms accessible; there is scope to elevate and enhance these activities.

There is a need to better coordinate, standardise, connect and upskill diagnostic labs to ensure that complete, accurate and high-quality data is collected and assessed at the national level.

[1091] Centers for Disease Control and Prevention. (2021, 27 October). Tracking *Candida auris*. Retrieved 17 November, 2021, from https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html
[1092] Dyet, K. (2021). Personal communication.

Improving surveillance in animals

As discussed in section 4.3.2, AMR surveillance in animals in Aotearoa New Zealand is limited and is not well connected to human AMR monitoring.

MPI is working to improve its surveillance of AMR in agriculturally important animals. Working with stakeholders, MPI is developing a draft AMR surveillance programme. This programme utilises submissions by veterinarians to the veterinary diagnostic laboratories, where sensitivity testing has been conducted, to provide information on the prevalence and trends in AMR across a number of pathogens that may cause disease in both animals and humans. This system will provide a more comprehensive overview of the prevalence of AMR in animal populations. Funding would be required to implement this proposal, and MPI is exploring options in this area.

In addition, there are examples of industry-led improvements. For example, herd-level testing of dairy cattle is being trialled in Aotearoa New Zealand,[1093] with some dairy vets are now participating in the project. AST is available and can theoretically be undertaken directly from samples taken by the milk processor, making it easy for farms to have testing done.[1094] Early data has already shown that susceptibility status differs from farm to farm, which highlights how important local susceptibility data is for developing future farm-specific antimicrobial management plans.

As discussed in section 4.3.2, several ad hoc studies have identified AMR in companion animals. We need a better understanding of the prevalence of AMR carriage among the companion animal population, given the close contact between people and their pets. Incorporating companion animals into integrated national AMR surveillance would also help to reveal whether there is transmission of MDROs or resistance genes between pets and people, and the relative importance of this transmission route. A paper presented at the 2020 European Congress of Clinical Microbiology and Infectious Diseases suggests that zoonotic transfer of MDROs between humans and pets is possible, as shown by genetic matching of MDRO isolates.[1095] However, only a small number of matches were made, which further suggests that the transmission route between humans and pets may not be a significant factor in MDRO acquisition.

We can look to overseas examples for inspiration

There are many countries that have much more developed surveillance and monitoring systems for AMR in animals compared to Aotearoa New Zealand. Some examples are collated below in Table 13. Denmark was one of the first countries to establish a surveillance and monitoring system for AMR that encompassed animals, in 1995 (the Danish Integrated Antimicrobial Resistance Monitoring and

Denmark was one of the first countries to establish a surveillance and monitoring system for AMR including in animals in 1995.

[1093] Castle, R., & McDougall, S. (2019). Introducing herd level antimicrobial susceptibility data into the veterinarian-dairy farmer relationship. *Australian Veterinary Journal, 97*(8), 289-289. https://doi.org/10.1111/avj.12813

[1094] Elanco. (2021). Dairy antibiogram. Retrieved 12 November, 2021, from https://dab.elanco.co.nz/

[1095] Hackmann, C., Gastmeier, P., Gruhl, D., *et al.* (2020. *The transmission risk of multidrug-resistant organisms between pets and humans: An exploratory case control study protocol*. Paper presented at the European Congress of Clinical Microbiology and Infectious Diseases. Retrieved from https://drive.google.com/file/d/1mmQiVFsXF09Sznw2JomcJ8zU_uFuj1DE/view; Gallagher, G.M. (2020). Study finds pets not a substantial reservoir for human multidrug-resistant infections. *Contagion Live*. Retrieved from https://www.contagionlive.com/view/study-finds-pets-not-a-substantial-reservoir-for-human-multidrugresistant-infections

Research Programme, 'DANMAP') (see Figure 39).[1096]

In Denmark, bacterial samples are routinely collected from both food and animals throughout the production line: at farms, vet practices, slaughterhouses, and retail stores.[1097] Isolates are tested at either private labs or through regional food control labs; this data is then collected by the National Food Institute (a unit of the Technical University of Denmark), which researches and communicates sustainable and value adding food and health solutions.[1098] This provides detailed information to support management actions. For example, it identifies the industries that have the highest percentage of AMR, to what antibiotics, and how these trends have changed year-to-year for *Campylobacter jejuni*, *Salmonella* species, and other bacteria.

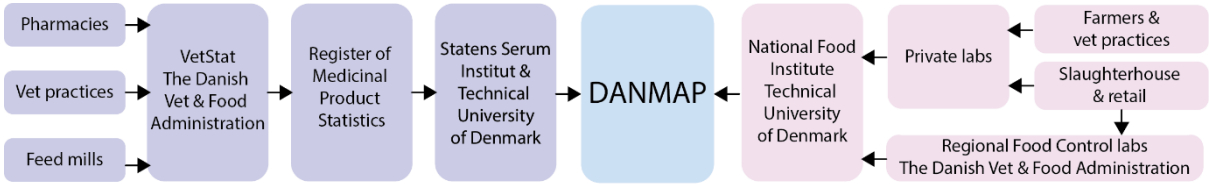


Figure 39: Data flow of food and food animal inputs into the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP). Diagram is adapted DANMAP 2019.[1099]

Further, Denmark collects information on antimicrobial use in animals as well. The Danish example may serve as inspiration to expand our current sampling and testing, potentially utilising our existing National Microbiological Database programme.[1100] It would be useful to examine how Denmark's National Food Institute collects AMR data from private labs and feeds this into DANMAP. In Aotearoa New Zealand, this data is not provided for collation by any one organisation (unless it is notifiable) and there is opportunity to channel more data into regular AMR surveillance. Data could potentially be provided to central government or to another coordinating body.

Table 13: AMR surveillance programmes in animals and food.

Country	Programme	Coordination
Norway[1101]	NORM-VET monitoring programme for AMR in the veterinary and food production sectors. Established in 2000.	NORM-VET is coordinated by the Norwegian Veterinary Institute. It feeds into the NORM surveillance programme (human AMR).
Denmark[1102]	Danish Integrated AMR Monitoring and Research Programme (DANMAP). Established in 1995.	DANMAP is run in collaboration by the National Food Institute and the National Veterinary Institute (human health components are run by the Statens Serum Institute).
Canada	Canadian Integrated Program for AMR Surveillance (CIPARS). Established in 2000. On-farm surveillance from 2006 (grower-finisher	The wider CIPARS (including human AMR) is coordinated by Public Health Agency of Canada. Private industry (including vets, livestock producers and abattoirs) are key collaborators.[1104]

[1096] Hammerum, A.M., Heuer, O.E., Emborg, H.-D.*, et al.* (2007). Danish integrated antimicrobial resistance monitoring and research program. *Emerging Infectious Diseases, 13*(11), 1632-1639. https://doi.org/10.3201/eid1311.070421
[1097] Ibid.
[1098] DTU Orbit. (n.d.). National Food Institute. Retrieved 29 October, 2021, from https://orbit.dtu.dk/en/organisations/national-food-institute
[1099] National Food Institute, Statens Serum Institut, & Danish Health Data Authority. (2019). *DANMAP 2019: Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark*. Denmark: Retrieved from https://www.danmap.org/reports/2019
[1100] Ministry for Primary Industries. (n.d., 14 September 2021). National Microbiological Databse programme. Retrieved 9 December, 2021, from https://www.mpi.govt.nz/food-business/food-monitoring-surveillance/national-microbiological-database-programme-meat/national-microbiological-database-programme/
[1101] Norwegian Veterinary Institute. (n.d.). NORM-VET reports. Retrieved 29 Septmeber, 2021, from https://www.vetinst.no/en/surveillance-programmes/norm-norm-vet-report
[1102] DANMAP. (2021). About DANMAP. Retrieved 29 September, 2021, from https://www.danmap.org/about-danmap
[1104] Deckert, A., Agunos, A., Avery, B.*, et al.* (2015). CIPARS: A one-health approach to antimicrobial resistance surveillance. *Online Journal of Public Health Informatics, 7*(1), e68. https://doi.org/10.5210/ojphi.v7i1.5734

Country	Programme	Coordination
	pigs), 2013 (broiler chickens) feedlot cattle and turkeys (2016).[1103]	
Netherlands	Monitoring of AMR and antibiotic usage in Animals. Established in 2002.	Reporting by the Central Veterinary Institute, the Netherlands Veterinary Medicines Authority, Utrecht University, the Dutch Food and Consumer Safety Authority, and the National Institute for Public Health and the Environment. Reporting is in conjunction with NethMAP (human AMR).
Germany	German veterinary monitoring system collects clinical AMR data from companion and food-producing animals. Established in 2001.[1105]	Data feeds into wider reporting on Antibiotic Consumption and the Spread of Antibiotic Resistance in Human and Veterinary Medicine in Germany.[1106]
United States	National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS).[1107] Established in 1996.	Collaboration among state and local public health departments, CDC, the US FDA and the US Department of Agriculture.[1108]

Baseline surveys in the environment and plant sectors are an important first step

As outlined in section 4.3.4, resistant pathogens have been detected in Aotearoa New Zealand's environment. However, there is a knowledge gap around the impact of environmental AMR on human, animal, and plants. We also don't know much about AMR in the crops and plants sector, which is a barrier to understanding the role it plays in the overall picture of AMR. The creation of new, rapid, and inexpensive tests and tools to diagnose plant diseases and characterise the resistome of the plant production environment will help to establish the resistance profile and issues in plants.

Environmental DNA could be collected **more regularly and systematically** to inform public health risk arising from both resistant microbes, and microbes generally.

A comprehensive and well-designed baseline study to inform future work would be an important first step to bringing the environment into an integrated, holistic approach to AMR. Broad surveillance may not be practical or financially feasible, but priority settings could be targeted such as sites impacted by human and or animal waste, sites where there may be opportunities for risk of exposure (e.g. specific rivers), or areas where we can track introduction of AMR (e.g. airports). To be most effective, any environmental monitoring should be designed around

There is potential for wastewater surveillance to play an ongoing role in AMR surveillance.

[1103] Government of Canada. (2020). *Canadian integrated program for antimicrobial resistance surveillance (CIPARS) 2018: Design and methods*. Guelph, Ontario: Public Health Agency of Canada. Retrieved from https://www.canada.ca/content/dam/phac-aspc/documents/services/surveillance/canadian-integrated-program-antimicrobial-resistance-surveillance-cipars/cipars-reports/2018-annual-report-design-methods/2018-annual-report-design-methods.pdf

[1105] Schwarz, S., Alesík, E., Grobbel, M.*, et al.* (2007). The BfT-GermVet monitoring program--aims and basics. *Berliner und Munchener Tierarztliche Wochenschrift, 120*(9-10), 357-362. https://doi.org/10.2376/0005-9366-120-357

[1106] Mesa Varona, O., Chaintarli, K., Muller-Pebody, B.*, et al.* (2020). Monitoring antimicrobial resistance and drug usage in the human and livestock sector and foodborne antimicrobial resistance in six European countries. *Infection and Drug Resistance, 13*, 957-993. https://doi.org/10.2147/IDR.S237038

[1107] https://www.cdc.gov/narms/index.html

[1108] United States Food and Drug Administration, C.f.D.C.a.P., & United States Department of Agriculture. (2020). *The national antimicrobial resistance monitoring system: Strategic plan 2021-2025*.

surveillance that is likely to gather actionable insights. Consideration should also be given to regularity to allow changes to be tracked over time.

Environmental DNA could be collected more regularly and systematically to inform public health risk arising from both resistant microbes, and microbes generally.[1109] The COVID-19 pandemic has led to widespread use of tools and approaches that have not previously been used routinely – for example, wastewater surveillance.[1110] There is potential for wastewater surveillance to play an ongoing role in AMR surveillance. A pilot study to test for the presence of antimicrobials, AMR genes, and organisms at one wastewater site is underway at ESR. Early findings suggest that wastewater monitoring may provide useful information on the development and spread of AMR in Aotearoa New Zealand.

However, genomic surveillance does not capture all forms of resistance and cannot replace the use of conventional phenotyping techniques. The approaches should be viewed as complementary.

5.4.2 Surveillance of diseases and outbreaks

We need better surveillance in human health

As with AMR data, there is opportunity to enhance surveillance for infectious diseases and outbreaks in an integrated, systematic, and nationally coordinated fashion that better supports a focus on equity. This will allow better use of data to proactively improve clinical decision making. Monitoring of human infections relies on health practitioners creating a case record in EpiSurv if a notifiable disease is suspected. This is a legal requirement. EpiSurv[1111] is Aotearoa New Zealand's national notifiable disease surveillance database, which ESR operates on behalf of MoH.

There are large numbers of disconnected surveillance systems for infectious diseases in Aotearoa New Zealand and this can make it difficult to identify gaps within the current system.[1112]

Some areas for improvement may include:

- Surveillance needs to include analysis of outbreaks, causal factors and appropriate interventions.
- Surveillance systems must be fit-for-purpose. An area where this could be improved is for infections that are often asymptomatic or latent, such as many STIs.
- Surveillance should draw from all parts of the health system including GPs, DHBs, hospitals, labs, and other health-related clinics.
- Improved ability to detect emerging infectious diseases before they have resulted in large numbers of infections is necessary.[1113]
- Ensuring that relevant data is collected to provide information on equity and to monitor equity outcomes over time.

[1109] Phiri, B.J., Hayman, D.T.S., Biggs, P.J*., et al.* (2020). Microbial diversity in water and animal faeces: A metagenomic analysis to assess public health risk. *New Zealand Journal of Zoology*, 1-14. https://doi.org/10.1080/03014223.2020.1831556
[1110] Hendriksen, R.S., Bortolaia, V., Tate, H*., et al.* (2019). Using genomics to track global antimicrobial resistance. *Frontiers in Public Health, 7*, 242. https://doi.org/10.3389/fpubh.2019.00242
[1111] Institute of Environmental Science and Research Limited (ESR). (2021). Sexually transmitted infection (STI) surveillance (dashboard). Retrieved 1 October, 2021, from https://www.esr.cri.nz/our-services/consultancy/public-health/sti/
[1112] Baker, M.G., Easther, S., & Wilson, N. (2010). A surveillance sector review applied to infectious diseases at a country level. *BMC Public Health, 10*(1), 332. https://doi.org/10.1186/1471-2458-10-332
[1113] Baker, M.G., & Fidler, D.P. (2006). Global Public Health Surveillance under New International Health Regulations. *Emerging Infectious Diseases, 12*(7), 1058-1065. https://doi.org/10.3201/eid1207.051497

As with AMR surveillance and data, the government's recent investment in health sector digital infrastructure and capability has scope to support improvements.

There are large numbers of disconnected surveillance systems for infectious diseases in Aotearoa New Zealand and this can make it difficult to identify gaps within the current system.

A kotahitanga approach

We need to connect up data from human, animal, food, plant and environmental sources. Aotearoa New Zealand's national laboratories for animals (the Animal Health Laboratory) and plants and the environment (the Plant Health and Environment Laboratory) are based at MPI. Compared with human infection monitoring, animal monitoring is less coordinated and involves private labs in addition to the Animal Health Laboratory. Plant data is periodically reviewed in detail but has no ongoing systematic analysis.[1114]

Human and animal health infectious diseases and microbes are reported on separately and equivalent data is not collected for each of these. However, several significant diseases in Aotearoa New Zealand, such as campylobacteriosis and salmonellosis, are zoonotic or foodborne. We need a plan, informed by public health epidemiology expertise, to ensure that helpful data is collected in comparable formats from human, animal, food and environmental sources. This is key to a system that is capable of generating insights to inform action.

5.4.3 Technology to facilitate better detection and surveillance

Pathogen identification (including the identification of drug-resistant pathogens) can be done using phenotypic methods such as antigen testing and culture-based tests and genotypic methods such as polymerase chain reaction (PCR) and WGS. Different diagnostic methods, which have their advantages and disadvantages, are explored below. It should be noted that while new technologies can help, wider use of existing approaches can also help to combat infectious disease and AMR.[1115]

Lab-based testing in human health

Lab testing involves both genotypic and phenotypic techniques

Labs in Aotearoa New Zealand conduct both genotypic and phenotypic diagnostics to identify the cause of an infection. The versatility, sensitivity, and potential for automation represent significant advantages for genotypic techniques like PCR.[1116]

Other methods include antigen testing, aptamers (a type of synthetic antibody), identification of proteins by mass spectrometry, and assays based on specific biochemical reactions by the

[1114] Veerakone, S., Tang, J.Z., Ward, L.I., *et al.* (2015). A review of the plant virus, viroid, liberibacter and phytoplasma records for New Zealand. *Australasian Plant Pathology, 44*(5), 463-514. https://doi.org/10.1007/s13313-015-0366-3

[1115] Lago, A., Godden, S.M., Bey, R., *et al.* (2011). The selective treatment of clinical mastitis based on on-farm culture results: I. Effects on antibiotic use, milk withholding time, and short-term clinical and bacteriological outcomes. *Journal of Dairy Science, 94*(9), 4441-4456. https://doi.org/10.3168/jds.2010-4046

[1116] Rath, P.-M., & Steinmann, J. (2018). Overview of commercially available PCR assays for the detection of *Aspergillus* spp. DNA in patient samples. *Frontiers in Microbiology, 9*(740). https://doi.org/10.3389/fmicb.2018.00740

organism.[1117] This removes the need to culture bacteria, which greatly reduces detection timeframes.

Speeding up susceptibility testing can support patient care and AMS

Rapid AST is a tremendous aid to using antimicrobials optimally. It provides an opportunity for clinicians to adjust treatment in a timely manner based on the susceptibility profile of the pathogen at hand, changing from a broad-spectrum antibiotic to one that is narrow spectrum, or to change from an ineffective agent to one that is effective. The wide use of rapid diagnostics to support appropriate antimicrobial use would likely help to reduce the development of AMR in addition to improving treatment.

Culture-based AST, the mainstay of AST in Aotearoa New Zealand at present (see section 5.4.1), can be sped up through the use of automated systems, microfluidics, and lasers and fluorescent dyes to detect the organism at much lower concentrations. There are also rapid growth-based susceptibility methods being developed for some bacterial species, which generate results more quickly than traditional culture-based methods.[1118] Genotypic alternatives to AST exist too – for example, the genome of a pathogen can be sequenced, working to identify specific genetic sequences that are known to be associated with drug-resistance.[1119] New techniques are exploring methods to detect MRSA using DNA nanosensors.[1120]

Point-of-care testing in human health

Point-of-care testing, where a diagnostic test such an antigen test is conducted without specialist lab services, can support rapid diagnostics. Rapid point-of-care testing can also support AMS, by providing diagnostic confirmation of the cause of an infection to guide judicious prescribing. For example, if testing in a GP's office confirmed that a patient's sore throat was caused by a virus, antibiotic prescribing could be ruled out.[1121]

In Aotearoa New Zealand point-of-care testing devices are not subject to effective regulations, which is likely to be addressed in the upcoming Therapeutic Products Bill.

In their call for action on AMR issued in 2017, the AMR Action Planning Group (a joint group between MoH and MPI) sought to have an increase in rapid on-site testing explored.[1122] But in Aotearoa New Zealand and abroad, uptake of point-of-care testing remains limited.

Because point-of-care testing is not conducted in the laboratory under controlled conditions there are caveats around the reliability of the test results. In Aotearoa New Zealand point-of-care testing

[1117] Reali, S., Najib, E.Y., Treuerné Balázs, K.E., *et al.* (2019). Novel diagnostics for point-of-care bacterial detection and identification. *RSC Advances, 9*(37), 21486-21497. https://doi.org/10.1039/C9RA03118A
[1118] Åkerlund, A., Jonasson, E., Matuschek, E., *et al.* (2020). EUCAST rapid antimicrobial susceptibility testing (RAST) in blood cultures: Validation in 55 European laboratories. *Journal of Antimicrobial Chemotherapy, 75*(11), 3230-3238. https://doi.org/10.1093/jac/dkaa333
[1119] Khan, Z.A., Siddiqui, M.F., & Park, S. (2019). Current and emerging methods of antibiotic susceptibility testing. *Diagnostics, 9*(2), 49.
[1120] Wang, J.-C., Tung, Y.-C., Ichiki, K., *et al.* (2020). Culture-free detection of methicillin-resistant *Staphylococcus aureus* by using self-driving diffusometric DNA nanosensors. *Biosensors and Bioelectronics, 148*, 111817. https://doi.org/10.1016/j.bios.2019.111817
[1121] Cohen, J.F., Pauchard, J.Y., Hjelm, N., *et al.* (2020). Efficacy and safety of rapid tests to guide antibiotic prescriptions for sore throat. *Cochrane Database of Systematic Reviews, 6*. https://doi.org/10.1002/14651858.CD012431.pub2
[1122] Ministry of Health and Ministry for Primary Industries. (2017). *Antimicrobial Resistance: New Zealand's current situation and identified areas for action.* Wellington, NZ: Ministry of Health and Ministry for Primary Industries.

devices are not subject to effective regulations, which is likely to be addressed in the upcoming Therapeutic Products Bill.[1123]

The New Zealand Institute of Medical Laboratory Science has issued a set of guidelines[1124] for the use of point-of-care testing, developed by the New Zealand Point-of-Care Testing Advisory Group. The guidelines, first released in 2014 and updated in 2018, identify a number of potential concerns with point-of-care testing, including the possibility of inaccurate results guiding clinical decision making, inadequate documentation of results, and increased workload for staff. In addition, with many rapid diagnostics being culture-independent, cultures will not be available for subsequent analyses unless deliberately factored into sampling. The New Zealand Institute of Medical Laboratory Science further calls for a strong framework of quality guidelines before point-of-care testing replaces laboratory testing.

An example of a point-of-care test in Aotearoa New Zealand

In one local example, South Link Health Services trialled a point-of-care diagnostic for C-reactive protein (CRP), which is a marker of inflammation that can be measured in blood. CRP concentrations tend to be higher in bacterial infections compared to viral infections. In this trial, a score of 20 mg/L or less suggested that a patient did not need antibiotics (score associated with an increased chance of a mild, usually viral, infection) while higher scores suggested that antibiotics might be appropriate (associated with an increased chance of a more serious, usually bacterial, infection). This test was rolled out in a few practices: those with low prescribing rates, moderate prescribing rates, and high prescribing rates. Prescriptions for antibiotics dropped by 40% in the high users, moderate users also dropped (but by less) while low users actually had a slight increase in antibiotic prescriptions.[1125]

A recent survey and review of point-of-care devices available in Europe[1126] found 72 brand-named devices in use for 56 infections (including viral, parasitic and bacterial infections), the most common uses being for influenza, HIV, malaria and legionnaire's disease. The survey found that, "other than for diagnosis, point-of-care testing was not widely used for public health functions such as disease surveillance, national reporting of infectious diseases or infection control." It also identified that point-of-care testing only infrequently replaced traditional diagnostic testing. The study reported that point-of-care testing could be used to improve the appropriateness of antimicrobial prescription.

Rapid testing for COVID-19

In the wake of the COVID-19 pandemic, a plethora of rapid antigen tests that can deliver results in as little as 15 minutes have been developed and deployed overseas.[1127] Now, these are available in Aotearoa New Zealand too – although PCR testing of nasal or saliva swabs remains the mainstay of Aotearoa New Zealand's COVID-19 testing approach.[1128] Rapid antigen tests are less sensitive than

[1123] Musaad, S.M.A., & Herd, G.C.E. (2019). Point-of-care testing governance in New Zealand through the lens of quality: An update on a national regulatory framework. *New Zealand Medical Journal, 132*(1499), 56-63.
[1124] New Zealand Point-of-Care Testing Advisory Group. (2018). *New Zealand best practice guidelines for point-of-care testing*. Retrieved from https://www.nzimls.org.nz/point-of-care-testing.html
[1125] Tilyard, M. (2021). Personal communication.
[1126] Hocking, L., George, J., Broberg, E.K*., et al.* (2021). Point of care testing for infectious disease in Europe: A scoping review and survey study. *Frontiers in Public Health, 9*(1562). https://doi.org/10.3389/fpubh.2021.722943
[1127] Peeling, R.W., Olliaro, P.L., Boeras, D.I*., et al.* (2021). Scaling up COVID-19 rapid antigen tests: Promises and challenges. *The Lancet Infectious Diseases, 21*(9), e290-e295. https://doi.org/10.1016/S1473-3099(21)00048-7; FIND. (n.d.). FIND evaluation of SARS-CoV-2 antigen (AG) detecting tests. Retrieved 10 December, 2021, from https://www.finddx.org/covid-19/sarscov2-eval/; Vandenberg, O., Martiny, D., Rochas, O*., et al.* (2021). Considerations for diagnostic COVID-19 tests. *Nature Reviews Microbiology, 19*(3), 171-183. https://doi.org/10.1038/s41579-020-00461-z
[1128] Unite Against COVID-19. (2021, 3 December). How testing works. Retrieved 10 December, 2021, from https://covid19.govt.nz/testing-and-tracing/covid-19-testing/how-testing-works/; Ministry of Health. (2021, 9 December). Rapid antigen testing. Retrieved 10 December, 2021, from https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-health-advice-public/assessment-and-testing-covid-19/rapid-antigen-testing

PCR tests, but are still useful for quickly identifying people in the acute infection phase with high viral loads, when they are likely to be most contagious.[1129] The WHO recommends use of rapid antigen tests with a minimum of 80% sensitivity and 97% specificity.[1130]

Different countries have used rapid antigen tests in different ways, from mass testing to focusing on high-risk asymptomatic people. For example, the UK uses regular testing to find cases in high-risk settings, while other countries such as Italy use rapid antigen testing to screen asymptomatic travellers at the border.

Rapid testing for foodborne, animal, and plant diseases

Rapid identification of pathogens contaminating food is currently usually PCR-based and has considerable economic impact, as well as public health benefits. It is widely available for common organisms including *Listeria* spp., *Salmonella* spp. and *E. coli* from laboratories including ESR, Hill Laboratories,[1131] and AsureQuality.[1132] Routine food testing would benefit from wider use of WGS. This would allow greater surveillance by increasing understanding of how resistant bacteria are moving through the food chain and consequently what action to take to reduce risk.[1133]

As with human health, point-of-care tests for infections in animals exist and continue to be developed. They have scope to support more judicious antimicrobial use. For example, a North American study found that the use of on-farm culture-based testing systems to identify when cows with mastitis symptoms would benefit from antibiotics, as compared to simply treating all cows with symptoms, led to a halving of antibiotic use without compromising animal health.[1134] An Ōtepoti Dunedin-based company, Mastaplex, has developed an on-farm system for mastitis diagnosis and evaluation of antibiotic susceptibility to guide antibiotic use that returns results within 24 hours.[1135] Evaluation of the system showed that it could support reduced antibiotic use.[1136] The test is being rolled out through veterinary practices in New Zealand.[1137]

Routine food testing would benefit from wider use of whole genome sequencing.

In plant health, genetic techniques have supported more rapid diagnostics. For example, a PCR-based assay for rapidly diagnosing Psa infection of kiwifruit vines has been developed by Plant and Food Research.[1138] Development of a

[1129] Crozier, A., Rajan, S., Buchan, I., *et al.* (2021). Put to the test: Use of rapid testing technologies for COVID-19. *BMJ, 372*, n208. https://doi.org/10.1136/bmj.n208
[1130] World Health Organization. (2021). *Antigen-detection in the diagnosis of SARS-CoV-2 infection: Interim guidance*. Retrieved from https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays
[1131] Hill Laboratories. (n.d.). Microbiology testing. Retrieved 16 November, 2021, from https://www.hill-laboratories.com/analytical-testing/food-microbiology-testing/
[1132] AsureQuality. (n.d.). Rapid micro testing. Retrieved 16 November, 2021, from https://www.asurequality.com/services/laboratory-testing/micro-rapid-testing/
[1133] Collineau, L., Boerlin, P., Carson, C.A., *et al.* (2019). Integrating whole-genome sequencing data into quantitative risk assessment of foodborne antimicrobial resistance: A review of opportunities and challenges. *Frontiers in Microbiology, 10*(1107). https://doi.org/10.3389/fmicb.2019.01107
[1134] Lago, A., Godden, S.M., Bey, R., *et al.* (2011). The selective treatment of clinical mastitis based on on-farm culture results: I. Effects on antibiotic use, milk withholding time, and short-term clinical and bacteriological outcomes. *Journal of Dairy Science, 94*(9), 4441-4456. https://doi.org/10.3168/jds.2010-4046
[1135] Mastaplex. (n.d.). About. Retrieved 17 November, 2021, from https://www.mastaplex.com/about
[1136] Bates, A., Laven, R., Bork, O., *et al.* (2020). Selective and deferred treatment of clinical mastitis in seven New Zealand dairy herds. *Preventive Veterinary Medicine, 176*, 104915. https://doi.org/10.1016/j.prevetmed.2020.104915
[1137] The Vet Centre. (n.d.). Mastatest – Our innovative new toy. Retrieved 17 November, 2021, from https://www.thevetcentrenorthland.co.nz/special-offer-item/mastatest-our-innovative-new-toy
[1138] Jayaraman, J., Chatterjee, A., Hunter, S., *et al.* (2021). Rapid methodologies for assessing *Pseudomonas syringae pv. actinidiae* colonization and effector-mediated hypersensitive response in kiwifruit. *Molecular Plant-Microbe Interactions®, 34*(8), 880-890. https://doi.org/10.1094/MPMI-02-21-0043-R

loop-mediated isothermal implication (LAMP) assay (discussed below) has scope to make it easier and cheaper to detect *Phytophthora agathidicida* (the cause of kauri dieback) as well as being more accurate than culture-based techniques.[1139]

Genetic and genomic technologies

Using genetic techniques to identify drug-resistant microbes and other pathogens

The two most widely applied genotypic techniques used to identify the presence of drug-resistance genes are PCR (through the amplification of target genes) and WGS. Both techniques are useful and have different strengths and weaknesses. Genotypic and phenotypic susceptibility testing may be used in conjugation to overcome some of the weaknesses.

A drawback associated with any genetic approach to testing for antimicrobial susceptibility is that, while we have good data for some microbes correlating genes with phenotype (i.e. behaviour of microbe), there are large numbers of microbes where data is lacking, and it would not be possible to predict a microbe's phenotype from its genotype. This means that markers for resistance that we don't know about might be missed, or genes that we think are associated with resistance might not actually be clinically relevant. Further, conventional genetic tests don't allow researchers to detect whether a certain gene is being expressed, so it is possible that a pathogen might carry a resistance gene but not express it (e.g. microbes with adaptive resistance mechanisms, see section 2.3.3).

In addition, PCR requires gene targets to be pre-selected so might miss resistance genes that aren't included in the test, including those that aren't known (while WGS has the advantage of being more comprehensive, covering the entire genome).

Furthermore, PCR and WGS require relatively sophisticated equipment and IT systems as well as trained personnel. This means that in many situations these technologies are best suited to use in a lab and not at the point-of-care. However, technological advancements that make genetic and genomic tests easier to conduct may increasingly make point-of-care testing possible. For example, amplification techniques besides PCR such as nucleic acid sequence-based amplification and LAMP are more easily automated for use in non-laboratory settings.[1140] LAMP assays for COVID-19 diagnosis have been developed, with a recent systematic review and meta-analysis finding both sensitivity and selectivity of greater than 95%.[1141]

A study in Melbourne used WGS to infer transmission pathways of drug-resistant organisms within hospitals.

Data from this study revealed that transmission was occurring on different wards than expected, leading to a change in focus for interventions and altered cleaning practices.

A key advantage of PCR and other gene amplifying techniques is that by using microwell plates and a range of primers with specific nucleotide sequences for different organisms and resistance genes (e.g. Multiplex PCR), multiple organisms, and whether they are likely to be resistant or not, can be tested for in a single run. Syndromic panels (panels of multiple PCR primers to test for organisms giving rise to specific

[1139] Winkworth, R.C., Nelson, B.C.W., Bellgard, S.E., *et al.* (2020). A LAMP at the end of the tunnel: A rapid, field deployable assay for the kauri dieback pathogen, *Phytophthora agathidicida*. *PLOS One, 15*(1), e0224007. https://doi.org/10.1371/journal.pone.0224007

[1140] bioMérieux. (n.d.). NUCLISENS EASYQ®. Retrieved 16 November, 2021, from https://www.biomerieux-diagnostics.com/nuclisens-easyqr

[1141] Subali, A.D., & Wiyono, L. (2021). Reverse Transcriptase Loop Mediated Isothermal Amplification (RT-LAMP) for COVID-19 diagnosis: A systematic review and meta-analysis. *Pathogens and Global Health, 115*(5), 281-291. https://doi.org/10.1080/20477724.2021.1933335

syndromes e.g. gastrointestinal infection) have been approved by the FDA and are widely commercially available with assay times of 2-6 hours.[1142] Multiplex PCR is currently used for the majority of gastrointestinal infection testing done in Aotearoa New Zealand.[1143]

The downsides to these comprehensive panels are their relatively expensive nature and their inability to detect novel or unexpected organisms or modes of resistance. They also have relatively high false positive and false negative rates for clinical samples and, for panels that detect resistance, the organism causing the most significant infection may not be the one carrying the resistance gene detected.[1144] Panels need to be updated to ensure they include relevant microbes and resistance profiles.[1145]

Whole genome sequencing

WGS can be indispensable for preventing and controlling infectious diseases. WGS allows incidence monitoring of pathogens at the genotype level and provides information on the spread of the infection.[1146] As described above, it can also be used to identify whether a given pathogen is likely to be drug-resistant. Information gathered through WGS can support action. For example, a study in Melbourne used WGS to infer transmission pathways of drug-resistant organisms within hospitals.[1147] Data from this study revealed that transmission was occurring on different wards than expected, leading to a change in focus for interventions and altered cleaning practices. In addition to being valuable for studying pathogen transmission, data from WGS could be used in the future to assist with vaccine and other drug development and identifying emerging trends in resistance.[1148]

WGS continues to become more efficient and cost-effective for use in both surveillance and diagnosis.[1149] WGS has become more prominent in public health surveillance worldwide, including in Aotearoa New Zealand, but there is not yet much data on the best way to integrate genomic data into traditional epidemiological investigations.[1150] Many jurisdictions, including the US, UK, and Europe routinely use WGS in public health surveillance.

There are multiple instances where WGS has been used or is in use to support epidemiological investigations in Aotearoa New Zealand in human and animal health, with studies on a range of pathogens including *Yersinia* spp.,[1151] *Salmonella enterica* serovar Typhimurium,[1152] *Campylobacter*

[1142] Dien Bard, J., & McElvania, E. (2020). Panels and syndromic testing in clinical microbiology. *Clinics in Laboratory Medicine, 40*(4), 393-420. https://doi.org/10.1016/j.cll.2020.08.001
[1143] Wright, J. (2021). Personal communication.
[1144] Leech, S. (2019). A closer look at multiplex panels for respiratory, gastrointestinal, and blood pathogens. *Clinical Lab Manager*, 14-15. Retrieved from https://www.clinicallabmanager.com/technology/a-closer-look-at-multiplex-panels-for-respiratory-gastro-intestinal-and-blood-pathogens-195
[1145] Imdad, A., Retzer, F., Thomas, L.S., *et al.* (2018). Impact of culture-independent diagnostic testing on recovery of enteric bacterial infections. *Clinical Infectious Diseases, 66*(12), 1892-1898. https://doi.org/10.1093/cid/cix1128
[1146] Revez, J., Espinosa, L., Albiger, B., *et al.* (2017). Survey on the use of whole-genome sequencing for infectious diseases surveillance: Rapid expansion of European national capacities, 2015-2016. *Front Public Health, 5*, 347. https://doi.org/10.3389/fpubh.2017.00347
[1147] Gorrie, C.L., Da Silva, A.G., Ingle, D.J., *et al.* (2021). Key parameters for genomics-based real-time detection and tracking of multidrug-resistant bacteria: A systematic analysis. *The Lancet Microbe, 2*(11), e575-e583. https://doi.org/10.1016/S2666-5247(21)00149-X
[1148] bioMérieux. (2020). Transforming infectious disease management with whole genome sequencing. Retrieved from https://www.biomerieuxconnection.com/2020/04/16/transforming-infectious-disease-management-with-whole-genome-sequencing/
[1149]European Centre for Disease Prevention and Control. (2018). *Monitoring the use of whole-genome sequencing in infectious disease surveillance in Europe 2015–2017*. Stockholm: ECDC. Retrieved from https://www.ecdc.europa.eu/sites/default/files/documents/monitoring-WGS-infectious-disease-surveillance-in-Europe-2015-2017-updated-Dec-2018.pdf
[1150] Ferdinand, A.S., Kelaher, M., Lane, C.R., *et al.* (2021). An implementation science approach to evaluating pathogen whole genome sequencing in public health. *Genome Medicine, 13*(1), 121. https://doi.org/10.1186/s13073-021-00934-7
[1151] Williamson, D.A., Baines, S.L., Carter, G.P., *et al.* (2016). Genomic insights into a sustained national outbreak of *Yersinia pseudotuberculosis*. *Genome Biology and Evolution, 8*(12), 3806-3814. https://doi.org/10.1093/gbe/evw285
[1152] Bloomfield, S., Benschop, J., Biggs, P., *et al.* (2017). Genomic analysis of *Salmonella enterica* serovar Typhimurium DT160 associated with a 14-year outbreak, New Zealand, 1998–2012. *Emerging Infectious Diseases, 23*(6), 906. https://doi.org/10.3201/eid2306.161934

spp.,[1153]MRSA,[1154] and vancomycin-resistant *Enterococcus faecalis*.[1155] WGS of all CPOs is performed and informs investigation of clusters and transmission in both hospitals and communities.[1156] In addition, ESR has been routinely sequencing all clinical STEC, *Salmonella* Typhimurium and Enteritidis, most *Vibrio parahaemolyticus*, and selected *Yersinia* since 2019 and has been integrating with Episurv data since this time for the purposes of public health and food safety investigations.[1157] The New Zealand Food Safety Science and Research Centre has a *Listeria monocytogenes* WGS programme that is underway.[1158]

WGS was also used to investigate how *Mycoplasma bovis* was introduced into Aotearoa New Zealand in 2017 (see section 3.5.1).[1159] This included sequencing of around 670 isolates: a process that can take some time, with acquisition of samples, culturing, batching for sequencing (to reduce costs) and then analysis, with models and dashboards to show phylogeny, spatial locations, clades, and inferred transmission pathways. Information is combined with epidemiological data to support the response, most recently in dealing with the Waitaha Canterbury cluster of *Mycoplasma bovis*. Similarly, sequencing for *Mycobacterium bovis* (see section 3.5 on bovine TB) has been undertaken in Aotearoa New Zealand over many years (for example, recent analysis of over 500 genomes from 1980s to 2020).[1160]

WGS was also used to investigate how ***Mycoplasma bovis*** was introduced into Aotearoa New Zealand in 2017.

Another successful application of WGS has been its use in the COVID-19 pandemic to identify variants of concern and to characterise and track clusters and transmission.[1161] WGS is of particular value when case numbers are low: being able to trace and tactically respond to cases has the greatest impact in preventing further spread of the disease. For example, whether the disease has entered via isolation breaches or where contact tracing is unable to make an epidemiological link. As the virus mutates as it spreads through a population, WGS can reveal whether there are likely links in transmission that have been missed.

[1153] Greening, S.S., Zhang, J., Midwinter, A.C., *et al.* (2021). Transmission dynamics of an antimicrobial resistant *Campylobacter jejuni* lineage in New Zealand's commercial poultry network. *Epidemics, 37*, 100521. https://doi.org/10.1016/j.epidem.2021.100521
[1154] Gonçalves da Silva, A., Baines, S.L., Carter, G.P., *et al.* (2017). A phylogenomic framework for assessing the global emergence and evolution of clonal complex 398 methicillin-resistant *Staphylococcus aureus*. *Microbial Genomics, 3*(1). https://doi.org/10.1099/mgen.0.000105
[1155] Rushton-Green, R., Darnell Rachel, L., Taiaroa, G., *et al.* Agricultural origins of a highly persistent lineage of vancomycin-resistant *Enterococcus faecalis* in New Zealand. *Applied and Environmental Microbiology, 85*(13), e00137-00119. https://doi.org/10.1128/AEM.00137-19
[1156] ESR. (2021). Personal communication.
[1157] Wright, J. (2021). Personal communication.
[1158] Institute of Environmental Science and Research Limited (ESR). (n.d.). Listeriosis in New Zealand. Retrieved 9 December, 2021, from https://www.esr.cri.nz/our-research/research-projects/listeriosis-in-new-zealand/
[1159] Browning, G., French, N., Garner, G., *et al.* (2021). *Report of the Technical Advisory Group on the Mycoplasma bovis programme* Retrieved from https://www.mbovis.govt.nz/assets/TAG-M.-bovis-report-July-2021-2.pdf; French, N. (2021). Personal communication.
[1160] Price-Carter, M., Brauning, R., de Lisle, G.W., *et al.* (2018). Whole genome sequencing for determining the source of *Mycobacterium bovis* infections in livestock herds and wildlife in New Zealand. *Frontiers in Veterinary Science, 5*(272). https://doi.org/10.3389/fvets.2018.00272; Crispell, J., Zadoks, R.N., Harris, S.R., *et al.* (2017). Using whole genome sequencing to investigate transmission in a multi-host system: Bovine tuberculosis in New Zealand. *BMC Genomics, 18*(1), 180. https://doi.org/10.1186/s12864-017-3569-x
[1161] Geoghegan, J.L., Ren, X., Storey, M., *et al.* (2020). Genomic epidemiology reveals transmission patterns and dynamics of SARS-CoV-2 in Aotearoa New Zealand. *Nature Communications, 11*(1), 1-7. https://doi.org/10.1038/s41467-020-20235-8; Geoghegan, J., Douglas, J., Ren, X., *et al.* (2021). Use of genomics to track coronavirus disease outbreaks, New Zealand. *Emerging Infectious Diseases, 27*(5), 1317. https://doi.org/10.3201/eid2705.204579; Swadi, T., Geoghegan, J., Devine, T., *et al.* (2021). Genomic evidence of in-flight transmission of SARS-CoV-2 despite predeparture testing. *Emerging Infectious Diseases, 27*(3), 687. https://doi.org/10.3201/eid2703.204714; Douglas, J., Geoghegan, J., Hadfield, J., *et al.* (2021). Real-time genomics for tracking severe acute respiratory syndrome coronavirus 2 border incursions after virus elimination, New Zealand. *Emerging Infectious Diseases, 27*(9), 2361. https://doi.org/10.3201/eid2709.211097

Data from sequencing is also uploaded to a global database which supports international response to the virus.

In another example, researchers at the University of Otago, led by Dr Htin Lin Aung, have been using WGS to unravel drug-resistant TB transmission in Myanmar, a high TB burden setting.[1162] WGS has also been deployed here in Aotearoa New Zealand to understand the introduction of TB,[1163] ongoing outbreaks and transmission patterns,[1164] and to elucidate the molecular determinants of multidrug resistant *Mycobacterium tuberculosis* isolates.[1165] In June 2021, WHO released a catalogue of mutations in *M. tuberculosis* and their association with drug resistance, based on genomes sequenced from over 38,000 isolates. This catalogue will help those using WGS to assess drug resistance in TB to understand the potential phenotypic effects of the sequences they observe.[1166]

There are many challenges associated with WGS that remain to be overcome. These include:

- Initial implementation costs and framework development.
- Need for greater expertise and training of staff to build capacity.
- Need to adapt and integrate with traditional epidemiological investigations.
- Need to integrate with historical typing methods.
- Need to communicate complex data to the people who use it.[1167]
- Establishing databases for storing digital WGS data.
- Improving the speed of processes, including transporting samples, processing and analysis and reporting.

However, research into the costs and benefits overseas have shown value in investing in these systems. In the US and Europe, lack of competition between suppliers of equipment made WGS less affordable, as well as lack of automation and cost of bioinformatics.[1168] However, these costs will likely reduce over time and were already balanced by the value in the benefits provided by the additional information. Those benefits ultimately present as reduced overall cases of illness, which is of key significance in a public health system that is under growing pressure. WGS is currently an underutilised tool in Aotearoa New Zealand.

Clinical metagenomics

Metagenomics is the study of a collection of genetic material from a mixed community of organisms. Instead of isolating a single pathogen species before conducting WGS, all organisms in a sample are sequenced together. Clinical metagenomics is an emerging technology that has several advantages over PCR testing and is starting to be implemented abroad in clinical settings.[1169] The decreasing cost of sequencing and the real-time nature of third generation sequencers like Oxford Nanopore means

[1162] Aung, H.L., Nyunt, W.W., Fong, Y.*, et al.* (2021). Genomic profiling of *Mycobacterium tuberculosis* strains, Myanmar. *Emerging Infectious Diseases, 27*(11), 2847. https://doi.org/10.3201/eid2711.210726
[1163] Mulholland, C.V., Shockey, A.C., Aung, H.L.*, et al.* (2019). Dispersal of *Mycobacterium tuberculosis* driven by historical European trade in the South Pacific. *Frontiers in Microbiology, 10*(2778). https://doi.org/10.3389/fmicb.2019.02778
[1164] Mulholland, C.V., Thorpe, D., Cursons, R.T.*, et al.* (2018). Evaluation of the rapid molecular diagnostic test for the New Zealand *Mycobacterium tuberculosis* Rangipo strain in a clinical setting. *The New Zealand Medical Journal, 131*(1478), 70-72.
[1165] Basu, I., Bower, J.E., Roberts, S.A.*, et al.* (2018). Utility of whole genome sequencing for multidrug resistant *Mycobacterium tuberculosis* isolates in a reference TB laboratory in New Zealand. *New Zealand Medical Journal, 131*(1487), 15-22.
[1166] World Health Organization. (2021). *Catalogue of mutations in Mycobacterium tuberculosis complex and their association with drug resistance*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.who.int/publications/i/item/9789240028173
[1167] Humblestone, L., Arnold, B., & Aung, H.L. (2021). Translating whole-genome-sequence data for drug-resistant *Mycobacterium tuberculosis* diagnostics in clinics. *The New Zealand Medical Journal, 134*(1533), 115-117.
[1168] Alleweldt, F., Kara, Ş., Best, K.*, et al.* (2021). Economic evaluation of whole genome sequencing for pathogen identification and surveillance–results of case studies in Europe and the Americas 2016 to 2019. *Eurosurveillance, 26*(9), 1900606.
[1169] Chiu, C.Y., & Miller, S.A. (2019). Clinical metagenomics. *Nature Reviews Genetics, 20*(6), 341-355. https://doi.org/10.1038/s41576-019-0113-7; d'Humières, C., Salmona, M., Dellière, S.*, et al.* (2021). The potential role of clinical metagenomics in infectious diseases: Therapeutic perspectives. *Drugs, 81*(13), 1453-1466. https://doi.org/10.1007/s40265-021-01572-4

that previously prohibitive hurdles (speed and cost) are now rapidly disappearing.[1170] It is now possible to generate a metagenome within the same time frame as a PCR reaction.

Initially this technology will be mainly used in uncertain, PCR-negative or high-priority cases. But as the technique becomes integrated into systems, experts foresee this technology to become the default.[1171] False positivity and negativity rates of these tests are under active investigation, but initial results point to a clear advantage over culture-based technologies.[1172] One downside of these metagenomic tests is that samples may not be kept, meaning they cannot be used to follow up cases by traditional diagnostic techniques and are not referred for surveillance.

Further research in Aotearoa New Zealand

Research groups in Aotearoa New Zealand are developing rapid diagnostics for infectious diseases and resistant pathogens. Examples are included below – this is not a comprehensive list but gives an indication of the types of work occurring. These include:

- At the University of Auckland, Associate Professor Fred Vanholsbeeck is developing laser-based techniques to identify pathogens.[1173]
- At the University of Otago, Professor Greg Cook's group is developing point-of-care testing for tuberculosis.[1174]
- At ESR, Matt Storey is leading a project to create a proof of concept implement of clinical metagenomics in a hospital setting.[1175]
- At Massey University, Dr Olin Silander is developing sequence enrichment methods for AMR profiling and identification.[1176]
- From Massey University, Professor Peter Lockhart and Dr Richard Winkworth's work on LAMP diagnostics has led to the launch of a company working to commercialise rapid genotypic tests for kauri dieback and other applications.[1177] They are also working in partnership with Pacific Island countries to utilise this technology in our broader region.[1178]

5.4.4 We can draw on overseas examples to inform our surveillance efforts

AMR surveillance

There are several examples of AMR surveillance systems in different countries, and efforts to establish systems for collating AMR data at the international level too. Examples are provided below.

[1170] Dulanto Chiang, A., & Dekker, J.P. (2020). From the pipeline to the bedside: Advances and challenges in clinical metagenomics. *The Journal of Infectious Diseases, 221*(Supplement_3), S331-S340. https://doi.org/10.1093/infdis/jiz151; Bowden, R., Davies, R.W., Heger, A., *et al.* (2019). Sequencing of human genomes with nanopore technology. *Nature Communications, 10*(1), 1869. https://doi.org/10.1038/s41467-019-09637-5

[1171] Moragues-Solanas, L., Scotti, R., & O'Grady, J. (2021). Rapid metagenomics for diagnosis of bloodstream and respiratory tract nosocomial infections: current status and future prospects. *Expert Review of Molecular Diagnostics, 21*(4), 371-380. https://doi.org/10.1080/14737159.2021.1906652

[1172] Duan, H., Li, X., Mei, A., *et al.* (2021). The diagnostic value of metagenomic next-generation sequencing in infectious diseases. *BMC Infectious Diseases, 21*(1), 62. https://doi.org/10.1186/s12879-020-05746-5

[1173] The University of Auckland. (n.d.). Take 10 with... Frédérique Vanholsbeeck. Retrieved 17 November, 2021, from https://www.auckland.ac.nz/en/science/our-research/take-10-with/take-10-with-physics/take-10-with-frederique-vanholsbeeck.html

[1174] University of Otago. (n.d.). Antimicrobial resistance. Retrieved 17 November, 2021, from https://micro.otago.ac.nz/our-people/teaching-research-and-support/greg-cook/cook-lab-project-c/

[1175] Institute of Environmental Science and Research Limited (ESR). (n.d.). Genomics. Retrieved 17 November, 2021, from https://www.esr.cri.nz/our-expertise/genomics-2/

[1176] Sajuthi, A., White, J., Ferguson, G., *et al.* (2020). Bac-PULCE: Bacterial strain and AMR profiling using long reads via CRISPR enrichment. *bioRxiv*, 2020.2009.2030.320226. https://doi.org/10.1101/2020.09.30.320226

[1177] Massey Ventures. (n.d.). Massey University launches diagnostics company Ampersand Technologies. Retrieved 9 December, 2021, from http://masseyventures.co.nz/news/massey-university-launches-diagnostics-company-ampersand-technologies/

[1178] Massey University. (2017, 1 August). *UNESCO science partnership building bridges in the Pacific* [Press release]. Retrieved from https://www.massey.ac.nz/massey/about-massey/news/article.cfm

Canada has more advanced AMR surveillance than many other countries (the Canadian Antimicrobial Resistance Surveillance System, CARSS).[1179] This system incorporates epidemiological and lab data on both AMR and antimicrobial use from human, production animal, and food sources. Canada also has the Canadian Integrated Program for Antimicrobial Resistance Surveillance to monitor trends in both AMR and antimicrobial use – mostly across humans, animals and the food supply chain.

In the US, the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) has been in operation since 1996.[1180] This public health surveillance system integrates resistance data from human, animal and food sources to track the antimicrobial susceptibility of intestinal bacteria. The system has recently expanded to include environmental pathogens too. This system allows for greater insight into transmission pathways (across sectors and geographically), helps to identify emerging resistance, and facilitates speedier outbreak responses.

OUTBREAK (One Health Understanding Through Bacterial Resistance to Antibiotics Knowledge) is a high-tech artificial intelligence surveillance system in development in Australia. The system is being designed to collect and analyse large quantities of AMR data to predict AMR and to explore intervention strategies. The system will cover human, animal and environmental AMR. This is a proactive approach to monitoring and surveillance and could inform prioritisation of new diagnostics, treatments, vaccines, and policies designed to prevent and reduce infection and rates of AMR. Models to predict the evolution of resistance will continue to improve in accuracy.[1181]

The state of Victoria in Australia has a CPE surveillance program: a comprehensive, prospective genomic and epidemiological surveillance and response system.[1182] This system, in operation since December 2015, has resulted in more detection of patients colonised with CPEs, a decrease in clinical infections of CPE, and identification of small outbreaks and transmission pathways.[1183]

The Centre for Disease Dynamics, Economic and Policy resistance map provides global information on AMR and use trends. However, the usefulness of the map is limited by the data availability – many countries do not have collected data, do not have it in a usable state, or have outdated data. Similarly, the WHO-led Global Antimicrobial Resistance and Use Surveillance System (GLASS) could benefit from greater global participation and data standardisation to improve the representativeness and quality of the data it receives (see section 2.4.3 for more details on GLASS).[1184]

[1179] Government of Canada. (2020). *Canadian integrated program for antimicrobial resistance surveillance (CIPARS) 2018: Design and methods*. Guelph, Ontario: Public Health Agency of Canada. Retrieved from https://www.canada.ca/content/dam/phac-aspc/documents/services/surveillance/canadian-integrated-program-antimicrobial-resistance-surveillance-cipars/cipars-reports/2018-annual-report-design-methods/2018-annual-report-design-methods.pdf

[1180] Centers for Disease Control and Prevention. (2020, 2 October). National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS). Retrieved 17 November, 2021, from https://www.cdc.gov/narms/index.html

[1181] Pinheiro, F., Warsi, O., Andersson, D.I.*, et al.* (2021). Metabolic fitness landscapes predict the evolution of antibiotic resistance. *Nature Ecology & Evolution*. https://doi.org/10.1038/s41559-021-01397-0

[1182] Victorian Government Department of Health. (2020). *Carbapenemase-producing Enterobacterales surveillance report*. Melbourne: Retrieved from https://www.health.vic.gov.au/infectious-diseases/carbapenemase-producing-enterobacterales-surveillance-report

[1183] Lane, C.R., Brett, J., Schultz, M.*, et al.* (2020). Search and contain: Impact of an integrated genomic and epidemiological surveillance and response program for control of carbapenemase-producing Enterobacterales. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciaa972

[1184] World Health Organization. (2021). *Global antimicrobial resistance and use surveillance system (GLASS) report 2021*. Geneva, Switzerland: World Health Organization.

Genomic approaches to tracking pathogens

With the rise of genomic technology, some countries have developed genome-based surveillance systems and efforts to establish gather and share data at the international level too. Examples are provided below.

In Australia, AusTrakka is a real-time pathogen genomics surveillance platform facilitating nationally integrated genomics epidemiology.[1185] The programme helps with identification of clusters and transmission pathways by matching up genomic data shared by public health labs in different states and territories. It currently has a focus on COVID-19, but the platform can be used for other areas of interest such as foodborne pathogens and STIs.

GenomeTrakr is a US-based network facilitating real-time sequence sharing of foodborne pathogens between remote laboratories. Independent labs from all over the world can plug into this platform but they need to use the metadata standard (i.e. rules on what metadata should accompany an isolate/sample), use the open platform, and use open data repository. This allows for international data analysis and identification of clusters. Labs from Australia, Canada and the UK have contributed.

PulseNet is another US-based surveillance system that connects up cases of foodborne, waterborne, and other zoonotic cases to identify outbreaks with standardised lab and analysis protocols.[1186] In operation since 1996, PulseNet has focused on WGS since 2013 to generate 'DNA fingerprints' to link cases. For example, molecular surveillance combined with epidemiology traced cases of a listeriosis across the US back to a single cheese-making place,[1187] and linked worldwide salmonellosis outbreaks to global shipping of turtles in the pet trade.[1188] Across the US, PulseNet prevents more than 266,500 illnesses from *Salmonella* spp., nearly 9,500 illnesses from *E. coli* and 56 from *Listeria* spp. every year, translating into US$507 million in reduced medical and productivity costs.[1189] PulseNet has expanded into seven regions covering 89 countries with PulseNet International, and Aotearoa New Zealand is a member via ESR.[1190]

Nextstrain is an international platform that aggregates genomic information on a range of pathogens (including SARS-CoV-2, influenza, measles, and *Mycobacterium tuberculosis*), uses bioinformatics to analyse their relationships to one another, and constructs interactive phylogenetic trees to depict those relationships.[1191] Microreact is a similar tool.[1192]

[1185] Communicable Diseases Genomics Network. (n.d.). AusTrakka. Retrieved 17 November, 2021, from https://www.cdgn.org.au/austrakka

[1186] Centers for Disease Control and Prevention. (2021, 29 September). PulseNet. Retrieved 17 November, 2021, from https://www.cdc.gov/pulsenet/index.html

[1187] Association of Public Health Laboratories. (2016). Stopping *Listeria* required an arsenal of tools and an army of experts. *APHL Blog* (Vol. 2021). Retrieved from https://www.aphlblog.org/stopping-listeria-requires-an-arsenal-of-tools-and-an-army-of-experts/

[1188] Basler, C., Bottichio, L., Higa, J., *et al.* (2015). Multistate outbreak of human *Salmonella* Poona infections associated with pet turtle exposure -United States, 2014. *Morbidity and Mortality Weekly Report, 64*(29), 804. https://doi.org/10.15585/mmwr.mm6429a7; Centers for Disease Control and Prevention. (2010). Multistate outbreak of human *Salmonella* Typhimurium infections associated with pet turtle exposure - United States, 2008. *Morbidity and Mortality Weekly Report, 59*(7), 191-196.

[1189] Scharff, R.L., Besser, J., Sharp, D.J., *et al.* (2016). An economic evaluation of PulseNet: A network for foodborne disease surveillance. *American Journal of Preventive Medicine, 50*(5), S66-S73. https://doi.org/10.1016/j.amepre.2015.09.018

[1190] PulseNet International. (2019, 30 August). New Zealand. Retrieved 17 November, 2021, from https://pulsenetinternational.org/networks/asiapacific/newzealand

[1191] Hadfield, J., Megill, C., Bell, S.M., *et al.* (2018). Nextstrain: Real-time tracking of pathogen evolution. *Bioinformatics, 34*(23), 4121-4123. https://doi.org/10.1093/bioinformatics/bty407

[1192] Argimón, S., Abudahab, K., Goater, R.J.E., *et al.* (2016). Microreact: Visualizing and sharing data for genomic epidemiology and phylogeography. *Microbial Genomics, 2*(11). https://doi.org/10.1099/mgen.0.000093

The Global Initiative on Sharing All Influenza Data (GISAID) is an international platform for the sharing of influenza genomes and related clinical, epidemiological, and geographic data. During the COVID-19 pandemic, the platform has expanded to carry SARS-CoV-2 data as well.[1193]

Molecular surveillance combined with epidemiology traced cases of a listeriosis across the US back to a single cheese-making place and linked worldwide salmonellosis outbreaks to global shipping of turtles in the pet trade.

[1193] GISAID. (n.d.). GISAID. Retrieved 9 December, 2021, from https://www.gisaid.org/

5.5 Treatments

Preventing all infectious disease is not possible: there will always be a place for treatments in human, animal, and plant health. This section explores AMS as a means to optimise antimicrobial use and prolong the effectiveness of existing treatments. In this report, we consider AMS to go beyond prescribing, promoting an 'ecosystem' that minimises opportunities for resistance to develop. In this way, it goes beyond antimicrobial use to consider other types of chemical exposures that could undermine antimicrobial effectiveness.

In this section of the report we also explore development of new antimicrobials and non-antimicrobial treatments like bacteriophages and antibodies.

5.5.1 Antimicrobial stewardship in human health

To conserve the effectiveness of existing antimicrobial treatments, we need a judicious approach that promotes appropriate use: the right antimicrobial, at the right dose, via the right route, for the right amount of time. This optimisation approach to antimicrobial use is called AMS, which aims to provide the best outcomes for both individuals (i.e. highest chance of cure of the infection, fewer adverse reactions and less disruption to the microbiome) and wider society (i.e. minimise the opportunities for AMR to develop and spread).

We need a judicious approach that promotes appropriate use: the right antimicrobial, at the right dose, via the right route, for the right amount of time.

Further, we consider AMS to extend beyond prescribing to describe an intergenerational kaitiakitanga (guardianship). This expanded AMS aims to promote an 'ecosystem' that minimises opportunities for resistance to develop. In this way, it goes beyond antimicrobial use to consider other types of chemical exposures that could undermine antimicrobial effectiveness (see section 2.3.2).

There is strong local and international evidence that AMS interventions work. Increasing compliance with guidance and reducing duration of treatment can be achieved, while careful reductions in antimicrobial use do not increase mortality.[1194] There is evidence that reducing antibiotic prescriptions in primary care in the UK led to reduced AMR.[1195] In a US analysis, AMS programmes were associated with a reduction in antibiotic use and in hospital-onset *C. difficile* infection rates.[1196]

Start smart – then focus

Public Health England has published an AMS toolkit for use in hospitals, based on a 'Start smart – then focus' approach.[1197] This approach, combined with regular and systematic auditing, provides a

[1194] Davey, P., Marwick, C.A., Scott, C.L., *et al.* (2017). Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database of Systematic Reviews, 2*. https://doi.org/10.1002/14651858.cd003543.pub4; McMullan, B.J., Mahony, M., Java, L., *et al.* (2021). Improving intravenous-to-oral antibiotic switch in children: A team-based audit and implementation approach. *BMJ Open Quality, 10*(1), e001120. https://doi.org/10.1136/bmjoq-2020-001120; Gardiner, S.J., Metcalf, S.C., Werno, A., *et al.* (2020). A persuasive approach to antimicrobial stewardship in Christchurch hospitals produced a sustained decrease in intravenous clarithromycin dosing and expenditure via a switch to azithromycin orally. *The New Zealand Medical Journal, 133*(1512), 22-30.

[1195] Hammond, A., Stuijfzand, B., Avison, M.B., *et al.* (2020). Antimicrobial resistance associations with national primary care antibiotic stewardship policy: Primary care-based, multilevel analytic study. *PLOS One, 15*(5), e0232903. https://doi.org/10.1371/journal.pone.0232903

[1196] Tamma, P.D., Miller, M.A., Dullabh, P., *et al.* (2021). Association of a safety program for improving antibiotic use with antibiotic use and hospital-onset *Clostridioides difficile* infection rates among US hospitals. *JAMA Network Open, 4*(2), e210235-e210235. https://doi.org/10.1001/jamanetworkopen.2021.0235

[1197] Public Health England. (2015). *Start smart – then focus: Antimicrobial stewardship toolkit for English hospitals*. London, UK: Public Health England. Retrieved from

useful framework for scaling up AMS activities in Aotearoa New Zealand, and ideas that should be captured in antimicrobial prescribing guidance (see section below).

'Start smart' means:

- Do not start antimicrobial therapy unless there is clear evidence of infection
- Take a thorough drug allergy history
- Initiate prompt effective antibiotic treatment within one hour of diagnosis (or as soon as possible) in patients with severe sepsis or life-threatening infections. Avoid inappropriate use of broad-spectrum antibiotics.
- Comply with local antimicrobial prescribing guidance.
- Document clinical indication, disease severity (if appropriate), drug name, dose and route on chart and in clinical notes
- Include review/stop date and duration
- Obtain cultures prior to commencing therapy where possible (but do not delay therapy)

'Then focus' means reviewing the clinical diagnosis and the continuing need for antibiotics at 48-72 hours and documenting a clear plan of action: the 'antimicrobial prescribing decision'. This may involve stopping or continuing treatment, switching the route (IV or oral), or changing the type of antimicrobial (broad or narrow spectrum).

Aotearoa New Zealand is lagging when it comes to AMS in human health

In the last decade, human health AMS activities in Aotearoa New Zealand have been relatively limited and fragmented. We don't have an operational national AMS plan or strategy, and we are lagging behind our peers, such as Australia.

AMS programmes are established in several DHBs across Aotearoa New Zealand; however, they vary in their size, **with near universal under-resourcing**.

Objective four of the *New Zealand AMR Action Plan* relates to AMS[1198] but implementation of actions related to this objective have been poor. Recommendations made in an HQSC scoping document on AMS nearly a decade ago have also not been achieved.[1199] There is significant room to elevate and embed the practice of AMS into human health systems in Aotearoa New Zealand.

AMS programmes are established in several DHBs across Aotearoa New Zealand; however, they vary in their size, with near universal under-resourcing when compared to FTE recommendations.[1200] A survey in 2016 found that just half of all DHBs had an AMS committee.[1201] Nine had dedicated AMS pharmacist resource and eight had a lead medical doctor with AMS responsibility (although this

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF

[1198] Ministry of Health and Ministry for Primary Industries. (2017). *New Zealand Antimicrobial Resistance Action Plan*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/publication/new-zealand-antimicrobial-resistance-action-plan

[1199] Thompson, I. (2013). *Antimicrobial stewardship in New Zealand: Scoping research*. Health Quality & Safety Commission. Retrieved from http://www.hqsc.govt.nz/assets/Infection-Prevention/PR/Antimicrobial-stewardship-report.pdf

[1200] Duguid, M., & Cruickshank, M. (2010). *Antimicrobial stewardship in Australian hospitals*. Sydney, Australia: Australian Commission on Safety and Quality in Health Care. Retrieved from https://www.safetyandquality.gov.au/sites/default/files/migrated/Antimicrobial-stewardship-in-Australian-Hospitals-2011.pdf

[1201] Gardiner, S.J., Pryer, J.A., & Duffy, E.J. (2017). Survey of antimicrobial stewardship practices in public hospitals in New Zealand district health boards. *The New Zealand Medical Journal, 130*(1458), 27-41.

… the country lacks a coordinated AMS plan, overarching leadership, and governance.

resource was largely insufficient for a comprehensive AMS programme).[1202] Only three reported having dedicated AMS ward rounds.

AMS programmes are absent from many smaller DHBs and rural hospitals.[1203] AMS activities may be occurring within private hospitals (in line with the Health and Disability Services Standard) but these lack visibility. In the community, AMS efforts are few, and the country lacks a coordinated AMS plan, overarching leadership, and governance.

Time, resourcing and a lack of access to AMS, infectious disease and clinical microbiology expertise are key barriers to expanding AMS initiatives in Aotearoa New Zealand, especially in smaller DHBs.[1204] National leadership and coordination are required to assist DHBs in developing effective programmes to improve antimicrobial use across both hospital and community settings.[1205]

The New Zealand Health and Disability Services Standard was updated in 2021 to include a strengthened focus on AMS programmes and implementation, requiring that service providers have a documented AMS programme that includes evaluation of effectiveness.[1206] However, the standards do not cover antimicrobial use in all healthcare settings, and there is scope to continue to build on the AMS aspects, in collaboration with AMS experts.

A recent article written by AMS experts and champions across Aotearoa New Zealand renewed the call for national leadership and coordination in AMS, outlining ten recommendations including the establishment of a national expert group and a national centre for AMS.[1207] The establishment of Health New Zealand provides an opportunity to accelerate and embed these coordinated approaches.

We can learn from overseas AMS experiences

We can look to overseas experiences and learn from them as we work to strengthen AMS at the national level in Aotearoa New Zealand.

- Australia, which also has high antimicrobial use in human health, is well ahead of us when it comes to national AMS activities, with a National Centre for AMS,[1208] national therapeutic guidelines for antibiotic prescribing,[1209] and the NAPS for auditing.[1210]

[1202] Gardiner, S. (2021). Personal communication.
[1203] Gardiner, S.J., Pryer, J.A., & Duffy, E.J. (2017). Survey of antimicrobial stewardship practices in public hospitals in New Zealand district health boards. *The New Zealand Medical Journal, 130*(1458), 27-41. ; Green, J.K., Gardiner, S.J., Clarke, S.L*., et al.* (2018). Antimicrobial stewardship practice in New Zealand's rural hospitals. *The New Zealand Medical Journal, 131*(1481).
[1204] Gardiner, S.J., Pryer, J.A., & Duffy, E.J. (2017). Survey of antimicrobial stewardship practices in public hospitals in New Zealand district health boards. *The New Zealand Medical Journal, 130*(1458), 27-41.
[1205] Ibid.
[1206] Standards New Zealand. (2021). NZS 8134:2021: Ngā paerewa Health and disability services standard. Retrieved from https://www.standards.govt.nz/shop/nzs-81342021/
[1207] Gardiner, S.J., Duffy, E.J., Chambers, S.T*., et al.* (2021). Antimicrobial stewardship in human healthcare in Aotearoa New Zealand: Urgent call for national leadership and co-ordinated efforts to preserve antimicrobial effectiveness. *New Zealand Medical Journal, 134*(1544), 113-128.
[1208] National Centre for Antimicrobial Stewardship. (n.d.). National Centre for Antimicrobial Stewardship. Retrieved 29 October, 2021, from https://www.ncas-australia.org/
[1209] Therapeutic Guidelines Australia. (n.d.). Antibiotic. Retrieved 15 November, 2021, from https://tgldcdp.tg.org.au/guideLine?guidelinePage=Antibiotic&frompage=etgcomplete
[1210] National Centre for Antimicrobial Stewardship. (n.d.). NAPS: National Antimicrobial Prescribing Survey. Retrieved 15 November, 2021, from https://www.naps.org.au/Default.aspx

- The UK is also forging ahead with AMS efforts, with Public Health England reporting regular surveillance of antimicrobial use and resistance since 2014.[1211] The National Institute for Health and Care Excellence has published a guideline with recommendations on AMS programmes[1212] which has been contextualised to Aotearoa New Zealand by bpac[nz].[1213]
- Evidence-based guidelines for implementing AMS are also available from the US[1214] and the WHO has released policy guidance on AMS activities.[1215] US pharmacists said that a supportive organisational culture, protected time for AMS, and a cohesive organisational structure were important for success in AMS initiatives.[1216]

AMS programmes may be tailored to each country and healthcare provider's context and need and may therefore comprise different interventions. Robust evaluation will be key to determining which interventions are successful and effective.[1217]

AMS is every healthcare worker's responsibility

AMS efforts are often spearheaded by specialist pharmacists or infectious disease physicians, but efforts will invariably be more powerful when they are multidisciplinary, inclusive and move beyond the archetypal medical hierarchy. [1218] Consideration needs to be given to establishing clear AMS leadership roles, as well as building up AMS knowledge throughout the workforce.

- **Pharmacists** have a leadership role to play in AMS due to their expertise in antimicrobial medicines.[1219] Pharmacy technicians could also be recruited into AMS programmes.[1220]
- **Infectious disease physicians'** expertise in the diagnosis and management of infections means they play an essential role in AMS.[1221]
- **Clinical microbiologists and medical lab scientists** are essential for effective AMS, which requires expertise in microbial detection, surveillance and AST.[1222]

[1211] Public Health England. (2020). English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report. Retrieved 16 November, 2021, from https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[1212] National Institute for Health and Care Excellence. (2015). *Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use*. Retrieved from https://www.nice.org.uk/guidance/ng15

[1213] bpac nz. (2017). *Antimicrobial stewardship: Systems and processes for effective antimicrobial medicine use within human health and healthcare in New Zealand*. Retrieved from https://bpac.org.nz/guidelines/3/docs/AntimicrobialStewardship.pdf

[1214] Barlam, T.F., Cosgrove, S.E., Abbo, L.M.*, et al.* (2016). Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clinical Infectious Diseases, 62*(10), e51-e77. https://doi.org/10.1093/cid/ciw118; Centers for Disease Control and Prevention. (2019). *The core elements of hospital antibiotic stewardship programs*. Atlanta, GA: US Department of Health and Human Services. Retrieved from https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf

[1215] World Health Organization. (2021). *WHO policy guidance on integrated antimicrobial stewardship activities* (9240025537). Retrieved from https://www.who.int/publications/i/item/9789240025530

[1216] Appaneal, H.J., Luther, M.K., Timbrook, T.T.*, et al.* (2019). Facilitators and barriers to antibiotic stewardship: a qualitative study of pharmacists' perspectives. *Hospital pharmacy, 54*(4), 250-258.

[1217] Dik, J.-W.H., Hendrix, R., Poelman, R.*, et al.* (2016). Measuring the impact of antimicrobial stewardship programs. *Expert review of anti-infective therapy, 14*(6), 569-575. ; ibid.

[1218] Broom, A., Broom, J., Kirby, E.*, et al.* (2015). What role do pharmacists play in mediating antibiotic use in hospitals? A qualitative study. *BMJ Open, 5*(11), e008326. https://doi.org/10.1136/bmjopen-2015-008326

[1219] Royal Pharmaceutical Society. (2017). *The pharmacy contribution to antimicrobial stewardship*. London, UK: Royal Pharmaceutical Society. Retrieved from https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Policy/AMS%20policy.pdf

[1220] Cheah, R., Rajkhowa, A., James, R.*, et al.* (2020). Case for antimicrobial stewardship pharmacy technicians in Australian hospitals. *Australian Health Review, 44*(6), 941-943. https://doi.org/10.1071/AH19236

[1221] Ostrowsky, B., Banerjee, R., Bonomo, R.A.*, et al.* (2018). Infectious diseases physicians: Leading the way in antimicrobial stewardship. *Clinical Infectious Diseases, 66*(7), 995-1003. https://doi.org/10.1093/cid/cix1093; Australian Commission on Safety and Quality in Health Care. (2018). Role of the infectious diseases service in antimicrobial stewardship*Antimicrobial Stewardship in Australian Health Care*. Sydney, NSW. Retrieved from https://www.safetyandquality.gov.au/sites/default/files/migrated/Chapter8-Role-of-infectious-diseases-service-in-antimicrobial-stewardship.pdf

[1222] Kelley, P. (2014). Antimicrobial stewardship: The role of the clinical microbiology service. *Pathology, 46*, S45. https://doi.org/10.1097/01.PAT.0000443495.55603.fb; Morency-Potvin, P., Schwartz, D.N., & Weinstein, R.A. (2017). Antimicrobial stewardship: How the microbiology laboratory can right the ship. *Clinical Microbiology Reviews, 30*(1), 381-407. https://doi.org/10.1128/CMR.00066-16

- **General practitioners**, on the frontline of community healthcare, need to make AMS a core part of their practice to reduce antimicrobial use, tackle AMR and ultimately protect patients.
- **Nurses** are involved in every aspect of patient's journey through the healthcare system and are well placed to influence antimicrobial use. In addition, nurses are responsible for 50% of non-medical prescriptions (see section 4.4.1). However, a lack of knowledge about AMS and AMR inhibits their ability to integrate it into their clinical practice: these education gaps need to be filled to optimise AMS.[1223]
- Other non-medical prescribers including **dentists, optometrists, and midwives** have a role to play in AMS and judicious prescribing. For example, midwives are able to prescribe some antimicrobials to mothers and newborns in their care. The New Zealand College of Midwives has published a consensus statement on AMR.[1224] There is a need for ongoing communication, education and support for midwives to implement best prescribing practice.[1225]
- **Aged care workers** look after older people, who are often more vulnerable to infection, and are a group with particularly high levels of antimicrobial use. Some AMS outreach into ARC is beginning to kick off and we need to accelerate this to tackle the growing burden of AMR in these settings.

AMS efforts are often spearheaded by specialist pharmacists or infectious disease physicians, but **efforts will invariably be more powerful when they are multidisciplinary**, inclusive and move beyond the archetypal medical hierarchy.

Education and continuing professional development for health workers is one way to ensure all relevant actors have the skills they need to support AMR. In the UK, the Royal Pharmaceutical Society has created a pilot programme offering free AMS training for pharmacists. It is a three-month, online programme aimed at pharmacists in both primary and secondary care.[1226] This type of ongoing, accessible training could be beneficial in Aotearoa New Zealand.

There is also potential for AMS initiatives to educate and change practice. Effective campaigns have been shown to make a difference while they are being run, such as the 'Document the indication' campaign run during World Antimicrobial Awareness Week in 2020 (discussed further below).

Further examples can be found at Canterbury DHB hospitals, where two multi-pronged AMS initiatives drawing on improved access to guidelines, education, pharmacist support, and agreement

[1223] Padigos, J., Ritchie, S., & Lim, A.G. (2020). Enhancing nurses' future role in antimicrobial stewardship. *Collegian, 27*(5), 487-498. https://doi.org/10.1016/j.colegn.2020.01.005
[1224] New Zealand College of Midwives. (2018). *Consensus statement: Antimicrobial resistance*. Retrieved from https://www.midwife.org.nz/wp-content/uploads/2019/05/Antimicrobial-Resistance.pdf
[1225] Anderson, J. (2021). Personal communication.
[1226] Royal Pharmaceutical Society, & Health Education England. (n.d.). RPS antimicrobial stewardship training: A behaviour change and quality improvement workforce intervention. Retrieved from https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/AMS/RPS%20AMS%20Training%20Brochure%20Nov%202020%20PDF.pdf?ver=2020-10-09-163412-333

from stakeholders, have been shown to be effective at changing antibiotic use practices, while also saving more than twice the annual investment in salaries for AMS roles.[1227]

Other improvements at hospitals within Canterbury DHB include evaluating the resource requirements for a post-prescription AMS ward round, using the electronic prescribing and administration system to better identify certain uses and intervene with guidance, establishing better internal educational resources, working with certain specialities to devise solutions to improve antimicrobial use, updating guidelines for certain uses, and improving documentation of the indication within prescriptions.[1228]

There is scope for Pharmac to strengthen its focus on AMS

When purchasing medicines, Pharmac uses the Government's health priorities to guide their decision making. AMS falls under priority three: prevention.[1229] A proactive, quality-use-of-medicines approach to tendering, with better integration between the commercial and clinical arms of Pharmac, may assist with AMS at a national level. In an example of good practice at play, recommendations from the tender committee have driven a shift to smaller sized tubes of topical antibiotics.[1230] This means that the amount dispensed better matches what the patient needs for the prescribed indication, and there are less likely to be leftover tubes of topical antibiotics in the cupboards at home that get used inappropriately. Integration between the commercial and clinical arms of Pharmac may also enable alternatives to antibiotics to be sought – for example, instead of oral antibiotics like tetracyclines for acne, we could be funding benzoyl peroxide as a first choice – or a measuring device could be dispensed alongside medicines to promote appropriate antimicrobial dosing.

A proactive, **quality-use-of-medicines approach** to tendering, with better integration between the commercial and clinical arms of Pharmac, may assist with AMS at a national level.

Some antibiotics have had restrictions put in place to support judicious use in the face of emerging AMR. These restrictions are put in place based on recommendations from Pharmac's infectious disease pharmacology and therapeutics advisory committee. However, there are additional antibiotics that could benefit from an intervention. For example:

- **Amoxicillin + clavulanic acid.**[1231] Use of this broad-spectrum antibiotic should be reserved for specific indications (e.g. mammal bites, diabetic foot ulcers) that are not suitable for narrower spectrum agents to reduce the emergence of AMR. While use has decreased in

[1227] Gardiner, S.J., Metcalf, S.C., Chin, P.K.*, et al.* (2018). Metronidazole stewardship initiative at Christchurch Hospitals–achievable with immediate benefits. *The New Zealand Medical Journal, 131*, 53-58. ; Gardiner, S.J., Metcalf, S.C., Werno, A.*, et al.* (2020). A persuasive approach to antimicrobial stewardship in Christchurch hospitals produced a sustained decrease in intravenous clarithromycin dosing and expenditure via a switch to azithromycin orally. *The New Zealand Medical Journal, 133*(1512), 22-30.
[1228] Gardiner, S.J., Basevi, A.B., Hamilton, N.L.*, et al.* (2020). Point prevalence surveys of antimicrobial use in adult inpatients at Canterbury District Health Board Hospitals. *The New Zealand Medical Journal, 133*(1525), 18-15.
[1229] Pharmac. (2020, 2 September). How the health priorities affect Pharmac's work. Retrieved 18 November, 2021, from https://pharmac.govt.nz/about/what-we-do/how-the-health-priorities-affect-pharmacs-work/
[1230] Copland, M. (2021). Personal communication.
[1231] bpac nz. (2011). Appropriate use of amoxicillin clavulanate. *Best Practice Journal, 38*, 28–33. ; Goodfellow Unit. (2019). Stop using Augmentin. Bring back the Augmentin-free office *New Zealand Doctor*. Retrieved from https://www.goodfellowunit.org/gems/stop-using-augmentin-bring-back-augmentin-free-office

recent years, there is still inappropriate prescribing that needs to be curbed among the 700,000 community prescriptions currently occurring per year. Across Aotearoa New Zealand, the average number of amoxicillin + clavulanic acid tablets prescribed by an individual community prescriber in 2020 was less than 1,000; however, the top ten prescribed an average of more than 20,000 – that is seven tablets per consultation for every single consultation for a whole year.[1232] Prescriber feedback (see discussion below) will be important to target these problematic and harmful prescribing practices while restrictions or special authorities could also be implemented.

- **Fluoroquinolones (e.g. ciprofloxacin, norfloxacin).** There are inconsistent restrictions on funding for these antibiotics in hospitals and in the community. For example, ciprofloxacin is restricted in hospitals but not in the community, whereas the opposite is true for norfloxacin. These need to be made consistent with restrictions in both settings. Resistance to fluoroquinolones is a growing problem and they should be reserved for serious bacterial infections unsuitable for alternative antibiotics in order to preserve their effectiveness.[1233] Use of fluoroquinolones is also accompanied by rare but serious adverse effects which have been the subject of international warnings by the US FDA and European equivalent.

We urgently need to ramp up AMS in community settings

In the community setting, there is a lack of a clear overarching body to monitor and manage antimicrobial use. Given Aotearoa New Zealand's comparatively high antimicrobial use in community, there is an urgent need to expand AMS programmes into primary care. This would be greatly supported by consistent national prescribing guidance (see below).

… there is **an urgent need** to expand AMS programmes into primary care.

Embedding clinical pharmacists in general practice

One way of working to achieve this is through embedding more clinical pharmacists within primary care practices to work on antimicrobial medicine optimisation and equipping and supporting them to engage in AMS. Primary care pharmacists are already in some GP surgeries and primary health organisations across Aotearoa New Zealand.[1234] This aligns with 'Focus area 2: Medicines management services' of the Pharmacy Action Plan 2016–2020.[1235] Expanding AMS expertise into aged care would also be beneficial, alongside upskilling community pharmacists already serving the aged care sector. The types of activities undertaken by these pharmacists in primary care include:[1236]

- Audits of prescribing practices and regular feedback to prescribers.
- Identifying prescribing issues and working to amend them.
- Discussions with GPs and nurses about the appropriateness of antibiotics.
- Assisting with selection of appropriate antibiotics and duration of therapy.
- Education of patients, especially around how antibiotics do not work for viral infections.

[1232] Tilyard, M. (2021). Personal communication.
[1233] bpac nz. (2021). Limiting the use of quinolone antibiotics. Retrieved 18 November, 2021, from https://bpac.org.nz/2021/quinolone.aspx
[1234] Boyina, S.Y., Stokes, T., Renall, A.*, et al.* (2020). Clinical pharmacist facilitators in primary care: A descriptive study of their roles and services provided in general practices of southern New Zealand. *Journal of Primary Health Care, 12*(1), 88-95. https://doi.org/10.1071/HC19073; Haua, R., Harrison, J., & Aspden, T. (2019). Pharmacist integration into general practice in New Zealand. *Journal of Primary Health Care, 11*(2), 159-169. https://doi.org/10.1071/HC18103
[1235] Ministry of Health. (2016). *Pharmacy Action Plan: 2016 to 2020*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/system/files/documents/publications/pharmacy-action-plan-2016-to-2020.pdf
[1236] Cockcroft, T. (2021). *Clinical pharmacists role: Antimicrobial stewardship in primary care*. WellSouth Primary Health Network.

- Developing regional standing orders for school nurses.
- Participating in academic research projects.

Pharmacist involvement in primary care can drive prescribing improvements, reduce prescribing errors and hospital admissions, and potentially reduce patient harm.[1237] For example, one clinical pharmacist prescriber in Aotearoa New Zealand recently conducted an audit of nitrofurantoin prescribing in their practice after discrepancies were noticed by a GP.[1238] The audit showed that only 33% of the total number of nitrofurantoin prescriptions for acute, uncomplicated UTIs were correctly prescribed. During this process, the pharmacist also noted discrepancies in regional guidelines around prescribing and discovered that the standing order for nitrofurantoin in the practice had been incorrectly written. This resulted in the following actions:

- Immediate amendment of the standing order for nitrofurantoin.
- Education for both GPs and nurses in the practice.
- Clarification of HealthPathways guidelines.
- Consultation with an infectious disease expert to ensure accuracy of messaging about duration of treatment.
- Request from the practice for pharmacist participation in review of all standing orders.
- Formation of a Clinical Reference Group to discuss matters of clinical appropriateness and accuracy.

This case study neatly demonstrates how the medicines expertise of pharmacists can be capitalised on in a collaborative manner to ensure the appropriateness and safety of prescribing.

Hospital and community AMS should be connected and consistent

Connections, consistency, and flow of AMS between hospitals and the community are required – after all, the delineation between primary and secondary care can be blurred. For example, discharge prescriptions from hospitals count as community prescribing and quite often these guide the next prescription in the community, meaning that practices within hospitals need to lead by example as they flow out. Connectivity between primary care and hospitals is also important as some of the expertise required for effective AMS sits in hospital settings (e.g. infectious disease specialists, microbiologists). At Canterbury DHB, the AMS Strategic Group includes a GP representative and a community pharmacist, to assist with connection into the community setting.

We can look to overseas evidence for ideas

- The NHS in England includes 'improving antibiotic prescribing in primary care' as one of its Quality Premium improvement measures.[1239] These measures provide a reward mechanism for regional health bodies (roughly equivalent to DHBs) for improving specific services and associated health outcomes. To further support this specific Quality Premium measure, NHS England established AMS hubs and provided open access to prescribing and infection data. A recent analysis found that most regional organisations report successful AMS improvement strategies.[1240]

[1237] Duck, B.J., Brown, V., Allan, W.*, et al.* (2017). Better than an iPad app, a clinical pharmacist in your practice. *International Journal of Integrated Care, 17*(3), 1–8. https://doi.org/10.5334/ijic.3219
[1238] Cockcroft, T. (2021). *Clinical pharmacists role: Antimicrobial stewardship in primary care*. WellSouth Primary Health Network.
[1239] National Health Service. (n.d.). Quality Premium. Retrieved 16 November, 2021, from https://www.england.nhs.uk/ccg-out-tool/qual-prem/
[1240] Allison, R., Lecky, D.M., Beech, E.*, et al.* (2020). What antimicrobial stewardship strategies do NHS commissioning organizations implement in primary care in England? *JAC-Antimicrobial Resistance, 2*(2), 1-10. https://doi.org/10.1093/jacamr/dlaa020

- In Canada, a study concluded that a local person or team responsible for AMS – including auditing and providing feedback on prescribing – was necessary for a successful AMS programme in the community care setting.[1241]
- A paper from Australian authors summarises evidence-based interventions trialled in the primary care setting and outlines how they could be implemented in a strategic way.[1242] The authors argue that sustainable uptake of AMS programs in primary care must be driven by a top-down approach, underpinned by a combination of behavioural and regulatory processes as well as ongoing funding.
- Further research from Australia investigated the attitudes and view of GPs and community pharmacists towards AMS in primary care.[1243] Community pharmacists indicated that they would need training in order to participate in AMS. Collaborative meetings and antimicrobial audits were supported as worthwhile, while policies to support collaboration were also viewed as necessary.
- A study from Sweden found that a single educational intervention aimed at influencing rates of antibiotic prescriptions did result in decreased prescribing – but only for a limited time. A multifaceted approach is needed for sustained impact.[1244]

Rural hospitals need bespoke AMS programmes and better connectivity to expertise

Lack of resources, personnel, and AMS education pose barriers to implementing AMS programmes in rural settings. A survey of rural hospital practitioners in Aotearoa New Zealand found that they generally have limited access to AMS education, feedback on antimicrobial prescribing and infrequent contact with infectious diseases and/or AMS expertise.[1245] Indeed, it may not make sense to have dedicated AMS staffing at a small hospital, but instead to upskill rural prescribers and provide visible pathways for them to connect with AMS expertise. Prescriber feedback, if generated and shared from a centralised antimicrobial prescribing data platform, would also be useful for benchmarking against their peers.

… national resourcing of expertise is uneven and this presents equity issues.

An AMS telemedicine service is one potential approach to strengthen AMS in regional and rural areas.[1246] For example, in Queensland, a hotline was staffed by an infectious disease consultant and AMS pharmacist to answer clinical questions during the work week. Weekly 'ward rounds' were conducted using telehealth, in addition to monthly education via telehealth and occasional outreach

[1241] Jeffs, L., McIsaac, W., Zahradnik, M., *et al.* (2020). Barriers and facilitators to the uptake of an antimicrobial stewardship program in primary care: A qualitative study. *PLOS One, 15*(3), e0223822. https://doi.org/10.1371/journal.pone.0223822

[1242] Avent, M.L., Cosgrove, S.E., Price-Haywood, E.G., *et al.* (2020). Antimicrobial stewardship in the primary care setting: From dream to reality? *BMC Family Practice, 21*(1), 134. https://doi.org/10.1186/s12875-020-01191-0

[1243] Saha, S.K., Kong, D., Thursky, K., *et al.* (2021). Divergent and convergent attitudes and views of general practitioners and community pharmacists to collaboratively implement antimicrobial stewardship programs in Australia: A nationwide study. *Antibiotics, 10*(1), 47. https://doi.org/10.3390/antibiotics10010047

[1244] Lampi, E., Carlsson, F., Sundvall, P.-D., *et al.* (2020). Interventions for prudent antibiotic use in primary healthcare: an econometric analysis. *BMC Health Services Research, 20*(1), 1-11.

[1245] Green, J.K., Gardiner, S.J., Clarke, S.L., *et al.* (2018). Antimicrobial stewardship practice in New Zealand's rural hospitals. *The New Zealand Medical Journal, 131*(1481).

[1246] Yam, P., Fales, D., Jemison, J., *et al.* (2012). Implementation of an antimicrobial stewardship program in a rural hospital. *American Journal of Health-System Pharmacy, 69*(13), 1142-1148. https://doi.org/10.2146/ajhp110512

visits onsite. This programme resulted in improvements in adherence to guidelines and appropriateness of antimicrobial prescribing, as well as a decrease in antibiotic use.[1247]

In Aotearoa New Zealand, national distribution of expertise and resources is uneven, and this presents equity issues. Some DHBs have infectious disease specialists and microbiologists, other regions can't access antimicrobials that require infectious diseases or microbiology approval for use because they lack straightforward access to those specialists. Infectious disease consultation services via telephone are undertaken in some DHBs on an ad hoc basis. While it is essential to connect regional and rural practitioners to this expertise, this service as it stands presents a potential source of clinical risk, putting some experts in a precarious position giving advice outside of their organisation and role based on limited information. Information provided over the phone between healthcare professionals is not always complete, and this can affect the quality of advice given. Expertise could be available in a more formal approach, perhaps with regional hubs, accompanied by specialist physician access to lab and clinical patient notes to maximise the accuracy of advice. Expanding this service to encompass AMS 'ward rounds' via telehealth and physical outreach could strengthen networks between expertise in main centres and rural practitioners.

We need nationally consistent antimicrobial prescribing guidance for human health

Aotearoa New Zealand does not have nationally consistent guidance for antimicrobial prescribing across hospital and community human health settings.

In 2016, 19 out of 20 DHBs had antimicrobial prescribing guidelines for use in hospitals.[1248] These are now increasingly regionally developed and made available through internal platforms (i.e. intranet) as well as apps.

In the community, some guidance has been developed by bpac^{nz} (although there is some variation in uptake, because guidance is also included in regional Community HealthPathways). The range of guidance available can create confusion and sometimes provides conflicting advice, while there is inefficient duplication of effort producing the variety of different guidelines.

The range of guidance available can create confusion and sometimes provides conflicting advice, while there is inefficient duplication of effort producing the variety of different guidelines.

Aotearoa New Zealand is small enough that antimicrobial prescribing guidance should be nationally consistent, with perhaps small local adaptations – for example to account for the differing prevalence of microbes (including drug-resistant ones), availability of resources and expertise, and population demographics.

[1247] Avent, M.L., Walker, D., Yarwood, T*., et al.* (2021). Implementation of a novel antimicrobial stewardship strategy for rural facilities utilising telehealth. *International Journal of Antimicrobial Agents, 57*(6), 106346. https://doi.org/https://doi.org/10.1016/j.ijantimicag.2021.106346

[1248] Gardiner, S.J., Pryer, J.A., & Duffy, E.J. (2017). Survey of antimicrobial stewardship practices in public hospitals in New Zealand district health boards. *The New Zealand Medical Journal, 130*(1458), 27-41.

Scoping work has been undertaken by ACC concluded that a collaborative, consensus-based project to develop national antibiotic guidance should be implemented. [1249] The next step is not yet decided but would likely require action by MoH, possibly shared with ACC. Paediatric infectious disease may be an 'easy win' first step for continuing this work, as Starship Children's Health already provides a consistent voice in paediatric care across the country, compared to a diversity of opinions among those involved with antimicrobial guideline writing for adults.

Once developed, guidance needs to be implemented. In order to be implemented, it needs to be accessible and easy to use. In some cases, visibility of existing guidelines to healthcare providers is variable. For example, a survey of rural hospital practitioners across Aotearoa New Zealand found a lack of internal consistency among responses from people working at the same hospital, suggesting that current uptake and awareness about available guidance is suboptimal.[1250]

National guidance should be widely disseminated, with easy and convenient access for prescribers (and others involved with antimicrobial use, e.g. pharmacists) and/or integration into prescribers' workflow. Providing a range of ways to access guidance may be necessary to ensure good uptake, but these should all be based on the same guidance. For example, this may involve deploying apps that can be used on-the-go[1251] as well as incorporating the guidelines into desktop applications such as HealthPathways.[1252] There also need to be mechanisms for auditing, updating and then disseminating updates to ensure prescribers are making decisions based on the most up-to-date information. Some consideration of how guidance gets transformed into standing orders, and how to link in with the NZ Formulary, would also be useful.

Decision support tools could help physicians adhere to guidance. For example, BPAC Inc[1253] have developed modules that integrate seamlessly with patient management systems.[1254] These contain a set of 'rules' based on evidence and best practice, and also pull out relevant data on the individual patient in question. The tool then generates a recommendation for how the clinician should proceed.

A meta-analysis and systematic review found that delayed prescribing is **a safe and effective strategy**.

[1249] Gasparini, J., Williamson, F., & Stephenson, P. (2020). *Development of national antibiotic guidance in New Zealand - A scoping report for ACC*. Syngergia.
[1250] Green, J.K., Gardiner, S.J., Clarke, S.L*., et al.* (2018). Antimicrobial stewardship practice in New Zealand's rural hospitals. *The New Zealand Medical Journal, 131*(1481).
[1251] Yoon, C.H., Ritchie, S.R., Duffy, E.J*., et al.* (2020). Impact of a smartphone app on prescriber adherence to antibiotic guidelines in adult patients with community acquired pneumonia or urinary tract infections. *Internal Medicine Journal, 50*(S1), 7-7. https://doi.org/10.1111/imj.5_14846; Starship. (2019, 27 August). *Starship hopes new app will help combat antibiotic resistance challenges* [Press release]. Retrieved from https://starship.org.nz/foundation/starship-hopes-new-app-will-help-combat-antibiotic-resistance-challenges/; Capital & Coast District Health Board. (2019, 24 January). *New mobile app to assist with clinical decisions* [Press release]. Retrieved from https://www.ccdhb.org.nz/news-publications/news-and-media-releases/2019-01-24-new-mobile-app-to-assist-with-clinical-decisions/
[1252] McGeoch, G., McGeoch, P., & Shand, B. (2015). Is HealthPathways effective? An online survey of hospital clinicians, general practitioners and practice nurses. *New Zealand Medical Journal, 128*(1408), 36-46.
[1253] Note that BPAC Inc is a sister organisation to bpac^{nz}, with both acronyms standing for Best Practice Advisory Centre. See more here: https://bpac.org.nz/faq.aspx
[1254] Inc, B. (2015). Bestpractice decision support. *Best Practice Journal, 69*, 7–9.

Delayed antimicrobial prescribing (or 'back pocket prescriptions') is another AMS tool that could be built into national guidance. This involves giving a patient a prescription but advising them not to fill it unless their symptoms persist or worsen.[1255] This can be useful for the patient, meaning they don't have to return for another consultation, and pay another fee, if they don't get better. A meta-analysis and systematic review found that delayed prescribing is a safe and effective strategy.[1256]

Stop and review dates are another tool that should be encouraged through national guidance. They are included as part of Public Health England's 'Start smart – then focus' approach to AMS[1257] and the National Centre for Antimicrobial Stewardship in Australia states that the patient's medical notes should "include documentation of the intended stop-date, or a review-date for the antimicrobial".[1258] Documenting these dates helps to ensure that patients aren't taking antimicrobials for an unnecessarily long period of time.[1259] They also provide a prompt to consider stopping antimicrobial treatment or switching to a different antimicrobial if appropriate.

Guidance is just one tool in the AMS toolbox and needs to be accompanied by a suite of other interventions. For example, in Ireland, GPs acknowledged their failure to implement guidelines – often because they felt pressure to prescribe, especially for fee-paying patients and in out of hours settings.[1260] This suggests that we also need to target the public's perceptions and understanding of appropriate antimicrobial use (see section 5.6).

Oversight of decision making and targets for both quantity and quality of antimicrobial prescribing are needed

To ensure best practice prescribing, we need to assess both quantity and quality of prescribing across hospitals and the community, and across the spectrum of prescribers. This relies on a foundation of comprehensive data collection coupled with standardisation and accessibility.

We need to leverage existing data and ensure it is centralised and accessible

Standardised data and surveillance in addition to a centralised system are needed to effectively monitor the quantity of antimicrobial use across Aotearoa New Zealand. As discussed in section 4.4.1, we do collect data on the quantity of antimicrobials prescribed in the community through the Pharmaceutical Collection, while hospitals also collect use data.

The next step is to standardise this data and bring it into a central platform, which could be supported by digitisation using common platforms across the health system. In this way, we can harness the data to monitor trends over time, benchmark different organisations, and better inform actions and interventions that support AMS.

[1255] bpac nz. (2015). Delayed antibiotic prescriptions for respiratory tract infections: does the strategy work? *Best Practice Journal, 68*, 14–18.

[1256] Stuart, B., Hounkpatin, H., Becque, T., *et al.* (2021). Delayed antibiotic prescribing for respiratory tract infections: Individual patient data meta-analysis. *BMJ, 373*, n808. https://doi.org/10.1136/bmj.n808

[1257] Public Health England. (2015). *Start smart – then focus: Antimicrobial stewardship toolkit for English hospitals*. London, UK: Public Health England. Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF

[1258] National Centre for Antimicrobial Stewardship. (n.d.). Antimicrobial stewardship. Retrieved 9 December, 2021, from https://www.ncas-australia.org/antimicrobial-formulary-and-restrictions

[1259] Allan, P., Newman, M., Oehmen, R., *et al.* (2016). The use of daily electronic prompts to help improve antimicrobial stewardship in a critical care unit. *Journal of Infection Prevention, 17*(4), 179-184. https://doi.org/10.1177/1757177416645346; Johnston, D.N., Keshtkar, F., & Campbell, W. (2019). The effect of re-audit and education on antibiotic prescribing practice at Causeway Hospital, Northern Ireland. *Irish Journal of Medical Science, 188*(4), 1149-1153. https://doi.org/10.1007/s11845-019-01995-9

[1260] O'Doherty, J., Leader, L.F., O'Regan, A., *et al.* (2019). Over prescribing of antibiotics for acute respiratory tract infections; a qualitative study to explore Irish general practitioners' perspectives. *BMC family practice, 20*(1), 1-9.

As most community prescriptions are electronically generated, including those in ARC facilities, there is immense opportunity to improve our ability to use aggregated data to understand antimicrobial use in various settings and to use this to feed back to prescribers.

There is immense opportunity to improve our ability to use aggregated data to understand antimicrobial use in various settings and to use this to feed back to prescribers.

To reduce quantity, we need to focus our efforts in the community

In section 4.4.1, we outlined the 'very high' volume and rates of antimicrobial use in the community as well as a spike in dispensing in winter months. This evidence suggests that our efforts to reduce unnecessary antimicrobial prescribing would be most effective if focused on the community. International evidence shows that around half of all antibiotic prescriptions dispensed in the community lack an indication and may provide little or no benefit.[1261] Furthermore, antibiotics, like other medicines, carry risk, can have side effects, and can result in adverse reactions or undesirable outcomes. For example, minor adverse effects of taking antibiotics can include rash and diarrhoea, while in rare cases, anaphylaxis can occur.[1262] Evidence also links antibiotics with childhood obesity and a disrupted microbiome, particularly if given early in life.[1263]

We should aim to safely reduce the volume of antimicrobials prescribed with targets for percentage reductions at a national level, as has been implemented in many jurisdictions.[1264] For example, this has been done in Sweden (36% over 5 years), France (25% over 5 years), UK (1% per year).[1265] Evidence from overseas has also found that sustained, substantial reductions in antimicrobial dispensing were not associated with overall increases in rates of serious infection.[1266] However, any targets need to be informed by solid evidence indicating the extent of inappropriate use, and should not result in antimicrobials being withheld from people whose health could be benefitted by their use, including people in population subgroups already estimated to be under prescribed antimicrobials (see section 4.4.1).

[1261] Fleming-Dutra, K.E., Hersh, A.L., Shapiro, D.J., *et al.* (2016). Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. *JAMA, 315*(17), 1864-1873. https://doi.org/10.1001/jama.2016.4151; Milani, R.V., Wilt, J.K., Entwisle, J., *et al.* (2019). Reducing inappropriate outpatient antibiotic prescribing: Normative comparison using unblinded provider reports. *BMJ Open Quality, 8*(1), e000351. https://doi.org/10.1136/bmjoq-2018-000351

[1262] Linder, J.A. (2008). Antibiotics for acute respiratory infections: Shrinking benefit, increasing risk, and the irrelevance of antimicrobial resistance. *Clinical Infectious Diseases, 47*(6), 744-746. https://doi.org/10.1086/591149

[1263] Chelimo, C., Camargo, C.A., Jr, Morton, S.M.B., *et al.* (2020). Association of repeated antibiotic exposure up to age 4 years with body mass at age 4.5 years. *JAMA Network Open, 3*(1), e1917577-e1917577. https://doi.org/10.1001/jamanetworkopen.2019.17577; Neuman, H., Forsythe, P., Uzan, A., *et al.* (2018). Antibiotics in early life: Dysbiosis and the damage done. *FEMS Microbiology Reviews, 42*(4), 489-499. https://doi.org/10.1093/femsre/fuy018

[1264] D'Atri, F., Arthur, J., Blix, H.S., *et al.* (2019). Targets for the reduction of antibiotic use in humans in the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) partner countries. *Eurosurveillance, 24*(28), 1800339. https://doi.org/10.2807/1560-7917.ES.2019.24.28.1800339; Mölstad, S., Löfmark, S., Carlin, K., *et al.* (2017). Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance. *Bulletin of the World Health Organization, 95*(11), 764-773. https://doi.org/10.2471/BLT.16.184374

[1265] Thomas, M. (2021). Personal communication.

[1266] Gulliford, M.C., Moore, M.V., Little, P., *et al.* (2016). Safety of reduced antibiotic prescribing for self limiting respiratory tract infections in primary care: Cohort study using electronic health records. *BMJ, 354*, i3410. https://doi.org/10.1136/bmj.i3410; Cars, T., Eriksson, I., Granath, A., *et al.* (2017). Antibiotic use and bacterial complications following upper respiratory tract infections: A population-based study. *BMJ Open, 7*(11), e016221. https://doi.org/10.1136/bmjopen-2017-016221

Implementing the National Antimicrobial Prescribing Survey would reveal the quality of prescribing

As discussed in section 4.4.1, Aotearoa New Zealand has previously had access to Australia's hospital NAPS which has been used sporadically in DHB hospitals to assess the quality of prescribing. Rolling this out nationally in a standardised fashion would allow us to compare hospitals and track changes over time. Data collected could inform targeted AMS interventions and allow tracking of progress or evaluation of effectiveness.

Additionally, there is an ARC module of NAPS that Aotearoa New Zealand could implement, if evaluated as suitable for the Aotearoa New Zealand context. Almost all ARC facilities in Aotearoa New Zealand have e-prescribing, which opens up many possibilities for data collection and analysis to better understand prescribing in ARC.

Almost all ARC facilities in Aotearoa New Zealand have e-prescribing, which **opens up many possibilities** for data collection and analysis to better understand prescribing in ARC.

To assess quality, we need to capture the indication

As discussed in section 4.4.1, we lack understanding of the quality of prescribing in the community, in part because there is no requirement for prescribers to include the reason for prescribing the antimicrobial (i.e. the indication) in the prescription and in the clinical/patient notes. The lack of national guidance and auditing to evaluate antimicrobial use against indication poses a hurdle to taking evidence-based and responsive action against problematic prescribing practices.

Other countries, such as Denmark and the UK, require all prescribers to document an indication for a prescription, facilitating AMS and audits of antimicrobial prescribing practices. Some public hospitals in Aotearoa New Zealand do require an indication to be documented and this could be implemented more widely through a legislative or funding requirement, national antimicrobial guidelines, and/or the prescribing software. For example, software providers could be required to include a list of indications in a dropdown box that must be completed before the script can be submitted. There is evidence from Auckland Hospital that ePrescribing improves documentation of indication.[1267] Some indications might warrant a 'free text' field; however, in some hospital settings where similar software steps have been implemented, prescribers have input 'x' or '.' to bypass without including a meaningful indication. If including the indication in the prescription is mandatory, credible indication document increases to about 80–85%.[1268]

[1267] Bowers, T.R., & Duffy, E.J. (2020). Quality of antimicrobial prescribing improved by the introduction of ePrescribing at Auckland City Hospital. *Health Informatics Journal, 26*(4), 2375-2382. https://doi.org/10.1177/1460458220905163
[1268] Gardiner, S. (2021). Personal communication.

‘Document the indication’ was the theme of the first DHB-led AMS initiative for World Antimicrobial Awareness Week in Aotearoa New Zealand in 2020 (see Figure 40). At Canterbury DHB, the initiative was associated with an approximate doubling in ‘credible’ voluntary indications in the prescription (~25% to 50%) at least in the short term.[1269] Ongoing education/feedback will be needed to push this up further and ensure it is sustained, as other DHBs have reported a drop in indications over time post-initiative.

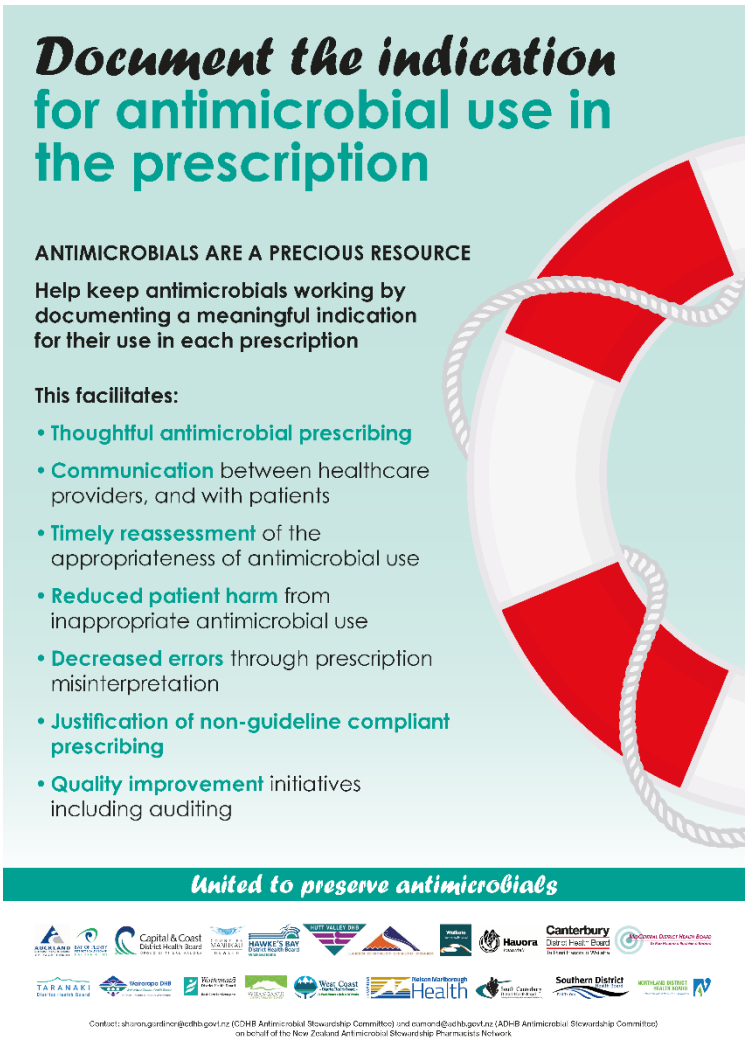


Figure 40: Poster used for World Antimicrobial Awareness Week in 2020. Image credit: Pharmaceutical Society of New Zealand.

Prescriber feedback is a key component of improvement efforts

Capturing indication is just the first step: this information then needs to be transformed into actions to improve quality of prescribing through benchmarking dashboards (i.e. the Open Prescribing database in the UK, with anonymised data on the drugs prescribed by GPs every month[1270]) or direct feedback to prescribers (as bpac^{nz} has provided in the past). In the UK, benchmarking prescribing data was reported as a powerful tool to engage practices, facilitating an element of competition and positive peer pressure.[1271]

In the UK, the NHS decreased antimicrobial prescribing using a few techniques, most of which have been deemed successful by clinical commissioning groups when surveyed. The findings show that combined national and local approaches are beneficial.[1272] These approaches strongly involved prescriber feedback, among other initiatives:

- **Financial incentives for improvement** – the UK’s equivalent of a DHB is rewarded for improvements through the NHS Quality Premium. This has the greatest influence on prioritisation of AMS by medicines management staff due to its national focus and financial incentive.

[1269] Ibid.
[1270] EBM DataLab. (2020). Explore England's prescribing data. Retrieved 12 November, 2021, from https://openprescribing.net/
[1271] Allison, R., Lecky, D.M., Beech, E., *et al.* (2020). What antimicrobial stewardship strategies do NHS commissioning organizations implement in primary care in England? *JAC-Antimicrobial Resistance, 2*(2), 1-10. https://doi.org/10.1093/jacamr/dlaa020; Hallsworth, M., Chadborn, T., Sallis, A., *et al.* (2016). Provision of social norm feedback to high prescribers of antibiotics in general practice: A pragmatic national randomised controlled trial. *The Lancet, 387*(10029), 1743-1752. https://doi.org/10.1016/S0140-6736(16)00215-4
[1272] Allison, R., Lecky, D.M., Beech, E., *et al.* (2020). What antimicrobial stewardship strategies do NHS commissioning organizations implement in primary care in England? *JAC-Antimicrobial Resistance, 2*(2), 1-10. https://doi.org/10.1093/jacamr/dlaa020

- **Benchmarking and feeding back antimicrobial prescribing data to primary care practitioners** – this was thought to be a powerful tool as no one wants to be the outlier, facilitating an element of competition and positive peer pressure, and encouraging practitioners to start questioning their prescribing practices and managing of patients, resulting in more appropriate prescribing behaviour. This allows individualised feedback and improvement.
- **AMS audits of community antibiotic prescribing** – these were thought to be very beneficial because they show potential avenues for improvement and allow peer review and self-reflection, but lack of engagement and limited staff resource to undertake audits could limit effectiveness.
- **Locally developed incentive/reward schemes to encourage AMS** – these were effective because financial incentives work and help to get the issue discussed and prioritised.
- **A letter from the most senior doctor in the government to alert to high use** – this raised awareness and encouraged change but was seen as less successful than other initiatives.
- **Removing barriers and facilitating AMS** – having dedicated staff and resource to support AMS makes a big difference.

In Aotearoa New Zealand, He Ako Hiringa has developed the EPiC dashboard, a prescribing data tool that can be used by GPs to explore their prescribing behaviours.[1273] EPiC also allows prescribers to compare their patient prescribing to all other prescribers within their practice and to the national dataset. This has been rolled out for diabetes, and dashboards for gout, cardiovascular disease and respiratory conditions are also being developed. This dashboard platform could be expanded to cover antimicrobial prescribing. Information on the EPiC dashboard can also be broken down to allow prescribers to look at their prescribing patterns by age, ethnicity, gender, and deprivation so that they can identify potential inequities in their prescribing practices.

A trial in Aotearoa New Zealand in 2019 exploring the effect of prescriber 'nudging' found that informing high-prescribing GPs that they prescribe more antibiotics than their peers led to a reduction in antibiotic prescribing.[1274] The top 30% of GPs prescribing antibiotics in each DHB in 2018 were identified, using data from the Pharmaceutical Collective. These GPs were randomised into an intervention and control group, with the intervention group being mailed a letter informing them that they prescribed more antibiotics than their peers. The letter also detailed the importance of appropriate antibiotic prescribing. In an attempt to avoid reduced prescribing among already underserved people, the letter also noted that Māori and Pacific peoples are often under prescribed and provided a visual breakdown of the GP's prescribing by ethnicity. For the four months following the intervention, those GPs who received the letter wrote 7.1% fewer antibiotic scripts than the control group and had an antibiotic prescribing rate that was 9.2% below that of the control group (measured as patients prescribed antibiotics per 1,000 patients prescribed any medicine). Low prescribers for Māori and Pacific peoples (but high overall) did not appear to reduce their overall prescribing at the expense of underserved groups, but more research into the equity impacts of this intervention is needed.

Improving antimicrobial dosing through therapeutic drug monitoring

Optimising antimicrobial dosing is important to ensure the amount of medicine taken is sufficient to treat infection without being excessive (and therefore elevating side effect risks and potentially promoting AMR). While dosing guidance can help, this can be supplemented with or supported by

[1273] He Ako Hiringa. (2021, 31 May). EPiC. Retrieved 18 November, 2021, from https://epic.akohiringa.co.nz/diabetesPatientDemographic
[1274] Chappell, N., Gerard, C., Gyani, A., *et al.* (2021). Using a randomised controlled trial to test the effectiveness of social norms feedback to reduce antibiotic prescribing without increasing inequities. *The New Zealand Medical Journal, 134*(1544), 13.

therapeutic drug monitoring, where the concentration of a drug in a patient's blood is tested to assess whether the dose is likely to be safe and effective.

Therapeutic drug monitoring is more established for some antimicrobials (e.g. aminoglycosides like gentamicin) than for others (e.g. β-lactams like flucloxacillin). Canterbury DHB have deployed a number of assays for β-lactams (the most commonly used class of antibiotics) to monitor concentration and have collaborated in multi-centre research to try to improve antimicrobial dosing regimens based on knowledge of the drug concentrations achieved.[1275] Measurement of antimicrobials like β-lactams may be particularly helpful for some patient groups such as those with critical illness, or at extremes of body weight or kidney function. Therapeutic drug monitoring is an emerging area of interest and a knowledge and capability gap that requires investment to fill.

The course duration conundrum

The justification underlying the traditional length of antibiotic courses – one to two weeks for many illnesses – is not fully understood.[1276] Emerging research suggests that under some conditions shorter courses may be just as effective as longer ones with lesser risk of AMR. In addition, a shorter course means patients experience fewer side effects and negative impacts on their healthy microbiome are reduced. [1277]

Emerging research suggests that under some conditions **shorter courses may be just as effective** as longer ones with lesser risk of AMR.

Clinical trial methodologies can be designed to specifically explore whether shorter courses of antimicrobials can be used without compromising patient health. If applied, these methodologies can help establish evidence-based course duration recommendations that are optimised to support patient health and more judicious antimicrobial use.[1278]

Evidence in support of shorter courses is beginning to be incorporated into clinical practice in the US. In June 2021, the American College of Physicians issued best practice advice for prescribing shorter courses of antibiotics for common bacterial infections including UTIs, cellulitis, community-acquired pneumonia, and acute bronchitis.[1279]

It should be noted that some infections do still require lengthy treatment, such as tuberculosis, infections around prosthetic joints, and as a strategy to prevent development of rheumatic heart disease.[1280]

[1275] Everts, R.J., Begg, R., Gardiner, S.J., *et al.* (2020). Probenecid and food effects on flucloxacillin pharmacokinetics and pharmacodynamics in healthy volunteers. *Journal of Infection, 80*(1), 42-53. https://doi.org/10.1016/j.jinf.2019.09.004; Everts, R.J., Gardiner, S.J., Zhang, M., *et al.* (2021). Probenecid effects on cephalexin pharmacokinetics and pharmacodynamics in healthy volunteers. *Journal of Infection, 83*(2), 182-189. https://doi.org/10.1016/j.jinf.2021.05.037; Gardiner, S.J., Drennan, P.G., Begg, R., *et al.* (2018). In healthy volunteers, taking flucloxacillin with food does not compromise effective plasma concentrations in most circumstances. *PLOS One, 13*(7), e0199370. https://doi.org/10.1371/journal.pone.0199370

[1276] Willms, A.R., Roughan, P.D., & Heinemann, J.A. (2006). Static recipient cells as reservoirs of antibiotic resistance during antibiotic therapy. *Theroretical Population Biology, 70*(4), 436-451. https://doi.org/10.1016/j.tpb.2006.04.001

[1277] Royer, S., DeMerle, K.M., Dickson, R.P., *et al.* (2018). Shorter versus longer courses of antibiotics for infection in hospitalized patients: A systematic review and meta-analysis. *Journal of Hospital Medicine, 13*(5), 336-342. https://doi.org/10.12788/jhm.2905; Spellberg, B., & Rice, L.B. (2019). Duration of antibiotic therapy: Shorter is better. *Annals of Internal Medicine, 171*(3), 210-211. https://doi.org/10.7326/m19-1509

[1278] Evans, S.R., Rubin, D., Follmann, D., *et al.* (2015). Desirability of Outcome Ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR). *Clinical Infectious Diseases, 61*(5), 800-806. https://doi.org/10.1093/cid/civ495

[1279] Lee, R.A., Centor, R.M., Humphrey, L.L., *et al.* (2021). Appropriate use of short-course antibiotics in common infections: Best practice advice from the American College of Physicians. *Annals of Internal Medicine, 174*(6), 822-827. https://doi.org/10.7326/M20-7355

[1280] Bernard, L., Arvieux, C., Brunschweiler, B., *et al.* (2021). Antibiotic therapy for 6 or 12 weeks for prosthetic joint infection. *New England Journal of Medicine, 384*(21), 1991-2001. https://doi.org/10.1056/NEJMoa2020198

Ensuring course duration prescribing practices align with emerging international evidence is one way to reduce antimicrobial use in Aotearoa New Zealand. Empowering prescribers with relevant evidence so that they can prescribe and advise their patients with confidence (e.g. on whether to stop a course of antibiotics when symptoms resolve) [1281] will support this.

5.5.2 AMS is important in animal health too

Veterinarians have a key role to play in the responsible use of antimicrobials in the animal health sector. Professional practice is regulated by the Veterinary Council of New Zealand, and the code of conduct includes product AMS expectations and appropriate use of antimicrobials.[1282] The Agricultural Compounds and Veterinary Medicines (ACVM) group at MPI regulates the use of veterinary medicines through the ACVM Act 1997.[1283] This legislation manages risks to public health, animal welfare, agricultural security, and trade in primary produce. Advertising of restricted antibiotics to end users is prohibited under the ACVM Act.[1284] The World Veterinary Association have collated a global repository of available guidelines for responsible use of antimicrobials in animal health.[1285]

There are multiple players responsible for AMS in animal health

Vets play a key role

The New Zealand Veterinary Association (NZVA) have developed judicious antibiotic use guidelines.[1286] The NZVA also has an aspirational goal that "by 2030, NZ Inc. will not need antibiotics for the maintenance of the health and welfare of animals".[1287] There is a common misconception that the goal relates to all use – however, it is about avoiding "blanket" prophylactic use, as the industry will always use antimicrobials for therapeutic needs. To support this, the NZVA developed a traffic light system to promote judicious use, particularly encouraging caution with antimicrobials that are of high importance in human health.

The NZVA also has an **aspirational goal** that "by 2030, NZ Inc. will not need antibiotics for the maintenance of the health and welfare of animals".

Beyond food-producing animals, vets treat both companion animals and wildlife – AMS is needed in these settings too, to make sure we retain effective antimicrobials to treat our pets and taonga species. Several countries, including Denmark, Sweden, France, Switzerland, the Netherlands, and the US have published antibiotic use guidelines specific to companion animals (or cats and dogs).[1288]

[1281] bpac nz. (2018). Antibiotics: The future is short. *bpac*. Retrieved from https://bpac.org.nz/2018/docs/antibiotics.pdf
[1282] Veterinary Council of New Zealand. (2020). *Code of professional conduct for veterinarians*. Retrieved from https://www.vetcouncil.org.nz/Web/Code_of_Professional_Conduct/Code_Of_Conduct.aspx
[1283] Ministry for Primary Industries. (n.d., 16 November 2020). ACVM guidance for veterinarians. Retrieved 18 November, 2021, from https://www.mpi.govt.nz/animals/veterinary-medicines-acvm/acvm-guidance-veterinarians/
[1284] New Zealand Veterinary Association. (n.d.). Antibiotic advertising guide for veterinarians. Retrieved 18 November, 2021, from https://www.nzva.org.nz/news/antibiotic-advertising/
[1285] World Veterinary Association. (2019, 26 June). Global repository of available guidelines for responsible use of antimicrobials in animal health. Retrieved 10 December, 2021, from https://worldvet.org/news.php?item=417
[1286] New Zealand Veterinary Association. (2018). *Antibiotic judicious use guidelines for the New Zealand veterinary profession: Dairy*. Wellington, NZ: New Zealand Veterinary Association. Retrieved from https://www.amrvetcollective.com/assets/guidelines/guide_dairy.pdf
[1287] New Zealand Veterinary Association. (n.d.). Antimicrobial resistance (AMR). Retrieved October 29, 2021, from https://www.nzva.org.nz/resource/general/amr/
[1288] World Veterinary Association. (2019, 26 June). Global repository of available guidelines for responsible use of antimicrobials in animal health. Retrieved 10 December, 2021, from https://worldvet.org/news.php?item=417

In Sweden, AMS programmes have been implemented at the vet clinic level,[1289] while the College of Veterinary Medicine at the University of Minnesota has published a handbook for implementing AMS in companion animal veterinary settings.[1290] These provide useful examples to learn from in order to boost AMS in companion animal veterinary practice here in Aotearoa New Zealand.

Farmers often make antimicrobial use decisions

Vets can prescribe to farmers ahead of the need to use the antimicrobials, so the day-to-day decision to use can actually sit with the farmer. This process begins with an annual consultation between the vet and the farmer that results in a herd health plan that outlines common diseases. This is written into a standing order and antimicrobials are left on the farm for farmers to administer as needed, according to the standing order which specifies the specific uses for which those antimicrobials are authorised. This means that the farmer has a lot of responsibility for on-farm antimicrobial use, so both vets and farmers are key players in AMS in the agricultural sector.

Industry initiatives can support AMS

Industry organisations also play a role in AMS. Some examples are included below:

- The poultry industry is proactively phasing out the use of zinc bacitracin.[1291]
- NZ Pork has taken the voluntary position to use fluoroquinolones and third and fourth generation cephalosporin antibiotics on their farms only under exceptional circumstances.[1292]
- Fonterra's Co-operative Difference programme, introduced in 2019, includes a requirement for farmers to develop an animal wellbeing plan that covers, among other things, strategies to minimise AMR.[1293]
- DairyNZ guidelines for dry cow management specify that antimicrobials should be used to treat existing infections or protect hight-risk cows, rather than being used at the herd level.[1294]

Industry initiatives to reduce antimicrobial use and improve AMS are in some instances partially driven by market access concerns. Maintaining access to markets in the UK, EU, US and others is likely to require changes in antimicrobial use practices and will require improvements in surveillance and monitoring data for antimicrobial use. Market pressure often comes from company-to-company requirements (such as those required by large supermarkets) rather than from government regulation. These policies may ban the use of certain antimicrobials or require reduction strategies to be in place. These changing expectations are of most importance to sectors with a high proportion of exports such as dairy, beef, and lamb, and in sectors where antimicrobial use is higher.[1295] Reducing antimicrobial use in food animals in Aotearoa New Zealand can improve the value proposition of our offering of primary products on the global market.

[1289] Guardabassi, L., & Prescott, J.F. (2015). Antimicrobial stewardship in small animal veterinary practice: From theory to practice. *Veterinary Clinics of North America: Small Animal Practice, 45*(2), 361-376. https://doi.org/10.1016/j.cvsm.2014.11.005

[1290] University of Minnesota. (2020). *Handbook of antimicrobial stewardship in companion animal veterinary settings*. (1st ed.). Retrieved from https://arsi.umn.edu/handbook-antibiotic-stewardship-companion-animal-veterinary-settings

[1291] PIANZ. (2021). Personal communication.

[1292] NZ Pork. (2021). Personal communication.

[1293] Fonterra. (2021). The co-operative difference animals factsheet. [Fact sheet]. Retrieved from https://www.fonterra.com/content/dam/fonterra-public-website/fonterra-new-zealand/campaign-images/codof/docs/co-operative-difference-animal-fact-sheet.pdf

[1294] Dairy NZ. (2020). Guideline 14: Decide dry cow management strategy. (pp. 6): SmartSAMM. Retrieved from https://www.dairynz.co.nz/media/5792839/smartsamm_guideline_14_dry_cow_strategy_march_2020.pdf

[1295] Nunan, C. (2020). *Farm antibiotics and trade deals – Could UK standards be undermined?*: Alliance to Save Our Antibiotics. Retrieved from https://saveourantibiotics.org/media/1864/farm-antibiotics-and-trade-could-uk-standards-be-undermined-asoa-nov-2020.pdf

Manufacturers and distributors of veterinary antimicrobial products can support AMS by not offering commercial inducements for antimicrobials, such as price breaks, rebates and free goods.

Denmark provides an example of good practice in pig farming

As discussed in section 4.4.2, antibiotic use in pigs is higher compared to other animal sectors in Aotearoa New Zealand. For pig farming, Denmark is recognised as a leader in its approach to tackling AMR.[1296] Key instruments of success in reducing antimicrobial use include:

- Close vet surveillance of antimicrobial use on farms which allows good data to be captured to inform interventions and allow tracking of success (VetStat database).
- Close vet-farmer relationships with a holistic approach to livestock health and husbandry. A 'Veterinary Advisory Service Contract' is mandatory for all large pig herds and requires at least 12 herd health visits a year.
- A 'Yellow Card Initiative'. This targets farms with the highest use of antibiotics and requires reduced use within a given timeframe, and if targets are not met may require reduced stocking density of animals.
- Continued strict biosecurity measures to avoid the introduction of new pathogens into herds
- Phasing out of antibiotic growth promoters.
- Collaborative research between the pig industry, universities, vets and government authorities.

The Danish pig farming sector has many fundamental differences to Aotearoa New Zealand's pig sector. For example, our farms are generally an order of magnitude larger than those in Denmark, are spaced much further apart geographically, our vet industry is smaller, and there are significant differences in the nature of government subsidies. However, there are still many lessons to be learned from Denmark's success that may be applicable across livestock sectors in Aotearoa New Zealand.

The system for monitoring antimicrobial use in plants and animals could be improved

The Aotearoa New Zealand government's self-assessment as part of the tripartite survey asserts that "on a regular basis, data is collected and reported to the OIE on the total quantity of antimicrobials sold for/used in animals nationally, by antimicrobial class, by species (aquatic or terrestrial), method of administration, and by type of use (therapeutic or growth promotion)."[1297] However, there is significant room for improvement in tracking when surveillance and monitoring systems here are compared to those in many other countries. The *New Zealand AMR Action Plan* published in 2017 includes that objective to "implement initiatives to strengthen national surveillance for AMR and antimicrobial consumption in animal

Ideally, we would have **open prescribing data for vets, or even on-farm documentation of actual antimicrobial use**…

… getting granular information from veterinary practices is difficult due to use of around 50 different databases throughout the country.

[1296] Food and Agriculture Organization, & Denmark Ministry of Environment and Food – Danish Veterinary and Food Administration. (2019). *Tackling antimicrobial use and resistance in pig production: Lessons learned from Denmark*. Rome: Retrieved from http://www.fao.org/3/CA2899EN/ca2899en.pdf

[1297] World Health Organization. (2020). Global database for the tripartite antimicrobial resistance (AMR) country self-assessment survey (TrACSS). Retrieved 4 August 2021 https://amrcountryprogress.org/

health and agriculture production".[1298] New Zealand Food Safety, part of MPI, is undertaking a scoping project on how it could collect antibiotic use data, providing a more refined picture compared to the current collection of sales data. Once the scoping project is complete, any preferred option for collecting such data would need to be funded to implement it.

In countries such as Denmark and Norway, data on antimicrobials that are used under veterinary supervision in animals is available at a farm level and for individual animal species. In comparison to Aotearoa New Zealand, this provides much more detailed and useful information to track volume and type of use. We do not currently have systems in place that would allow for this type of data to be collected centrally. Additional detail is gained from relatively small-scale and periodic sampling or surveys but is not gathered in a consistent or strategic way (see section 4.4.2).

In Denmark, the VetStat database, which is considered to be complete and have high accuracy, contains all medicine prescribed by vets for animals.[1299] For each individual prescription:

- There is information on amount, active substance, target species, age group, diagnosis group, and farm identifier.
- Active compounds are recorded in a unit that measure how many kilograms of animal that can be treated per day,[1300] which allows comparison across records.

As discussed in section 4.4.2, antimicrobial sales data paints a broad picture but lacks the detail useful to drive targeted interventions. Ideally, we would have open prescribing data for vets, or even on-farm documentation of actual antimicrobial use, available in an accessible (potentially digital) format. Currently, getting granular information from veterinary practices is difficult due to use of around 50 different databases throughout the country. The sector would benefit from improved data collection and integration on antimicrobial use to inform decisions.

In the absence of such a system, there are other data sources that could potentially be sourced and analysed in the interim. For example, an Australian study used pet insurance data as a source of information. This could be an option for sourcing data here too.[1301]

And in the plant sector, we need a better understanding of AMR patterns and how antimicrobials are used in order to inform AMS and antimicrobial use guidelines (see section 4.4.3). Given we see resistance in plant pathogens too (for example, see section 3.5.1 on Psa), judicious use is needed to contain AMR. Alternatives to antimicrobial use specific to the plant sector are discussed in section

In the plant sector, we need **a better understanding of AMR patterns and how antimicrobials are used** in order to inform AMS and antimicrobial use guidelines.

[1298] Ministry of Health and Ministry for Primary Industries. (2017). *New Zealand Antimicrobial Resistance Action Plan*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/publication/new-zealand-antimicrobial-resistance-action-plan
[1299] Andersen, V.D., & Hald, T. (2017). *Interventions aimed at reducing antimicrobial usage and resistance in production animals in Denmark* (2578-6865). Washington, DC: National Acadamy of Medicine.
[1300] Known as "animal defined daily doses per kilogram" (ADDkg).
[1301] Hardefeldt, L.Y., Selinger, J., Stevenson, M.A*., et al.* (2018). Population wide assessment of antimicrobial use in dogs and cats using a novel data source – A cohort study using pet insurance data. *Veterinary Microbiology, 225*, 34-39. https://doi.org/https://doi.org/10.1016/j.vetmic.2018.09.010

5.5.5. One key challenge will be determining an appropriate standard denominator to characterise antimicrobial use so that trends within and across countries can be monitored in kind.[1302]

5.5.3 Safe disposal is part of good stewardship

Improperly handled antimicrobial waste can lead to environmental contamination. Antimicrobial waste can enter the environment as the result of unsafe disposal of unused medicines by the public and healthcare professionals, insufficient wastewater treatment (especially from hospitals and antimicrobial manufacturers) and leaching from landfills.[1303] In addition, use of antimicrobials in animal health, including on farms, and in plant health can lead to antimicrobial waste entering the environment, including through runoff and animal excretions. As well as conducting more research on the presence of antimicrobials and AMR in the environment and exploring the impacts of this (see sections 2.3.2 and 4.4.4), measures can be taken to reduce environmental contamination.

Disposal of antimicrobials in human health is covered by the *Management of healthcare waste* standard, from 2002;[1304] however, clear and accessible guidelines for disposal of antimicrobials are lacking. In practice, we don't have great visibility over what happens to unused antimicrobials. In the home, medicine is sometime inappropriately disposed of via general rubbish disposal or via the sink or toilet. These methods of disposal result in medicines being in landfill sites and waterways, where environmental contamination can occur.

Globally, awareness programmes on proper disposal, and access to safe disposal at pharmacies and other sites, have **achieved significant increases in the proportion of medicine disposed of safely**.

In the Tāmaki Makaurau Auckland and Waikato regions there is a project called DUMP (disposal of unwanted medicines properly), which is supported by the DHBs, Auckland Council and International Waste Limited.[1305] This project enables people to return unused or out-of-date medicine to any pharmacy for disposal. Once at a pharmacy, disposal practices vary across the country.[1306] In 2019, the Pharmaceutical Society of New Zealand and MoH led an 'antibiotic amnesty' as part of World Antimicrobial Awareness Week.[1307] This initiative aimed to encourage consumers to return unused antibiotics to their pharmacy for proper disposal. Pharmacies were encouraged to record amounts returned for several weeks. Globally, awareness programmes on proper disposal, and access to safe disposal at pharmacies and other sites, have achieved significant increases in the proportion of medicine disposed of safely.[1308]

[1302] Food and Agriculture Organization Antimicrobial Resistance Working Group. (2018). *Antimicrobial resistance and foods of plant origin: Summary report of an FAO meeting of experts*. Retrieved from http://www.fao.org/3/BU657en/bu657en.pdf

[1303] Caban, M., & Stepnowski, P. (2021). How to decrease pharmaceuticals in the environment? A review. *Environmental Chemistry Letters*, 1-24.

[1304] Standards New Zealand. (2002). *Management of healthcare waste*. Retrieved from https://www.standards.govt.nz/shop/nzs-43042002/

[1305] Auckland Council. (2020). Disposal of unwanted medicines properly. Retrieved 16 November, 2021, from http://www.saferx.co.nz/assets/Documents/8a1b8877b7/DUMP-leaflet.pdf

[1306] Nelmes Bisset, A. (2019). A bitter pill: Why can't we recycle medication?, *RNZ*. Retrieved from https://www.rnz.co.nz/news/in-depth/380632/a-bitter-pill-why-can-t-we-recycle-medication

[1307] Pharmaceutical Society of New Zealand. (2019, 15 November). *'Antibiotic Amnesty:' Together we can keep antibiotics working* [Press release]. Retrieved from https://www.nzdoctor.co.nz/article/undoctored/antibiotic-amnesty-together-we-can-keep-antibiotics-working

[1308] Zeeshan Qadar, S.M., Thane, G., & Haworth-Brockman, M. (2021). *A call to action: An evidence review on pharmaceutical disposal in the context of antimicrobial resistance in Canada*. National Collaborating Centre for Infectious Diseases in partnership with National Collaborating Centre for Environmental Health. Retrieved from https://nccid.ca/publications/a-call-to-action-an-evidence-review-on-pharmaceutical-disposal-in-the-context-of-antimicrobial-resistance-in-canada/

Aotearoa New Zealand could benefit from a sustained, nationwide programme as the protocols for how to dispose of medicine varies region to region. For example, not all pharmacies are required or funded to receive unwanted medicines. Research also suggests that bottom-up, community-based approaches may be more effective than top-down approaches in enacting behavioural change in the public.[1309]

In the farming sector, there are regulations in place that minimise environmental contamination regarding usage, run-off and restrictions on farming activities. Further work is currently underway in this area under the Government's Essential Freshwater package, which may result in improvements in this area.[1310] In addition, in 2020 the government announced that agrichemicals and their containers (including veterinary medicines) should be prioritised for regulated product stewardship schemes under the Waste Minimisation Act 2008,[1311] which has scope to create improved systems for disposal of unused antimicrobials and contaminated containers.

There is also potential to use additional techniques to reduce pollution in wastewater. These include filtration techniques, chlorination, anaerobic techniques, oxidation processes and many others. Specific waste treatment procedures could also be applied more vigorously to healthcare-associated wastewater, using techniques such as thermal, irradiation, biological or mechanical processes.

There are challenges in assessing what technologies are most effective and cost-efficient. In many instances, these aspects are not investigated and reported on in a way that allows ready comparison between different systems that have been implemented in different countries. Many new technologies have thus far only been tested within a lab environment or in limited pilot studies.

5.5.4 Development of new antimicrobials

The development pipeline is running dry

As mentioned in section 2.2.3, we cannot rely on developing new antimicrobials alone to solve the AMR problem. Although the rise of AMR to existing drugs has been identified as a developing issue for some time, the number of new antimicrobial drugs that make it to market – and particularly drugs exploiting novel antimicrobial mechanisms of action – has been diminishing. As of December 2020, around 43 new antibiotics with the potential to treat serious bacterial infections were in clinical development,[1312] but with high attrition rates from research and development through to

The number of new antimicrobial drugs that make it to market – and particularly drugs exploiting novel antimicrobial mechanisms of action – has been diminishing.

[1309] Anwar, M., Iqbal, Q., & Saleem, F. (2020). Improper disposal of unused antibiotics: an often overlooked driver of antimicrobial resistance. *Expert Review of Anti-infective Therapy, 18*(8), 697-699. https://doi.org/10.1080/14787210.2020.1754797
[1310] Ministry for the Environment. (2021). *Freshwater farm plan regulations: Discussion document*. Wellington: Ministry for the Environment. Retrieved from https://consult.environment.govt.nz/freshwater/freshwater-farm-plan-regulations/supporting_documents/freshwaterfarmplanregulationsdiscussiondocument.pdf
[1311] New Zealand Government. (2020). *Declaration of Priority Products Notice 2020*: New Zealand Gazette. Retrieved from https://gazette.govt.nz/notice/id/2020-go3343
[1312] The Pew Charitable Trusts. (2021). *Antibiotics currently in global clinical development*. Retrieved from: https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development

market entry,[1313] this is unlikely to be enough to meet the world's need for drugs that can tackle resistant microbes.

There are multiple challenges associated with developing and successfully commercialising new antimicrobials. One of the leading challenges is technical – finding new mechanisms of action is difficult. However, other barriers are associated with the costs of antimicrobial development and the difficulty of recovering those costs.[1314]

Antimicrobials are typically prescribed over a short period of time, and in the case where new antimicrobials are being used to treat infections resistant to existing compounds, only rarely. This is particularly the case when compounds are used as a 'last resort' to preserve their activity. This means that only very small amounts of a new antimicrobial will be used, which makes them very expensive using the traditional cost-per-dose pricing model to recover development, approval, manufacturing, and distribution costs. Furthermore, the population, and agencies who fund pharmaceuticals, are accustomed to antimicrobial drugs being relatively inexpensive.

Only very small amounts of a new antimicrobial will be used, which makes them very expensive using the traditional cost-per-dose pricing model to recover development, approval, manufacturing, and distribution costs.

2019 bankruptcies

With the majority of new antimicrobials being developed by small, pre-revenue companies rather than the large pharmaceutical firms that previously dominated the field, the risk of bankruptcy for companies attempting to fill the antimicrobial drug gap is considerable.[1315] In 2019, two biopharmaceutical companies filed for bankruptcy when income from the sale of their recently approved antibiotics did not yield sufficient returns to cover the costs of their development.

Achaogen's antibiotic plazomicin, designed to treat complicated UTIs caused by MDROs, was authorised by the US FDA in 2018. However, the drug earned less than US$1 million for the company, forcing Achaogen to file for bankruptcy less than a year after its drug was approved, despite clinical need. Achaeogen also had other antibiotics in development at the time of its bankruptcy.[1316] Later in 2019, another biopharmaceutical company, Melinta Therapeutics, also filed for bankruptcy. At the time, it had four antibiotics in its portfolio, including recently approved delafloxacin, a novel fluoroquinolone.[1317]

Getting sufficient data for regulatory authorities to approve a new antimicrobial is also difficult and expensive. Placebo controlled trials where known treatments are available are generally deemed

[1313] The Pew Charitable Trusts. (2021, 9 March). Analysis shows continued deficiencies in antibiotic development since 2014. Retrieved 28 July, 2021, from https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2019/five-year-analysis-shows-continued-deficiencies-in-antibiotic-development

[1314] Kfoury, J. (2014). The paradox of antibiotics pricing. *LEK Consulting Executive Insights, 16*(46).

[1315] The Pew Charitable Trusts. (2021, 9 March). Tracking the global pipeline of antibiotics in development, March 2021. Retrieved 19 July, 2021, from https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development

[1316] Dall, C. (2019). Achaogen bankruptcy raises worry over antibiotic pipeline. *CIDRAP News*. Retrieved from https://www.cidrap.umn.edu/news-perspective/2019/04/achaogen-bankruptcy-raises-worry-over-antibiotic-pipeline; Mullard, A. (2019). Achaogen bankruptcy highlights antibacterial development woes. *Nature Reviews Drug Discovery, 18*(411). https://doi.org/10.1038/d41573-019-00085-w

[1317] Dall, C. (2019). Antibiotic developer Melinta files for bankruptcy. *CIDRAP News*. Retrieved from https://www.cidrap.umn.edu/news-perspective/2019/12/antibiotic-developer-melinta-files-bankruptcy

unethical, including in situations where there are existing antimicrobials that might have a marginal benefit against a drug-resistant organism. Furthermore, events where new antimicrobials will be of most use – that is, cases of infections resistant to all current antimicrobials – are rare and occur without warning, making it difficult to plan and conduct large trials. These issues add to both the time and cost of gathering the data for approval and lower the chance of success.

What's the solution?

To combat these issues, we can explore ways to reduce the costs of developing new antimicrobials and/or increase the financial rewards associated with successful antimicrobial development. Several potential solutions have been put forward, including some that are already being implemented. A review in 2016 found 47 different schemes globally looking to incentivise the development of new antimicrobials.[1318] These include both government policies to incentivise the development of new antimicrobials and the establishment of research consortia (usually involving a mix of government, private, and charity funding) to lower the costs of development.

The UK has launched a subscription-style payment scheme for antimicrobials (adopting the so-called 'Netflix Model'). The scheme was announced in 2019 and introduced in 2020 with two drugs (Cefiderocol manufactured by Shionogi, and ceftazidime + avibactam manufactured by Pfizer).[1319] Access to the medicines by NHS patients who need them will be provided for an annual fee, negotiated with the suppliers, rather than based on a set number of doses supplied. This is a promising initiative which decouples the revenue of the company from the volume purchased, but it is too early in the scheme to know whether it will be successful. Legislation currently under consideration in the US (the 'PASTEUR Act') looks to introduce a similar model there, with a focus on stimulating the development of antimicrobials with novel mechanisms of action and structures,[1320] and will hopefully be more effective than the 2012 GAIN Act.

The GAIN Act in the US

The Generating Antibiotic Incentives Now (GAIN) Act was introduced by the US Congress in 2012. It offers a longer period of exclusivity from generics and an accelerated approval regime for new antimicrobial products termed Qualified Infectious Disease Products. However, while the Act was welcomed by the industry on its introduction,[1321] it has been criticised for not providing sufficient incentives for developing genuinely new modes of antibiotic treatment.[1322]

Acknowledging the difficulties of developing new antimicrobials, the International Federation of Pharmaceutical Manufacturers and Associations,[1323] has organised the AMR Action Fund, launched in 2020, to support the clinical development of novel antimicrobials (see also section 2.4.3). The Federation includes the majority of the world's major pharmaceutical manufacturing companies and national associations (including Medicines New Zealand). The fund expects to invest more than US$1

[1318] Renwick, M.J., Brogan, D.M., & Mossialos, E. (2016). A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *The Journal of Antibiotics, 69*(2), 73-88. https://doi.org/10.1038/ja.2015.98
[1319] Perkins, M., & Glover, D. (2020). How the 'NHS model' to tackle antimicrobial resistance (AMR) can set a global standard. Retrieved from https://www.england.nhs.uk/blog/how-the-nhs-model-to-tackle-antimicrobial-resistance-amr-can-set-a-global-standard/
[1320] Infectious Diseases Society of America. (2021, 16 June). *Renewed introduction of the PASTEUR Act returns AMR to national agenda* [Press release]. Retrieved from https://www.idsociety.org/news--publications-new/articles/2021/renewed-introduction-of-the-pasteur-act-returns-amr-to-national-agenda/; Vorperian, S., & Quake, S. (2021). The PASTEUR Act can help win the war against superbugs. *Stat News*. Retrieved from https://www.statnews.com/2021/06/25/pasteur-act-help-fight-superbugs-antimicrobial-resistance/
[1321] Biotechnology Innovation Organization. (2013, 11 October). *GAIN Act: A great first step* [Press release]. Retrieved from https://www.bio.org/blogs/gain-act-great-first-step
[1322] Darrow, J.J., & Kesselheim, A.S. (2020). Incentivizing antibiotic development: Why isn't the Generating Antibiotic Incentives Now (GAIN) Act working? *Open Forum Infectious Diseases, 7*(1). https://doi.org/10.1093/ofid/ofaa001
[1323] International Federation of Pharmaceutical Manufacturers & Associations. (n.d.). IFPMA in brief. Retrieved 5 November, 2021, from https://www.ifpma.org/

billion to bring two to four new antibiotics to patients by 2030.[1324] The Fund involves more than 20 pharmaceutical companies, including the major suppliers of existing drugs, philanthropies, development banks and multilateral organisations. Pfizer[1325] and Merck[1326] have pledged US$100 million each to the Fund which will focus on investing in new start-ups and biotech companies to bring new drugs to market.

What's happening in Aotearoa New Zealand?

Aotearoa New Zealand has a number of research groups looking to develop new antimicrobials. Examples are included below – this is not a comprehensive list but gives an indication of the types of work occurring across the country.

- The Ferrier Research Institute at Victoria University of Wellington has a programme to develop new treatments for drug-resistant tuberculosis (TB) and other antimicrobial compounds.[1327]
- A number of other research efforts are underway at Victoria University of Wellington. This includes work led by Professor David Ackerley (metagenomic-driven drug discovery[1328] and antibiotic repurposing[1329]), Dr Wanting Jiao (computational approaches to drug design[1330]), and Professor Emily Parker (designing β-lactamase inhibitors).[1331]
- Groups at the University of Auckland are looking for new antimicrobial compounds, including that of Associate Professor Siouxsie Wiles (looking at compounds from New Zealand fungi),[1332] Distinguished Professor Dame Margaret Brimble (looking at lipopeptide antibiotics and new compounds derived from thermophilic soil bacteria)[1333], and Dr Ghader Bashiri (compounds from soil bacteria).[1334] Dr Stephanie Dawes is leading work on synergistic antibiotic drug combinations.[1335]
- Research into new drugs to treat TB is being undertaken by the Auckland Cancer Society Research Centre, in collaboration with international organisations and with funding from the University of Auckland. This work, formerly led by Distinguished Professor Sir Bill Denny and

[1324] AMR Action Fund. (n.d.). About us. Retrieved 26 July, 2021, from https://amractionfund.com/about-us/
[1325] Pfizer. (2020, 9 July). *Pfizer pledges $100 million to new industry fund to help fight growing threat of antimicrobial resistance* [Press release]. Retrieved from https://investors.pfizer.com/investor-news/press-release-details/2020/Pfizer-Pledges-100-Million-to-New-Industry-Fund-to-Help-Fight-Growing-Threat-of-Antimicrobial-Resistance/default.aspx
[1326] Merck. (2020, 9 July). *Addressing antibiotic resistance is more critical than ever. Here's why.* [Press release]. Retrieved from https://www.merck.com/stories/addressing-antibiotic-resistance-is-more-critical-than-ever/
[1327] Victoria University of Wellington. (n.d.). Infectious diseases. Retrieved 17 November, 2021, from https://www.wgtn.ac.nz/ferrier/research/infectious-diseases
[1328] Health Research Council. (2016). Biodiscovery and biosynthesis of new drug candidates. Retrieved 9 December, 2021, from https://www.hrc.govt.nz/resources/research-repository/biodiscovery-and-biosynthesis-new-drug-candidates
[1329] Health Research Council. (2018). Repurposing the anthelmentic niclosamide to combat Gram negative superbugs. Retrieved 9 December, 2021, from https://www.hrc.govt.nz/resources/research-repository/repurposing-anthelmentic-niclosamide-combat-gram-negative-superbugs
[1330] Health Research Council. (2019). Developing computational tools to design highly potent antibiotics. Retrieved 9 December, 2021, from https://www.hrc.govt.nz/resources/research-repository/developing-computational-tools-design-highly-potent-antibiotics
[1331] Health Research Council. (2019). Tackling antimicrobial resistance. Retrieved 9 December, 2021, from https://www.hrc.govt.nz/resources/research-repository/tackling-antimicrobial-resistance
[1332] Grey, A.B.J., Cadelis, M.M., Diao, Y.*, et al.* (2021). Screening of fungi for antimycobacterial activity using a medium-throughput bioluminescence-based assay. *Frontiers in Microbiology, 12*(2525). https://doi.org/10.3389/fmicb.2021.739995
[1333] The University of Auckland. (n.d.). Brimble group. Retrieved 17 November, 2021, from https://brimble.chem.auckland.ac.nz/; Wilson, Z.E., & Brimble, M.A. (2021). Molecules derived from the extremes of life: A decade later. *Natural Product Reports, 38*(1), 24-82. https://doi.org/10.1039/D0NP00021C
[1334] Auckland Medical Research Foundation. (2020). Has New Zealand helped find the world's next antibiotic? Retrieved from https://www.medicalresearch.org.nz/post/has-new-zealand-helped-find-the-world-s-next-antibiotic
[1335] Health Research Council. (2020). Designing synergistic combinations to prevent antibiotic resistance. Retrieved 9 December, 2021, from https://www.hrc.govt.nz/resources/research-repository/designing-synergistic-combinations-prevent-antibiotic-resistance

now by Dr Hamish Sutherland, has led to the successful discovery of multiple new drugs, some of which have been brought to clinical trials.[1336]

- Distinguished Professor Greg Cook at the University of Otago is looking at the development of new antibiotic compounds in both human and animal health, including for agricultural use.[1337] Professor Cook is also exploring the use of high-throughput bacterial genetics techniques to identify new antibiotics and antibiotic combinations to treat drug-resistant TB.[1338]
- Dr Joanne Hicks at the University of Waikato is leading work to explore novel treatment approaches for drug-resistant *Neisseria gonorrhoeae*.[1339]
- Dr Ishwar Singh at the University of Lincoln is working on modifying a new antibiotic isolated from a soil bacterium to make it easier to produce.[1340]
- Professor Jack Heinemann's group at the University of Canterbury is looking for alternative chemistries to be used in product formulations that don't cause resistance in the first place.[1341]
- At the Maurice Wilkins Centre, the AMR flagship project aims to produce novel antimicrobials that target a number of high priority drug-resistant bacterial pathogens including MDROs and *Mycobacterium tuberculosis*.[1342]

5.5.5 Other approaches and therapies

There are many new approaches and therapies that are being researched and trialled to use in addition to, or instead of, antimicrobial therapies. As AMR issues continue to intensify, the focus on developing alternative therapies has grown. This is because viable alternative therapies could allow us to reduce antimicrobial use (and therefore mitigate AMR) while also allowing us to fight drug-resistant infections in people, plants, and animals. Table 14 summarises a small selection of some approaches being explored; see appendix 7.6 for further details and approaches.

Table 14: Selection of new therapies that could be used in conjunction with or as an alternative to antimicrobial therapy

Approach	Summary
Monoclonal antibodies	Antibodies could be used as an alternative to antimicrobials.[1343] A key challenge is to enable antibodies to target a range of pathogens rather than a limited spectrum. There are large upfront costs and scaling costs, but there have been some success stories in clinical trials.[1344] Resistance to antibodies is also possible, but use of antibody cocktails can help to

[1336] Global Alliance for TB Drug Development. (2020). Evaluate safety, tolerability, PK of TBAJ-876 in healthy adults. [Clincial trial]. Retrieved from https://ClinicalTrials.gov/show/NCT04493671; Global Alliance for TB Drug Development. (2021). Evaluation of the safety, tolerability, PK of TBAJ-587 in healthy adults. [Clinical trial]. Retrieved from https://ClinicalTrials.gov/show/NCT04890535

[1337] University of Otago. (n.d.). Antimicrobial resistance. Retrieved 17 November, 2021, from https://micro.otago.ac.nz/our-people/teaching-research-and-support/greg-cook/cook-lab-project-c/

[1338] Health Research Council. (2020). Combating antimicrobial resistance with high-throughput bacterial genetics. Retrieved 9 December, 2021, from https://www.hrc.govt.nz/resources/research-repository/combating-antimicrobial-resistance-high-throughput-bacterial-genetics

[1339] Health Research Council. (2021). Repurposing anti-viral immunity to combat *Neisseria gonorrhoeae*. Retrieved 9 December, 2021, from https://www.hrc.govt.nz/resources/research-repository/repurposing-anti-viral-immunity-combat-neisseria-gonorrhoeae; Health Research Council. (2019). Cysteine biosynthesis and infection, gonorrhoea's weak link? Retrieved 9 December, 2021, from https://www.hrc.govt.nz/resources/research-repository/cysteine-biosynthesis-and-infection-gonorrhoeas-weak-link

[1340] University of Lincoln. (n.d.). Saving the world from antimicrobial resistance. Retrieved 17 November, 2021, from https://www.lincoln.ac.uk/home/researchatlincoln/casestudies/antimicrobialresistance/

[1341] Heinemann, J. (2021). Personal communication.

[1342] Maurice Wilkins Centre. (n.d.). Addressing antimicrobial resistance (including TB). Retrieved 29 November, 2021, from https://www.mauricewilkinscentre.org/sub-pages/research/infectious-disease/addressing-anti-microbial-resistance-including-tb/

[1343] Baker, S.J., Payne, D.J., Rappuoli, R., *et al.* (2018). Technologies to address antimicrobial resistance. *Proceedings of the National Academy of Sciences, 115*(51), 12887-12895. https://doi.org/10.1073/pnas.1717160115

[1344] Zurawski, D.V., & McLendon, M.K. (2020). Monoclonal antibodies as an antibacterial approach against bacterial pathogens. *Antibiotics, 9*(4), 155. https://doi.org/10.3390/antibiotics9040155

	mitigate this risk.[1345] Anti-SARS-CoV-2 monoclonal antibodies have been developed and shown to have clinical benefit in treating and preventing COVID-19.[1346]
Bacteriophage therapies[1347]	Bacteriophages are a type of virus that infects bacteria. They have been used therapeutically since their discovery in the early 1900s but have not been used systematically in infection management since antibiotics became widely used in the 1940s.[1348] In Aotearoa New Zealand there are bacteriophages approved as processing aids in food, for example, to eradicate or reduce the presence of *Listeria monocytogenes* and *E. coli*. However, there are none approved here for clinical use. A recent trial in Australia used bacteriophage therapy in patients with severe *Staphylococcus aureus* infections to assess safety, though further trials are needed to assess efficacy.[1349] Globally, robust trials are few and mostly unsuccessful thus far, and coordinated effort is needed to define the role and likely candidates for bacteriophage therapy.[1350] As well as being used instead of antibiotics, bacteriophages may be used in combination with them.[1351]
Lysins	Bacteriophage endolysins (lysins) are a type of enzyme that is produced by bacteriophages, which can kill bacteria by breaking through the bacterial cell wall.[1352] The lysins structurally damage the bacterial cell wall. So far, bacteria have not developed resistance to the lysins. The majority of research into the use of lysins has been against *Staphylococcus aureus,* though the use of lysins against gram-negative bacteria is also being explored.[1353]
Microbiome-affecting therapies[1354] (including probiotics and prebiotics)	The microbiome (the microorganisms within our body) and immune system (which fights off infections) can work together to prevent or fight infection.[1355] The microbiome of humans and animals can be manipulated by the introduction of small collectives of microbes, whole communities of microbes, nutrients, or other growth factors that benefit the microbiota by strengthening or restoring beneficial functions or otherwise exclude invasive or antibiotic-resistant strains and species. For some microbiome-affecting therapies, more research is needed. For others, such as faecal transplants to treat recurrent *Clostridium diificule* infections,[1356] are already commonly used. In animals, medium-chain fatty acids,[1357] phytogenic feed additives,[1358] and bacterial feeds[1359] among the approaches

[1345] Ku, Z., Xie, X., Davidson, E.*, et al.* (2021). Molecular determinants and mechanism for antibody cocktail preventing SARS-CoV-2 escape. *Nature Communications, 12*(1), 469. https://doi.org/10.1038/s41467-020-20789-7

[1346] National Institutes of Health. (2021, 19 October 2021). Anti-SARS-CoV-2 monoclonal antibodies. Retrieved 29 November, 2021, from https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

[1347] Hesse, S., Malachowa, N., Porter, A.R.*, et al.* (2021). Bacteriophage Treatment Rescues Mice Infected with Multidrug-Resistant *Klebsiella pneumoniae* ST258. *mBio, 12*(1), e00034-00021. https://doi.org/10.1128/mBio.00034-21; Doxzen, K. (2021). Engineered viruses can fight the rise of antibiotic-resistant bacteria. *The Conversation*. Retrieved from https://theconversation.com/engineered-viruses-can-fight-the-rise-of-antibiotic-resistant-bacteria-154337

[1348] Wu, N., & Zhu, T. (2021). Potential of therapeutic bacteriophages in nosocomial infection management. *Frontiers in Microbiology, 12*(83). https://doi.org/10.3389/fmicb.2021.638094

[1349] Petrovic Fabijan, A., Lin, R.C.Y., Ho, J.*, et al.* (2020). Safety of bacteriophage therapy in severe *Staphylococcus aureus* infection. *Nature Microbiology, 5*(3), 465-472. https://doi.org/10.1038/s41564-019-0634-z

[1350] Khalid, A., Lin, R.C.Y., & Iredell, J.R. (2021). A phage therapy guide for clinicians and basic scientists: Background and highlighting applications for developing countries. *Frontiers in Microbiology, 11*, 599906-599906. https://doi.org/10.3389/fmicb.2020.599906

[1351] Berryhill, B.A., Huseby, D.L., McCall, I.C.*, et al.* (2021). Evaluating the potential efficacy and limitations of a phage for joint antibiotic and phage therapy of *Staphylococcus aureus* infections. *Proceedings of the National Academy of Sciences, 118*(10), e2008007118. https://doi.org/10.1073/pnas.2008007118

[1352] Ghose, C., & Euler, C.W. (2020). Gram-negative bacterial lysins. *Antibiotics, 9*(2), 74. https://doi.org/10.3390/antibiotics9020074

[1353] Theuretzbacher, U., Outterson, K., Engel, A.*, et al.* (2020). The global preclinical antibacterial pipeline. *Nature Reviews Microbiology, 18*(5), 275-285. https://doi.org/10.1038/s41579-019-0288-0

[1354] CARB-X. (2020, 20 November). *Vedanta Biosciences' new VE303 drug will prevent life-threatening C. difficile infections by boosting the body's microbiome* [Press release]. Retrieved from https://carb-x.org/spotlight/spotlight-vedanta-biosciences/

[1355] Relman, D.A., & Lipsitch, M. (2018). Microbiome as a tool and a target in the effort to address antimicrobial resistance. *Proceedings of the National Academy of Sciences, 115*(51), 12902-12910. https://doi.org/10.1073/pnas.1717163115

[1356] Mullish, B.H., Quraishi, M.N., Segal, J.P.*, et al.* (2018). The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: Joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut, 67*(11), 1920. https://doi.org/10.1136/gutjnl-2018-316818; Baunwall, S.M.D., Lee, M.M., Eriksen, M.K.*, et al.* (2020). Faecal microbiota transplantation for recurrent *Clostridioides difficile* infection: An updated systematic review and meta-analysis. *EClinicalMedicine, 29*. https://doi.org/10.1016/j.eclinm.2020.100642

[1357] Jackman, J.A., Boyd, R.D., & Elrod, C.C. (2020). Medium-chain fatty acids and monoglycerides as feed additives for pig production: Towards gut health improvement and feed pathogen mitigation. *Journal of Animal Science and Biotechnology, 11*(1), 44. https://doi.org/10.1186/s40104-020-00446-1

[1358] Murugesan, G.R., Syed, B., Haldar, S.*, et al.* (2015). Phytogenic feed additives as an alternative to antibiotic growth promoters in broiler chickens. *Frontiers in Veterinary Science, 2*(21). https://doi.org/10.3389/fvets.2015.00021

[1359] Upadhaya, S.D., Rudeaux, F., & Kim, I.H. (2019). Efficacy of dietary *Bacillus subtilis* and *Bacillus licheniformis* supplementation continuously in pullet and lay period on egg production, excreta microflora, and egg quality of Hyline-Brown birds. *Poultry Science, 98*(10), 4722-4728. https://doi.org/10.3382/ps/pez184

	being explored, with reduced access to antimicrobials for animal husbandry in some countries driving exploration.
Host modulation	Host modulation looks at how to help the host (patient) fight bacteria, particularly how the immune system can be supported to eliminate bacteria.[1360] There are a number of approaches to host-directed therapy including modulating innate immune cell function, modulating adaptive immune responses, programmed cell death, and metabolism.[1361]
Prodrugs	Prodrugs are molecules with little to no pharmacological activity that can be converted into an active drug inside the body. In Aotearoa New Zealand, prodrug antimicrobials that activate in the presence of infection are being developed for livestock.[1362]
Repurposing existing antimicrobials	A biopharmaceutical company in Australia is undertaking clinical trials with STM-001, consisting of the widely used antibiotic vancomycin repurposed with permeator technology that allows the antibiotic to effectively penetrate resistant bacteria.[1363]

Plant-specific alternative approaches

There are a number of techniques that are specific to use in plants that could provide alternative approaches to antimicrobial use. Examples are included in Table 15. Some of these techniques are discussed in section 3.5.1 in the context of Psa.

Table 15: Examples of plant-specific alternatives to antimicrobial treatments[1364]

Approach	Summary
Selective breeding	Selective breeding can be used to decrease host plant susceptibility to diseases. This can be achieved both through conventional plant breeding or through genetic modification. An example of the use of genetic modification includes the deployment of cisgenes to plants, which then provide the plant with resistance to a given disease, e.g. resistance to scab (apples) and late blight (potatoes).[1365] Selective breeding for reduced pathogen susceptibility is also possible in animals (e.g. reduced *Staphylococcus aureus* in cows,[1366] reduced parasite susceptibility in deer).[1367]
Use of biologicals	Biologicals (probiotics, prebiotics, bacteriophages) and biorational compounds can be used for disease control in plants. For example, probiotic microbes applied to the soil can help protect plants against harmful microbes, while also assisting in converting organic materials into a state that can help the growth and health of the plants.[1368] The use of bacteriophages is also possible to combat particular diseases and has the potential to adapt to new strains of drug-resistant bacteria. While their use is not yet common, many pesticide companies are now investing in this area of research.[1369]
Microbiome and soil health	Exploitation of the microbiome and soil health has the ability to help control plant diseases. Soil is incredibly biodiverse and bacteria-rich: one gram of soil can contain a billion bacterial

[1360] Theuretzbacher, U., Outterson, K., Engel, A., *et al.* (2020). The global preclinical antibacterial pipeline. *Nature Reviews Microbiology, 18*(5), 275-285. https://doi.org/10.1038/s41579-019-0288-0

[1361] Kilinç, G., Saris, A., Ottenhoff, T.H., *et al.* (2021). Host-directed therapy to combat mycobacterial infections. *Immunological Reviews, 301*(1), 62-83. https://doi.org/10.1111/imr.12951

[1362] One Health Aotearoa. (2020, 11 September). *Otago Innovation's Proof of Concept winners tackle antibiotic resistance* [Press release]. Retrieved from https://onehealth.org.nz/otago-innovations-proof-of-concept-winners-tackle-antibiotic-resistance/

[1363] Neville, L.F., Shalit, I., Warn, P.A., *et al.* (2021). In vivo targeting of *Escherichia coli* with vancomycin-arginine. *Antimicrobial Agents and Chemotherapy, 65*(4), e02416-02420. https://doi.org/10.1128/AAC.02416-20; SuperTrans Medical. (2021, 11 February). *'Supercharger' to revive mainstay antibiotic in global fight against antibiotic resistance* [Press release]. Retrieved from https://www.prnewswire.com/news-releases/supercharger-to-revive-mainstay-antibiotic-in-global-fight-against-antibiotic-resistance-301225560.html

[1364] Food and Agriculture Organization Antimicrobial Resistance Working Group. (2018). *Antimicrobial resistance and foods of plant origin: Summary report of an FAO meeting of experts*. Retrieved from http://www.fao.org/3/BU657en/bu657en.pdf

[1365] Mann, A., Nehra, K., Rana, J.S., *et al.* (2021). Antibiotic resistance in agriculture: Perspectives on upcoming strategies to overcome upsurge in resistance. *Current Research in Microbial Sciences, 2*, 100030. https://doi.org/https://doi.org/10.1016/j.crmicr.2021.100030

[1366] Heimes, A., Brodhagen, J., Weikard, R., *et al.* (2020). Cows selected for divergent mastitis susceptibility display a differential liver transcriptome profile after experimental *Staphylococcus aureus* mammary gland inoculation. *Journal of Dairy Science, 103*(7), 6364-6373. https://doi.org/10.3168/jds.2019-17612

[1367] Deer Industry NZ. (2020). The CARLA breeding value: Using genes to combat internal parasites. [Fact sheet]. Retrieved from https://www.deernz.org/assets/Deer-Facts/DeerFact_CARLA_V7-web.pdf

[1368] Zia, R., Shuja, M.N., Ali, M., *et al.* (2021). Plant probiotics: Technical challenges and emerging solutions for enhancing food crops *Soil Microbiomes for Sustainable Agriculture* (pp. 379-405): Springer.

[1369] Buttimer, C., McAuliffe, O., Ross, R.P., *et al.* (2017). Bacteriophages and bacterial plant diseases. *Frontiers in Microbiology, 8*, 34. https://doi.org/10.3389/fmicb.2017.00034

	cells.[1370] While there are opportunities to develop new strategies for biome and soil health, it is equally important that services already provided by soil are not further degraded by human activities, including through the introduction of antimicrobials.

[1370] Zhu, Y.-G., Zhao, Y., Zhu, D.*, et al.* (2019). Soil biota, antimicrobial resistance and planetary health. *Environment International, 131*, 105059. https://doi.org/https://doi.org/10.1016/j.envint.2019.105059

5.6 Empowering people and building capability

People sit at the heart of our efforts to combat infectious disease and AMR, and everyone has a role to play. This section explores the importance of engaging with the public so that they can contribute to efforts to combat infectious disease and AMR, and the value of fostering research collaboration domestically and internationally.

5.6.1 Bringing the public along on the journey

Throughout this report, we have noted opportunities to strengthen training, education, and workforce capacity for people involved directly in antimicrobial prescribing, dispensing, and administration, AMR surveillance, and infectious disease prevention, control, and treatment. This section addresses how we can empower the public to support the mission of combatting infectious disease and AMR. We focus on effective communication and health literacy, but these must be characterised by a kotahitanga approach from the grassroots. Communication must involve listening as much as it involves speaking, and it must be diverse rather than one-size-fits-all.

Communication must involve listening as much as it involves speaking, and it must be diverse rather than one-size-fits-all.

Bolstering health literacy is key to combatting infectious disease and AMR

Health literacy is defined by MoH as a person's "capacity to find, interpret and use information and health services to make effective decisions for their health and wellbeing."[1371] Going beyond the individual, a 2015 health literacy framework produced by MoH acknowledged roles for the health system, health organisations, health workforce, and individuals and whānau in championing health literacy – the whole health system has a role to play in ensuring people can access and utilise information that will promote their health.[1372]

International studies have highlighted that health literacy is closely linked to health outcomes. As summarised in *Kōrero Mārama: Health Literacy and Māori*, research suggests that people with low health literacy: are less likely to use prevention services like screening; have less knowledge of their illness, treatment and medicines; are more likely to use emergency services; and are less likely to manage their long-term condition.[1373] Bolstering health literacy therefore has scope to support our efforts to combat infectious disease and AMR, linking closely to prevention, disease control, and AMS.

A 2006 national study examining health literacy among New Zealand adults (the most current national study available) found that 56.2% of adult New Zealanders had poor health literacy skills,[1374] highlighting the need to bolster health literacy among the general population, including through

[1371] Ministry of Health. (n.d., 21 May 2015). Health literacy. Retrieved 9 December, 2021, from https://www.health.govt.nz/our-work/making-services-better-users/health-literacy
[1372] Ministry of Health. (n.d.). *A framework for health literacy*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/system/files/documents/publications/a-framework-for-health-literacy-may15.pdf
[1373] Ministry of Health. (2010). *Kōrero Mārama: Health literacy and Māori – Results from the 2006 adult literacy and life skills survey*. Wellington, NZ: Ministry of Health. Retrieved from https://www.moh.govt.nz/notebook/nbbooks.nsf/0/4559082D3B05C11FCC2576CE006835A1/$file/korero-marama.pdf
[1374] Health Literacy NZ. (n.d.). What is health literacy? Retrieved 9 December, 2021, from https://www.healthliteracy.co.nz/page/about-health-literacy/

promoting literacy, numeracy, and critical thinking in the education system, as well as tailoring health services and communication to support access to and understanding of key information.

Based on the results of the same 2006 study, Māori were found to be more likely to have low health literacy, with four out of five Māori males and three out of four Māori females having poor health literacy skills.[1375] A study exploring health literacy in Indigenous people, looking at Canada, Australia, and New Zealand, suggested that Western-centric conceptualisations of health and knowledge may play a role in health literacy disparities, and encouraged the development of policies and guidelines that ensure the diverse strengths and needs of Indigenous people are accounted for in the way health literacy is promoted.[1376]

In addition to general health literacy, knowledge specific to antimicrobials and AMR could also be strengthened in Aotearoa New Zealand. This need is recognised in the *New Zealand AMR Action Plan*, the first objective of which is to "improve awareness and understanding of AMR through effective communication, education and training."[1377] There is little evidence exploring New Zealanders' understanding of AMR and antimicrobial use, although one study looking at immigrant ethnic groups in Aotearoa New Zealand from 2010, only a minority knew about AMR, with many participants misunderstanding how antibiotics work and what they work against. For example, fewer than half of participants were sure that antibiotics were not useful for colds and flu.[1378]

Australia's national science agency conducted a survey in 2020 to explore knowledge about antimicrobial use and AMR. A similar study would be valuable in the New Zealand context. The Australian study found that only 8.5% of people were confident that they knew the difference between a virus and bacteria and, for numerous diseases or symptoms that can't be treated with antibiotics, respondents reported that they thought antibiotic use was appropriate (e.g. 47% of respondents thought flu could be treated with antibiotics).[1379]

47% of respondents thought flu could be treated with antibiotics.

Interventions to improve understanding of antimicrobial use have been shown to be effective. For example:

- In a randomised controlled trial in Tāmaki Makaurau Auckland in 2018, patients at two GPs were provided with a brief presentation on a tablet during their wait prior to consultation. One presentation discussed the futility of antibiotic treatment for upper respiratory tract infections, one discussed the adverse effects of antibiotics, and the third presentation was a control. Both interventions resulted in a decrease in patient expectation of receiving antibiotics.[1380]

[1375] Ministry of Health. (2010). *Kōrero Mārama: Health literacy and Māori – Results from the 2006 adult literacy and life skills survey*. Wellington, NZ: Ministry of Health. Retrieved from https://www.moh.govt.nz/notebook/nbbooks.nsf/0/4559082D3B05C11FCC2576CE006835A1/$file/korero-marama.pdf

[1376] Boot, G.R., & Lowell, A. (2019). Acknowledging and promoting Indigenous knowledges, paradigms, and practices within health literacy-related policy and practice documents across Australia, Canada, and New Zealand. *International Indigenous Policy Journal, 10*(3), 1-28. https://doi.org/10.18584/iipj.2019.10.3.8133

[1377] Ministry of Health and Ministry for Primary Industries. (2017). *New Zealand Antimicrobial Resistance Action Plan*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/publication/new-zealand-antimicrobial-resistance-action-plan

[1378] Norris, P., Ng, L.F., Kershaw, V., *et al.* (2010). Knowledge and reported use of antibiotics amongst immigrant ethnic groups in New Zealand. *Journal of Immigrant and Minority Health, 12*(1), 107.

[1379] OUTBREAK. (2020, 14 May). *Public information key to combatting rising superbug threat* [Press release]. Retrieved from https://outbreakproject.com.au/2020/05/14/public-information-key-to-combatting-rising-superbug-threat/

[1380] Perera, A.I., Thomas, M.G., Petrie, K.J., *et al.* (2021). Reducing expectations for antibiotics in patients with upper respiratory tract infections: A primary care randomized controlled trial. *The Annals of Family Medicine, 19*(3), 232. https://doi.org/10.1370/afm.2672

- In an Auckland hospital, approximately 300 patients were shown one of three posters about antibiotic use: one highlighting the futility of antibiotics for viral infections, one highlighting the risk of adverse events associated with unnecessary antibiotic use, and the third highlighting the issue of AMR. Patients who viewed the posters reported significantly reduced expectations to receive antibiotics for a cold, with the poster highlighting futility being the most effective.[1381]
- In a UK study, a brief digital intervention was shown to reduce participant's belief about the necessity of antibiotics, increase their concerns relating to antibiotics, and increase knowledge about antibiotics and AMR.[1382] The digital tool profiled the person's individual beliefs and then tailored messages to address specific problematic beliefs.

Rangatahi engaging with AMR

Enhancing health literacy should start with our tamariki and rangatahi, through incorporation into school curricula or activities. We piloted a hui approach with students from Aorere College in Tāmaki Makaurau Auckland, inviting students to consider AMR scenarios: what would be the impacts, challenges and potential solutions? We were impressed with the breadth and depth of the students' ideas, many of which were the same as those posed by the experts on our panel and reference group. The COVID-19 response appeared to play a role in their understanding of health issues such as AMR, inspiring some of their solutions. Further details on the hui can be found in Appendix 7.7.

Effective communication is key

Effective communication can empower the public to combat infectious disease and AMR. Aotearoa New Zealand's approach to mass public communication during the early stages of the COVID-19 pandemic was praised,[1383] and lessons can be drawn from this experience and applied to other aspects of health in Aotearoa New Zealand, including in the animal and plant spheres. Key strengths of the approach to public communication during the pandemic include:

- Involving scientists and experts in communication campaigns, with international polling suggesting that scientists hold a high level of public trust.[1384] Other spokespeople have also played important roles in supporting our Covid-19 response. For example, gang leaders have played a role in encouraging vaccine uptake in hard-to-reach communities.[1385]
- Timely and transparent communication, with regular press conferences and the sharing of information underlying key decisions.[1386]
- The prominent use of te reo Māori and New Zealand sign language, and provision of key health and vaccine information in over 30 languages.[1387]

[1381] Ritchie, S.R., Rakhmanova, L., Out-O'Reilly, E.*, et al.* (2019). The use of a poster to reduce expectations to receive antibiotics for a common cold. *European Journal of Clinical Microbiology & Infectious Diseases, 38*(8), 1463-1469. https://doi.org/10.1007/s10096-019-03572-5

[1382] Chan, A.H.Y., Horne, R., Lycett, H.*, et al.* (2021). Changing patient and public beliefs about antimicrobials and antimicrobial resistance (AMR) using a brief digital intervention. *Frontiers in Pharmacology, 12*. https://doi.org/10.3389/fphar.2021.608971

[1383] Beattie, A., & Priestley, R. (2021). Fighting COVID-19 with the team of 5 million: Aotearoa New Zealand government communication during the 2020 lockdown. *Social Sciences & Humanities Open, 4*(1), 100209. https://doi.org/10.1016/j.ssaho.2021.100209

[1384] Edelman. (2021). *Edelman Trust Barometer 2021*. Retrieved from https://www.edelman.com/sites/g/files/aatuss191/files/2021-03/2021%20Edelman%20Trust%20Barometer.pdf

[1385] Hendry-Tennent, I. (2021, 3 November). Members from NZ's most notorious gangs band together to promote COVID-19 vaccine amid Delta outbreak, *Newshub*. Retrieved from https://www.newshub.co.nz/home/new-zealand/2021/11/members-from-nz-s-most-notorious-gangs-band-together-to-promote-covid-19-vaccine-amid-delta-outbreak.html

[1386] New Zealand Government. (2021, 6 December). COVID-19 updates. Retrieved 9 December, 2021, from https://www.beehive.govt.nz/feature/covid-19-updates

[1387] Unite Against COVID-19. (n.d., 7 December 2021). Translations. Retrieved 9 December, 2021, from https://covid19.govt.nz/languages-and-resources/translations/

- A clear national strategy and alert level system,[1388] which filtered down to clear communication.

Aside from the top-down communication, we also saw people band together to provide comprehensive and holistic services that suited their communities. For example, self-determination/rangatiratanga and a people-centred (rather than plan-oriented) approach were key factors in a successful COVID-19 response for Taranaki Māori.[1389] This demonstrates the need to empower and trust communities to do the mahi in ways that work for them.

Mass communication isn't the only area where communication can support positive health outcomes. One-on-one conversations, such as those that occur between patients and healthcare workers and vets and farmers or pet owners, also represent an opportunity to communicate effectively to combat infectious disease and AMR. One-on-one communication should be tailored depending on the person being engaged with to acknowledge the diversity of languages, educational and cultural backgrounds, and learning styles in Aotearoa New Zealand.

In an example of the value of effective one-on-one communication in human health, a UK study found that internet-based training in enhanced communication skills could sustainably reduce inappropriate antibiotic prescribing for respiratory tract infections by GPs. The communication training covered patient-centred communication, including eliciting concerns and exploring expectations, exchanging information, agreeing on management, and summing up.[1390] In animal health, a study in The Netherlands focused on importance of effective communication between vets and farmers for the management of mastitis. The study found that communication was most effective when the vet used a means of communication that accounted for the different learning styles of farmers, was pro-active, involved personalised messages, provided a realistic frame of reference for the farmers, and was consistent with messages being received by farmers from other sources.[1391]

Effective communication is particularly important in the face of rising mis- and disinformation.

Effective communication is particularly important in the face of rising mis- and disinformation abroad and in Aotearoa New Zealand, and an increasingly diverse and digitised information landscape. Evidence-based approaches for combating mis- and disinformation are continually being tested. Evidence syntheses are available, for example in the Debunking Handbook[1392] and Conspiracy Theory Handbook,[1393] to support communication strategies to combat mis- and disinformation. Combatting mis- and disinformation can also be supported with education, including interventions to promote media

[1388] Unite Against COVID-19. (n.d., 3 December 2021). History of the COVID-19 alert system. Retrieved 9 December, 2021, from https://covid19.govt.nz/about-our-covid-19-response/history-of-the-covid-19-alert-system/
[1389] Manuirirangi, K., & Jarman, J. (2021). The Taranaki COVID-19 response from a Māori perspective: Lessons for mainstream health providers in Aotearoa New Zealand. *The New Zealand Medical Journal, 134*(1533), 122-124.
[1390] Little, P., Stuart, B., Francis, N.*, et al.* (2019). Antibiotic prescribing for acute respiratory tract infections 12 months after communication and CRP training: A randomized trial. *The Annals of Family Medicine, 17*(2), 125. https://doi.org/10.1370/afm.2356
[1391] Lam, T., Jansen, J., van den Borne, B.H.P.*, et al.* (2011). What veterinarians need to know about communication to optimise their role as advisors on udder health in dairy herds. *New Zealand Veterinary Journal, 59*(1), 8-15. https://doi.org/10.1080/00480169.2011.547163
[1392] Lewandowsky, S., Cook, J., Ecker, U.*, et al.* (2020). *The debunking handbook*.
[1393] Lewandowsky, S., & Cook, J. (2020). *The conspiracy theory handbook*.

literacy[1394] and educate people about disinformation tactics.[1395] In Aotearoa New Zealand, Te Pūnaha Matatini's Disinformation Project led by Kate Hannah is exploring the prevalence and nature of COVID-19 mis- and disinformation narratives.[1396]

5.6.2 Strengthening research

There is excellent mahi happening in Aotearoa in the infectious disease and AMR research space. Throughout this report, we have highlighted some of this work, but there is more besides happening throughout the country. In a 2020 poll exploring New Zealanders' thoughts on health and medical research, doing research on antibiotic resistance was ranked among the top areas of importance for health research (with 77% considering it to be extremely important).[1397] Other priorities included doing research to make our health system more effective and efficient, and engaging in vaccine research. With COVID-19 highlighting the importance of infectious disease research to New Zealand and the world, there is likely elevated public appetite for further research and investment in this space.

This section focuses on research connectivity between stakeholders across the human, animal, plant, and environmental health interface, with valuable inclusion of mātauranga Māori, as well as the importance of international collaboration, including with Pacific partners.

A kotahitanga approach to research

In developing a unified and integrated Aotearoa New Zealand response to the challenge of infectious diseases and AMR, we need to strengthen connections between people and systems, creating partnerships that can have a real impact. Te ao Māori can provide a framework for building many of these connections and embracing the holistic view that is needed to tackle AMR and infectious disease. This means embracing the One Health framework in a way that works for Aotearoa New Zealand,[1398] including by working to overcome barriers to interdisciplinary collaboration (see section 2.4.3).[1399]

Te ao Māori can provide a framework for building many of these connections and embracing the holistic view that is needed to tackle issues with AMR.

[1394] Guess, A.M., Lerner, M., Lyons, B., *et al.* (2020). A digital media literacy intervention increases discernment between mainstream and false news in the United States and India. *Proceedings of the National Academy of Sciences, 117*(27), 15536. https://doi.org/10.1073/pnas.1920498117

[1395] Basol, M., Roozenbeek, J., & van der Linden, S. (2020). Good news about bad news: Gamified inoculation boosts confidence and cognitive immunity against fake news. *Journal of Cognition, 3*(1), 1-9. https://doi.org/10.5334/joc.91

[1396] Hannah, K., Hattotuwa, S., & Taylor, K. (2021). Working Paper: Mis- and disinformation in Aotearoa New Zealand from 17 August to 5 November 2021. Retrieved from https://www.tepunahamatatini.ac.nz/2021/11/09/mis-and-disinformation/

[1397] New Zealanders for Health Research. (2020). *New Zealand speaks! 2020 Kantar NZHR Opinion Poll.* Retrieved from https://www.nz4healthresearch.org.nz/report/

[1398] Harrison, S., Baker, M.G., Benschop, J., *et al.* (2020). One Health Aotearoa: A transdisciplinary initiative to improve human, animal and environmental health in New Zealand. *One Health Outlook, 2*(1), 1-6. https://doi.org/10.1186/s42522-020-0011-0

[1399] Errecaborde, K.M., Macy, K.W., Pekol, A., *et al.* (2019). Factors that enable effective One Health collaborations - A scoping review of the literature. *PLOS One, 14*(12), e0224660. https://doi.org/10.1371/journal.pone.0224660

Multisectoral efforts are key – there needs to be engagement and coordination of efforts across government and within industry, professional societies, NGOs, community organisations, tangata whenua, and academia. This includes strengthening of the science-policy interface and the improved coordination of different streams of advice, expertise, and data. In Australia, the Australia AMR Network initiative provides an example of a multisectoral approach to tackling AMR in human health, connecting researchers, industry, and government.[1400]

A 2021 MBIE stocktake of the research, science, and innovation sector found considerable room for greater collaboration between the business community and crown research institutes, universities, and polytechnics.[1401] Within the academic community, the MBIE report demonstrated that collaboration is on the rise, with papers increasingly being written by multiple authors. In addition, those papers with multiple authors were found to be more impactful than papers written by solo authors.

COVID-19 provides an opportunity to learn from what worked and what could have gone better and to retain and build many of the networks established during the response.[1402] The COVID-19 experience underscores an urgent need to refocus our efforts on infectious disease and AMR threats in an integrated, coordinated way that is consistent with Te Tiriti o Waitangi and emphasises equity. With a 2020 paper finding Māori and Pacific scientists are underrepresented in universities and crown research institutes in Aotearoa New Zealand, with little change in representation from 2008 to 2018,[1403] this represents an area where improvements could be made, with a diverse research community being crucial to supporting good health and wellbeing outcomes for all New Zealanders.[1404]

The recent announcement of NZ$36 million in funding for research that focuses on the prevention, control and management of infectious diseases[1405] is a welcome boost to this field of study. It is great to see this encompasses a focus on joining up expertise across disciplines, including human, animal, and environmental health and connecting to policy. The government's recent announcement of $10 million to support the development of a vaccine against group A *Streptococcus*, which will complement work already happening in Australia, is also a welcome investment.[1406]

International connections strengthen us and the global community

As well as highlighting domestic research and initiatives, this report has drawn on international insights. Engaging with research from overseas is crucial to combatting infectious disease and AMR given the transboundary nature of these threats and the wealth of expertise that exists beyond our borders. In addition, engaging internationally provides a way for Aotearoa New Zealand to support

[1400] MTPConnect. (n.d.). Australian Antimicrobial Resistance Network - AAMRNet. Retrieved 9 December, 2021, from https://www.mtpconnect.org.au/Category?Action=View&Category_id=266

[1401] Ministry of Business Innovation and Employment. (2021). *The research, science and innovation report - 2021*. Retrieved from https://mbienz.shinyapps.io/research-science-innovation-report/pdf/research-science-and-innovation-system-performance-report-2021.pdf

[1402] Murdoch, D.R., Crengle, S., Frame, B., *et al.* (2021). "We have been warned"- Preparing now to prevent the next pandemic. *The New Zealand Medical Journal, 134*(1536), 8-11.

[1403] McAllister, T.G., Naepi, S., Wilson, E., *et al.* (2020). Under-represented and overlooked: Māori and Pasifika scientists in Aotearoa New Zealand's universities and crown-research institutes. *Journal of the Royal Society of New Zealand*, 1-16. https://doi.org/10.1080/03036758.2020.1796103

[1404] Swartz, T.H., Palermo, A.-G.S., Masur, S.K., *et al.* (2019). The science and value of diversity: closing the gaps in our understanding of inclusion and diversity. *The Journal of Infectious Diseases, 220*(Supplement_2), S33-S41. https://doi.org/10.1093/infdis/jiz174

[1405] Verrall, A. (2021, 19 September). *Government funding to fight infectious diseases* [Press release]. Retrieved from https://www.beehive.govt.nz/release/government-funding-fight-infectious-diseases

[1406] Verrall, A. (2021, 19 November). *Funding for vaccine development to help prevent rheumatic fever* [Press release]. Retrieved from https://www.beehive.govt.nz/release/funding-vaccine-development-help-prevent-rheumatic-fever

other countries, including those in the Pacific Islands region to which we have close physical, social, historical, political, and cultural connections.

In our near neighbourhood, we engage in research collaborations, education, and capacity building activities with Australia and Pacific Island countries. For example:

- Australia and New Zealand IPC professionals can undertake education and credentialling through the Australasian College for IPC.[1407]
- Through various programmes including Polynesia Health Corridors and the New Zealand Medical Assistance Team, MoH and the Ministry of Foreign Affairs and Trade (MFAT) work with Pacific Island countries to strengthen health systems,[1408] support essential medicines access,[1409] build lab capacity,[1410] and respond to health emergencies.[1411] Aotearoa New Zealand is also working in partnership with Pacific Island countries to support COVID-19 vaccine access and rollout.[1412]
- The closest physical containment level 4 (PC4) lab to Aotearoa New Zealand is located in Australia,[1413] necessitating collaboration in the event that this kind of facility is needed to support training, research, or diagnosis.

The MBIE research, science and innovation report mentioned above highlights the sustained growth in international research collaborations engaged in by New Zealand researchers. In 2020, roughly 56% of academic publications had international co-authors, up from 39% in 2010.[1414] In addition, New Zealand papers with international co-authors were found to be cited more frequently, highlighting that international collaboration can increase the impact of our research.

Future research needs

Research needs and knowledge gaps have been highlighted throughout this report. What follows is a non-exhaustive summary of key areas that could benefit from stepped up research in the infectious disease and AMR space, across human, animal, plant, and environmental health.

- Consistent reporting on the quantity and quality of antimicrobial use.
- Improved surveillance of AMR and infectious diseases, including to support trend analysis and epidemiological studies, facilitated by continued research into and uptake of detection technologies.
- Identification of drivers behind trends in antimicrobial use, AMR, and infectious disease prevalence.
- Improved modelling and forecasting of AMR and infectious disease trajectories.

[1407] Australasian College for Infection Prevention and Control. (n.d.). Australasian College for Infection Prevention and Control. Retrieved 9 December, 2021, from https://www.acipc.org.au/

[1408] New Zealand Foreign Affairs and Trade. (n.d.). *Activity development: Health corridors - Strengthening health systems*. Retrieved from https://www.mfat.govt.nz/assets/Aid/IATI/ACT-0100717.pdf; New Zealand Foreign Affairs and Trade. (2020). *Strategic intentions 2020–2024*. Wellington, NZ: Ministry of Foreign Affairs and Trade. Retrieved from https://www.mfat.govt.nz/assets/About-us-Corporate/MFAT-strategies-and-frameworks/MFAT-Strategic-Intentions-2020-2024.pdf

[1409] Kings, J. (2019, 3 October). *Improved access to essential medicines for Polynesia* [Press release]. Retrieved from https://www.mfat.govt.nz/en/media-and-resources/improved-access-to-essential-medicines-for-polynesia/

[1410] Clark, M., & White, P. (2015). *Evaluation of the strengthening Pacific health laboratory systems activity*. Wellington, NZ: Allen + Clarke. Retrieved from https://www.mfat.govt.nz/assets/Uploads/Strengthening-Pacific-Health-Laboratory-Systems-Activity-Evaluation-report.pdf

[1411] Ministry of Health. (n.d., 7 June 2013). NZMAT background. Retrieved 9 December, 2021, from https://www.health.govt.nz/our-work/emergency-management/new-zealand-medical-assistance-team/about-new-zealand-medical-assistance-team/nzmat-background

[1412] Mahuta, N., & Sio, A.W. (2021, 13 May). *Further COVID-19 vaccine and economic support for the Pacific* [Press release]. Retrieved from https://www.beehive.govt.nz/release/further-covid-19-vaccine-and-economic-support-pacific

[1413] Ministry for Primary Industries. (2021, 1 October). Explore our new biocontainment laboratory. Retrieved 9 December, 2021, from https://www.mpi.govt.nz/science/laboratories/national-biocontainment-laboratory/explore-our-new-biocontainment-laboratory/

[1414] Ministry of Business Innovation and Employment. (2021). *The research, science and innovation report - 2021*. Retrieved from https://mbienz.shinyapps.io/research-science-innovation-report/pdf/research-science-and-innovation-system-performance-report-2021.pdf

- Contextualising solutions for Aotearoa New Zealand and developing solutions of our own, encompassing prevention, detection, and treatment of infectious diseases and AMR.
- Trialling and assessing targeted actions, including operational and implementation research.
- Exploration, trialling, and implementation of strategies to improve health literacy, optimise antimicrobial use, and encourage compliance with measures to prevent, control, and treat infectious diseases, including those caused by resistant pathogens.
- Increasing understanding of the presence of antimicrobials and resistant microbes in the environment, the routes to environmental contamination, and the impacts on human, animal, and plant health.

Improved surveillance should be prioritised as a first step to improve our knowledge base. Central to any research and interventions going forward is good data on the prevalence of drug-resistant microbes and infectious diseases in Aotearoa New Zealand. A surveillance sector review conducted in 2009 found a range of gaps, as well as a lack of integration, particularly when it comes to monitoring upstream disease hazards.[1415] Without good data on the prevalence of drug-resistant microbes and infectious diseases, we lack a nuanced understanding of the size and nature of issues, the emerging trends, and impact of any targeted actions.

This strengthened surveillance has scope to support better outbreak responses and control. We should learn from our experiences with Psa, *Mycoplasma bovis*, kauri dieback, myrtle rust, COVID-19, and campylobacteriosis to ensure we are well-placed and prepared to respond effectively to another incursion or outbreak. This approach needs better access and transparency of data to understand risk factors and transmission pathways.

Improved surveillance should be prioritised as a first step to improve our knowledge base.

[1415] Baker, M.G., Easther, S., & Wilson, N. (2010). A surveillance sector review applied to infectious diseases at a country level. *BMC Public Health, 10*(1), 332. https://doi.org/10.1186/1471-2458-10-332

6 Glossary: Terms and abbreviations

Resistant or non-susceptible?

In this report, 'antimicrobial resistance' is used to describe microbes that are completely non-responsive to safe levels of antimicrobials as well as microbes that are still responsive to antimicrobials but not fully susceptible, perhaps requiring higher concentrations of antimicrobials to control than previously. Sometimes we refer to 'non-susceptible isolates' where this is the term used in the relevant study or source.

Term/abbreviation	Meaning
ACC	Accident Compensation Corporation
ACVM	Agricultural Compounds and Veterinary Medicines
adaptive resistance	adaptive resistance occurs when bacteria's ability to survive an antibiotic is temporarily increased
AMR	antimicrobial resistance
AMS	antimicrobial stewardship
antibiotic	antibiotics are medicines that destroy or slow down the growth of bacteria
antifungal	destroys or inhibits growth of fungi
antigen testing	test that relies on biochemistry (e.g. presence of proteins or antibodies) that is commonly used to rapidly diagnose infectious diseases
antiparasitic	manages infections caused by parasites
antiviral	manages infections causes by viruses
antimicrobial	antimicrobials kill or slow the growth of microorganisms
antimicrobial resistance (AMR)	the ability of a microbe to survive exposure to an antimicrobial
antimicrobial susceptibility testing (AST)	testing that determines the specific antimicrobials that a particular bacteria or fungus is sensitive to
ARC	aged residential care
AST	antimicrobial susceptibility testing
bacteria	bacteria are single-celled organisms that can live inside and outside other organisms
bactericidal	able to kill bacteria
bacteriophage, or phage	bacteriophages are viruses that can destroy bacteria
bacteriostatic	suppressing bacterial growth
biocide	substances that destroy living things
biofilm	microbes that are adhered to a surface
biosecurity	actions to prevent the spread of harmful organisms
CDC	US Centers for Disease Control and Prevention
CLAB	central line-associated bacteraemia, a type of bloodstream infection
clarithromycin	clarithromycin is an antibiotic used to treat infections such as chest infections and is a useful alternative for people with a penicillin
conjugation	conjugation occurs when DNA is transferred from one bacteria to another through structures in the cell membranes
cordon sanitaire	the restriction of movement of people into or out of a defined geographic area to control the spread of infectious disease
CPE	carbapenemase-producing Enterobacterales
CPO	carbapenemase-producing organism
CRE	carbapenem-resistant Enterobacterales
culture-based	testing involving culturing or growing a bacterial sample in a lab.
DALY	disability-adjusted life year, measurement that represents the loss of the equivalent of one year of full health
DHB	District Health Board
elimination	in infectious disease, refers to reduction to zero or a specified low number of new cases of a disease within a given area
eradication	in infectious disease, refers to permanently reducing to zero the number of new cases of a disease
ESBL	extended spectrum β-lactamase
ESKAPE	used to refer to six pathogens characterised by their ability to cause severe disease and death, high levels of multidrug resistance, and role in fatal hospital-acquired infections

Term/abbreviation	Meaning
ESR	Institute of Environmental Science and Research Ltd
exposome	the collective environmental exposures that an individual has experienced (e.g. through birth, air, water, food, social contact etc.).
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
fluoroquinolone	a class of antibiotics that can be used to treat a range of severe infections
FMD	foot-and-mouth disease
FTE	full-time equivalent
fungi	spore producing organisms (e.g. moulds, yeasts).
fungicide	substances that are toxic to fungi
GBD	Global Burden of Diseases, Injuries, and Risk Factors Study
genome	the collective genetic information of an organism
genotypic testing	genetic techniques to identify drug-resistant microbes (e.g. PCR and WGS).
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GP	general practice / general practitioner
gram negative/positive	Bacteria can be gram positive or gram negative. Gram-positive bacteria have a cell wall made of a thick layer of proteins with sugars attached. Gram-negative bacteria have a cell wall with a thin layer of protein-sugar molecules, plus an outer layer of fatty sugars called lipopolysaccharides. This extra layer provides gram-negative bacteria with additional protection against some antibiotics, detergents, and the immune system. Note that in this report we have followed the CDC preferred usage: 'Gram should be capitalized and never hyphenated when used as Gram stain; gram negative and gram positive should be lowercase and only hyphenated when used as a unit modifier.'[1416]
HAI	healthcare-associated infection
healthcare-associated infection (HAI)	an infection that originates in hospital or is otherwise acquired during the process of receiving healthcare
HEPA	high efficiency particulate air
herbicide	substances that are toxic to plants
HGT	horizontal gene transfer
HIV	human immunodeficiency virus
horizontal gene transfer (HGT)	the movement of genetic information between genomes (other than between parent to offspring)
HQSC	Health Quality & Safety Commission
ICU	intensive care unit
infection prevention control (IPC)	measures taken to reduce the occurrence and spread of infections, encompassing interventions like vaccination, hand hygiene, and ventilation
infectious	able to be transmitted between people, through the environment, organisms etc
integron	a collection of genes that allows genetic material – in the form of a gene cassette – to be exchanged between organisms and then correctly integrated and expressed in the recipient organisms genome.
IPC	infection prevention and control
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
MERS	Middle East Respiratory Syndrome
metagenomics	the study of a collection of genetic material (genomes) from a mixed community of organisms
MBIE	Ministry of Business, Innovation and Employment
MDRO	multidrug-resistant organism
metaphylaxis	mass medication of healthy animals when the disease of interest is present within the group
methicillin	a semisynthetic derivative of penicillin that is used to treat *Staphylococcus* infections
MfE	Ministry for the Environment
microorganisms	microorganisms are microscopic organisms such as bacteria and fungi.

[1416] Centers for Disease Control and Prevention. (2021, 22 April). Preferred usage. Retrieved 13 December, 2021, from https://wwwnc.cdc.gov/eid/page/preferred-usage

Term/abbreviation	Meaning
mobile genetic element	a type of genetic material that can move around within a genome or can be transferred from one species to another; the main agents of horizontal gene transfer
MoH	Ministry of Health
MPI	Ministry for Primary Industries
mRNA	messenger RNA
MRSA	methicillin-resistant *Staphylococcus aureus*
NAPS	National Antimicrobial Prescribing Survey
NDM	New Delhi metallo-β-lactamase enzyme
NHS	National Health Service in England
NIPCEG	National Infection Prevention and Control Expert Group
NIWA	National Institute of Water and Atmospheric Research
NZVA	New Zealand Veterinary Association
OECD	Organisation for Economic Co-operation and Development
One Health	term used globally to describe a collaborative, multisectoral, and transdisciplinary approach to achieve desired health outcomes in society, explicitly recognising the interconnectedness of people, plants, animals, and environment
OPMCSA	Office of the Prime Minister's Chief Science Advisor
OXA-48	a common type of carbapenemase
Pacific peoples	a collective term describing a diverse population of more than 16 distinct ethnic groups, languages and cultures
parasites	organisms that live in or on other organisms
pathogens	microorganisms that can cause disease
PCR	polymerase chain reaction
pesticide	substances that are toxic to organisms harmful to crops and animals.
phenotypic	relating to the observable characteristics of an individual
phenotypic testing	phenotypic techniques to identify drug-resistant microbes (e.g. antigen testing and culture-based tests)
PHO	Primary Health Organisation
PIANZ	Poultry Industry Association of New Zealand
plasmid	small, free-floating sections of genetic material that exist in bacterial cells
point-of-care testing	testing and rapid analysis of results provided close to or near the patient
polymerase chain reaction (PCR)	a technique used to amplify small segments of DNA
PPE	personal protective equipment
Psa	*Pseudomonas syringae pv. actinidiae*
resistome	antimicrobial resistance genes in communities of bacteria
RSV	respiratory syncytial virus
SARS	Severe Acute Respiratory Syndrome
SSI	surgical site infection
STEC	Shiga toxin-producing *Escherichia coli*
STI	sexually transmitted infection
susceptibility	when microorganisms are unable to grow in the presence of an antimicrobial agent
TB	tuberculosis
telemedicine	delivering medical care via technology.
transduction	the process by which genetic material is transferred by a virus from one bacterium to another
transformation	the genetic alteration of a cell due to the uptake of genetic material from the cell's surroundings
transposon	transposons are genetic material that can move from one area of a genome to another
vancomycin	vancomycin is an antibiotic used to treat serious infections caused by gram-positive bacteria resistant to other treatments e.g. MRSA
virus	infective agents that replicate within a host organism.
VRE	vancomycin-resistant enterococci
UTI	urinary tract infection
WGS	whole genome sequencing
WHO	World Health Organization
whole genome sequencing	a comprehensive method for analysing entire genomes
zoonotic	can be transmitted between species, from animal to human

7 Appendices

7.1 Terms of reference

Agreed with the Prime Minister in April 2021

Background

In 2018, our Office published a short summary detailing why antimicrobial resistance (AMR) poses an imminent threat to Aotearoa New Zealand.[1417] Since then, the COVID-19 pandemic has turned the threat of infectious disease into reality and shown how vulnerable we are to infectious disease when effective treatment is not available. A silver lining from the COVID-19 pandemic may be that people now understand the social disruption from an untreatable infection and consequently there is social and cultural licence to take infectious disease more seriously.

Aim of project

This project seeks to build on our short AMR summary and other local reports and workstreams[1418] to provide a localised and detailed evidence synthesis and recommendations to mitigate the risk of infectious disease and AMR in Aotearoa New Zealand.

This would be valuable to:

- Remind officials and the public of the continuing importance of infectious disease and the potential impact of increasing AMR, and inspire action in these areas.
- Examine the impacts of COVID-19 on development of AMR and efforts to counter it.
- Ensure that planning for the next pandemic does not focus exclusively on viruses and includes the potential for a pandemic caused by a drug-resistant microorganism.

We will convene a diverse panel of local experts to steer the project, specifically including people with expertise on how infectious disease spreads in and affects our more vulnerable communities and how to prevent this. Throughout the project, the team will also engage with a wider reference group of stakeholders to receive their input and feedback.

Draft scope

The scope for the project will be finalised in conjunction with the expert panel at the first panel meeting. The research will be evidence-based and aim to provide a holistic approach to addressing infectious disease and AMR in Aotearoa New Zealand.

Summary of workstreams

1. **Context:** This workstream will analyse the global and local context and explain the approach taken for the report.
2. **Prevention and risk mitigation of infectious diseases.** Prevention is better than cure. This workstream will focus on general solutions to reducing the incidence of infections in Aotearoa, and policy levers to pull, including discussion of challenges and barriers to each approach.
3. **Infectious diseases in Aotearoa New Zealand:** This workstream will take an Aotearoa New Zealand-specific focus, summarising the evidence for infectious diseases (human, animal,

[1417] Office of the Prime Minister's Chief Science Advisor. (2018, 20 December). Antimicrobial resistance: An imminent threat to Aotearoa New Zealand. Retrieved 24 November, 2021, from https://www.pmcsa.ac.nz/topics/antimicrobial-resistance-and-infectious-disease/antimicrobial-rsistance/

[1418] Including but not limited to: Royal Society Te Apārangi. (2017). *Antimicrobial Resistance – Implications for New Zealanders Evidence Update*. Wellington, New Zealand: ; Ministry of Health and Ministry for Primary Industries. (2017). *Antimicrobial Resistance: New Zealand's current situation and identified areas for action.* Wellington, NZ: Ministry of Health and Ministry for Primary Industries.

plant) and highlight the diseases of particular concern and knowledge gaps for Aotearoa New Zealand. We will then have three 'spotlight' workstreams to highlight general issues and solutions for specific infections of concern.

4. **Spotlight on drug-resistant infections in Aotearoa New Zealand:** This workstream will focus on the threat of drug-resistant infections (antimicrobial resistance, AMR) as the big slow-burning pandemic for infectious diseases, summarising Aotearoa New Zealand-specific evidence (human, animal, plant and presence in the environment), knowledge gaps, and local solutions. It will not be a comprehensive review of all drug-resistant infections but will discuss some infections in Aotearoa that illustrate the emerging threat of AMR, e.g. methicillin-resistant *Staphylococcus aureus* (MRSA), urinary tract infections and gonorrhoea.
5. **Spotlight on group A *Streptococcus* and rheumatic fever in Aotearoa New Zealand:** This workstream will focus on a specific infection and its major complication that highlights the issues with health inequities, issues with access to antimicrobials, and limited accessibility of antibiotics. It will examine holistic solutions to infection prevention and control.
6. **Spotlight on *Campylobacter* infections in Aotearoa New Zealand:** This workstream will focus on a food- and water-borne infection that has high and growing incidence rates in Aotearoa New Zealand and emerging risk of drug-resistant strains, and will examine specific solutions to reduce these rates.

Process

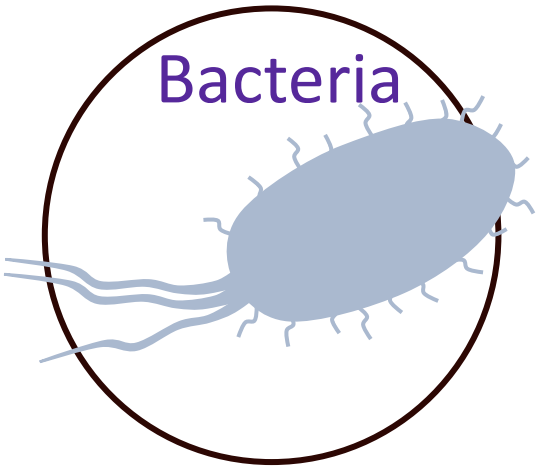
- Call for nominations of the expert panel and wider reference group will be sought from the key institutional contact lists. The panel shortlisting will actively seek to support a diverse and balanced panel. Expert panel approached to guide the Office of the Prime Minister's Chief Science Advisor in preparing the report.
- Wide stakeholder engagement will be included with an open reference group process.
- The membership of the panel and wider reference group will be public and processes open.
- The panel will provide guidance to the Office of the Prime Minister's Chief Science Advisor in preparing a summary of the peer-reviewed evidence and developing recommendations.
- Once a draft has been agreed by the group, the material will be circulated to a wider group of experts for peer review.
- The report will be delivered to the Prime Minister and later made public on the PMCSA website.

Timeline

March 2021	Project scope drafted Call for nominations via key institutional contacts
April 2021	Panel established Project scope and panel membership uploaded onto PMCSA website
May-September 2021	Research and engagement
October-November 2021	Finalising report
December 2021	Likely release date

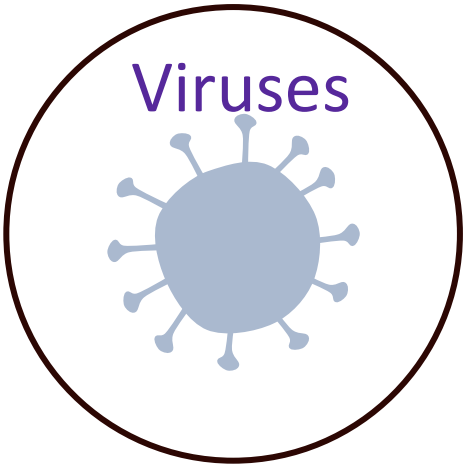
7.2 Meet the microbes infographic

MEET THE MICROBES



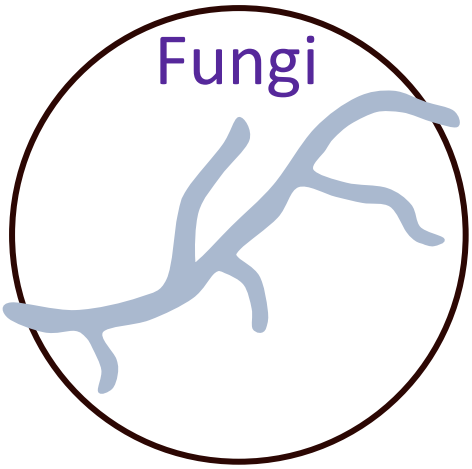
Bacteria are single-celled organisms that come in a variety of shapes including rods, spheres, and spirals. Some have an appendage called a flagellum to help them move. They are found in soil, the deep ocean, radioactive waste, suspended in the air, and in and on humans, animals, and plants, among other places. Some bacteria are helpful, such as the human gut bacteria that support digestion and other healthy functions. But other bacteria (or even healthy bacteria under certain conditions) can cause disease.

E.g. Gram-positive: *Mycobacterium tuberculosis*, *Staphylococcus aureus*; Gram-negative: *Campylobacter jejuni, Neisseria gonorrhoeae*



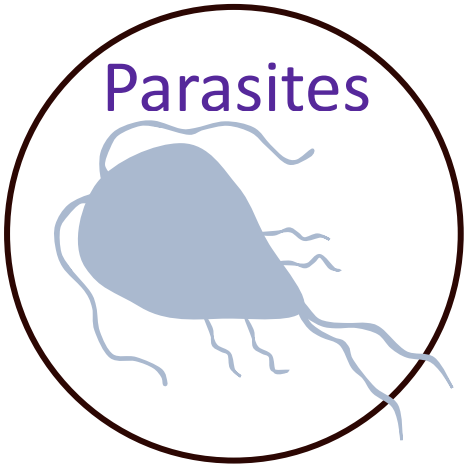
Viruses are biological entities that are smaller than bacteria. They lack cells, consisting simply of genetic material surrounded by a protein layer (and sometimes a lipid envelope). Viruses require the machinery of a host cell to replicate. Viruses come in a variety of different shapes and use different types and configurations of genetic material (e.g. RNA vs DNA, single stranded vs double stranded). They can infect a range of organisms including humans, animals, plants, and bacteria.

E.g. SARS-CoV-2, influenza, human immunodeficiency viruses, *Measles morbillivirus*



Fungi comprise a group of living things that ranges from large, multicellular organisms like mushrooms to microorganisms such as yeasts. Fungi have a unique cell wall structure that distinguishes them from plants, animals, and other microbes. They have many human uses including in food (e.g. edible mushrooms and yeast for brewing and baking) and medicine (e.g. as a source of antimicrobials and a research tool). Some fungi can be pathogenic, causing disease in humans, animals, and plants.

E.g. *Austropuccinia psidii*, *Candida albicans*,*Trichophyton rubrum, Aspergillus fumigatus*



Parasites require a host to complete their life cycle – the host could be an animal, plant, fungus, protozoan, or bacterium. Parasites harm their host in some way, for example by feeding on them. There are three main types of parasite that cause disease in humans:

- Protozoa – microscopic, single-celled organisms (e.g. *Giardia duodenalis, Plasmodium falciparum*, *Toxoplasma gondii*)
- Helminths – large, multicellular organisms (e.g. tapeworms, flukes)
- Ectoparasites – a parasite that lives on the outside of its host (e.g. ticks, fleas, lice, mites)

7.3 WHO critical antimicrobials

Critically important antimicrobials for human medicine.[1419] Antibiotics that have Pharmac funding restrictions in Aotearoa New Zealand are generally only used when supported by a certain specialty (e.g. infectious diseases or microbiology) or if the prescriber is following a DHB guideline. NB: This does not cover potential "off label" uses.

Antimicrobial class	Example	Use in Aotearoa New Zealand
Aminoglycosides	gentamicin	Used in human health (available for use in DHB hospitals, community use with restrictions). Used in animal health.
Ansamycins	rifampicin	Used in human health (Pharmac funding restrictions, community use with restrictions). Not commonly used – for specific indications.
Carbapenems and other penems	meropenem	Used in human health (Pharmac funding restrictions). Broad spectrum and use could be reduced.
Cephalosporins (3rd, 4th and 5th generation)	ceftriaxone, cefepime, ceftaroline, ceftobiprole	Used in human health (ceftriaxone available for used in DHB hospitals and community use with restrictions, cefepime and ceftaroline have Pharmac funding restrictions and tend not to be used commonly). Used in animal health
Glycopeptides	vancomycin	Used in human health (Pharmac funding restrictions, community use with restrictions)
Glycylcyclines	tigecycline	Used in human health (Pharmac funding restrictions). Tends not to be used that commonly.
Lipopeptides	daptomycin	Used in human health (Pharmac funding restrictions). Tends not to be used that commonly.
Macrolides and ketolides	azithromycin, erythromycin, telithroymcin	Used in human health (azithromycin available for use in DHB hospitals and community use with restrictions, erythromycin available for use in DHB hospitals and community use without restrictions). Used in animal health.
Monobactams	aztreonam	Used in human health (Pharmac funding restrictions). Tends not to be used that commonly.
Oxazolidinones	linezolid	Used in human health (Pharmac funding restrictions). Tends not to be used that commonly.
Penicillins (antipseudomonal)	piperacillin	Only used in human health in conjunction with tazobactam (broad spectrum and use could be reduced).
Penicillins (aminopenicillins)	amoxicillin	Used in human health, including community use without restrictions. Used in animal health
Penicillins (aminopenicillin with beta-lactamase inhibitors)	amoxicillin-clavulanic-acid	Used in human health (available for use in DHB hospitals and community use without restrictions). Broad spectrum and use could be reduced. Used in animal health.
Phosphonic acid derivatives	fosfomycin	Used in human health (Pharmac funding restrictions). Tends not to be used that commonly.

[1419] Organization, W.H. (2019). Critically important antimicrobials for human medicine.

Antimicrobial class	Example	Use in Aotearoa New Zealand
Polymyxins	colistin	Used in human health (Pharmac funding restrictions). Not commonly used – fairly toxic can be used as last resort for some MDROs. Possible animal use (most likely polymyxin B used in topical preparations, such as eye, ear and skin ointment, not given systematically).
Quinolones	ciprofloxacin	Used in human medicine (Pharmac funding restrictions and community use without restrictions). Used in animal health.
Drugs used solely to treat tuberculosis or other mycobacterial diseases	isoniazid	Used in human health (Pharmac funding restrictions). Not commonly used – for specific indications.

7.4 Selected countries' AMR action plans

The *Tripartite Global Action Plan on Antimicrobial Resistance 2015* (see section 2.4.3) provided a blueprint for many countries to create their own national action plan. WHO maintains an online library of publicly accessible national action plans on AMR.[1420] Different countries have adapted the objectives of the *Tripartite plan* to different extents; for example, both Aotearoa New Zealand and Ireland align very closely to the *Tripartite plan* objectives. In contrast, countries such as the UK and US have plans or strategies that pre-date the *Tripartite plan*. Some countries also have objectives relating to governance and international collaboration, which are themes not explicitly included in the *Tripartite plan* objectives. Below, we display the objectives of selected countries in terms of how they align to the themes of the Tripartite plan objectives.

Country/ organisation	Years covered	Objective themes							Notes
		Awareness	Surveillance and research	Infection prevention and control	Antimicrobial stewardship	Investment in new medicines, diagnostics, vaccines etc.	Governance	International collaboration	
Tripartite Global Action Plan on Antimicrobial Resistance 2015[1421]	2015 onwards	Objective one: Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.	Objective two: Strengthen the knowledge and evidence base through surveillance and research.	Objective three: Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures.	Objective four: Optimize the use of antimicrobial medicines in human and animal health.	Objective five: Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.	-	-	
New Zealand[1422]	2017–2022	Objective one: Awareness and understanding – Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.	Objective two: Surveillance and research – Strengthen the knowledge and evidence base about antimicrobial resistance through surveillance and research.	Objective three: Infection prevention and control – Improve infection prevention and control measures across human health and animal care settings to prevent infection and transmission of micro-organisms.	Objective four: Antimicrobial stewardship – Optimise the use of antimicrobial medicines in human health, animal health and agriculture, including by maintaining and enhancing the	Objective five: Governance, collaboration and investment – Establish and support clear governance, collaboration and *investment arrangements for a sustainable approach* to countering antimicrobial resistance.	Objective five: Governance, collaboration and investment – Establish and support *clear governance,* collaboration and investment arrangements for a sustainable approach to		New Zealand's AMR Action Plan is analysed further in appendix 7.5 and the scorecard accompanying the foreword.

[1420] World Health Organization. (n.d.). Library of AMR national action plans. Retrieved 26 July, 2021, from https://www.who.int/teams/surveillance-prevention-control-AMR/national-action-plan-monitoring-evaluation/library-of-national-action-plans

[1421] Ibid.

[1422] Ministry of Health and Ministry for Primary Industries. (2017). *New Zealand Antimicrobial Resistance Action Plan*. Wellington, NZ: Ministry of Health. Retrieved from https://www.health.govt.nz/publication/new-zealand-antimicrobial-resistance-action-plan

Country/ organisation	Years covered	Objective themes							Notes
		Awareness	Surveillance and research	Infection prevention and control	Antimicrobial stewardship	Investment in new medicines, diagnostics, vaccines etc.	Governance	International collaboration	
					regulation of animal and agriculture antimicrobials.		countering antimicrobial resistance.		
Australia	2015–2019[1423]	Objective one: Increase awareness and understanding of antimicrobial resistance, its implications and actions to combat it, through effective communication, education and training.	Objective three: Develop nationally coordinated One Health surveillance of antimicrobial resistance and antimicrobial usage. Objective five: Agree a national research agenda and promote investment in the discovery and development of new products and approaches to prevent, detect and contain antimicrobial resistance.	Objective four: Improve infection prevention and control measures across human health and animal care settings to help prevent infections and the spread of resistance.	Objective two: Implement effective antimicrobial stewardship practices across human health and animal care settings to ensure the appropriate and judicious prescribing, dispensing and administering of antimicrobials.	Objective five: Agree a national research agenda and promote investment in the discovery and development of new products and approaches to prevent, detect and contain antimicrobial resistance.	Objective seven: Establish and support clear governance arrangements at the local, jurisdictional, national and international levels to ensure leadership, engagement and accountability for actions to combat antimicrobial resistance.	Objective six: Strengthen international partnerships and collaboration on regional and global efforts to respond to antimicrobial resistance.	Australia has published a final progress report outlining action achieved as a result of the first 2015–2019 plan.[1424]
	2020–2040[1425]	3. Greater engagement in the	5. Integrated surveillance and response to	2. Prevention and control of infection and the spread of	4. Appropriate usage and	6. A strong collaborative research agenda across all sectors.	1. Clear governance for antimicrobial	7. Strengthen global	

[1423] Australian Government Department of Health & Department of Agriculture. (2015). *Responding to the threat of antimicrobial resistance: Australia's First National Antimicrobial Resistance Strategy 2015–2019*. Retrieved from https://www.amr.gov.au/resources/national-amr-strategy

[1424] Australian Government Department of Health & Department of Agriculture. (2021). *Final progress report: Australia's first national antimicrobial resistance strategy 2015–2019*. Retrieved from https://www.amr.gov.au/resources/final-progress-report-australias-first-national-antimicrobial-resistance-strategy-2015

[1425] Australian Government Department of Health, & Australian Government Department of Agriculture Water and the Environment. (2020). *Australia's National Antimicrobial Resistance Strategy – 2020 and Beyond*. Canberra, Australia: Retrieved from https://www.amr.gov.au/resources/australias-national-antimicrobial-resistance-strategy-2020-and-beyond

Country/ organisation	Years covered	Objective themes							Notes
		Awareness	Surveillance and research	Infection prevention and control	Antimicrobial stewardship	Investment in new medicines, diagnostics, vaccines etc.	Governance	International collaboration	
		combat against resistance.	resistance and usage. 6. A strong collaborative research agenda across all sectors.	resistance.	stewardship practices.		resistance initiatives.	collaboration and partnerships.	
UK	2013–2018[1426]	3. Improving professional education, training and public engagement.	5. Better access to and use of surveillance data. 6. Better identification and prioritisation of AMR research needs.	1. Improving infection prevention and control practices.	2. Optimising prescribing practice.	4. Developing new drugs, treatments and diagnostics.	7. Strengthened international collaboration.		The UK also has a 20-year vision for AMR, published in 2019.[1427]
	2019–2024[1428]			Reducing need for and unintended exposure to antimicrobials.	Optimising use of antimicrobials.	Investing in innovation, supply and access to tackle AMR.			
Canada[1429]	2017 onwards		1. Strengthen governance structures to generate knowledge and information on AMR and AMU in humans, agriculture and animals through	3. Reduce the need for antimicrobial treatment by promoting infection prevention and control practices to decrease infection rates in healthcare, community and animal settings.	2. Promote, facilitate and measure appropriate AMU in humans and animals to conserve the effectiveness of antimicrobials that are critical to human and animal	4. Support the advancement of research and innovative approaches for the identification, characterization and real time detection of microorganisms including resistant bacteria, the treatment	1. Strengthen governance structures to generate knowledge and information on AMR and AMU in humans, agriculture and animals through		

[1426] Department of Health. (2013). *UK five-year antimicrobial resistance strategy 2013–2018*. Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf

[1427] Department of Health and Social Care. (2019). *Contained and controlled: The UK's 20-year vision for antimicrobial resistance*. Retrieved from https://www.gov.uk/government/publications/uk-20-year-vision-for-antimicrobial-resistance

[1428] Department of Health and Social Care. (2019). *Tackling antimicrobial resistance 2019–2024: The UK's five-year action plan*. Retrieved from https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024

[1429] Public Health Agency of Canada. (2017). *Tackling antimicrobial resistance and antimicrobial use: A pan-Canadian framework for action*. Retrieved from https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/tackling-antimicrobial-resistance-use-pan-canadian-framework-action.html

Country/ organisation	Years covered	Objective themes							Notes
		Awareness	Surveillance and research	Infection prevention and control	Antimicrobial stewardship	Investment in new medicines, diagnostics, vaccines etc.	Governance	International collaboration	
			the monitoring, detection and tracking of resistant organisms to develop and monitor interventions. 4. Support the advancement of research and innovative approaches for the identification, characterization and real time detection of microorganisms including resistant bacteria, the treatment and prevention of infections as well as basic and behavioural research.		health, and to limit the development and spread of resistant organisms within and among populations.	and prevention of infections as well as basic and behavioural research.	the monitoring, detection and tracking of resistant organisms to develop and monitor interventions.		
US	2014 (Strategy),[1430] 2015–2020 (Action plan),[1431] 2020–2025		2. Strengthen national One-Health surveillance efforts to combat resistance.	1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections.	1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections.	3. Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.		5. Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance,	

[1430] US Government. (2014). *National strategy for combating antibiotic-resistant bacteria*. Retrieved from https://www.cdc.gov/drugresistance/us-activities/national-strategy.html
[1431] Federal Task Force on Combating Antibiotic-Resistant Bacteria. (2015). *National action plan for combating antibiotic-resistant bacteria 2015–2020*. Retrieved from https://www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

Country/ organisation	Years covered	Objective themes							Notes
		Awareness	Surveillance and research	Infection prevention and control	Antimicrobial stewardship	Investment in new medicines, diagnostics, vaccines etc.	Governance	International collaboration	
	(Action plan)[1432]					4. Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.		control, and antibiotic research and development.	
Denmark[1433]	2017 (Strategy)	4. Information and guidance on resistance and transmission.	3. Enhanced knowledge to improve targeted measures.	2. Greater efforts to prevent infections and to facilitate antibiotic alternatives.	1. A prudent use of antibiotics to reduce the incidence of resistance.			5. A strong international cooperation to minimise the development of antibiotic resistance.	Denmark also has a National Action Plan on Antibiotics in Human Healthcare 2017–2020.[1434]
Ireland[1435]	2017–2020	Objective 1: Improve awareness and knowledge of antimicrobial resistance.	Objective 2: Enhance surveillance of antibiotic resistance and antibiotic use.	Objective 3: Reduce the spread of infection and disease.	Objective 4: Optimise the use of antibiotics in human and animal health.	Objective 5: Promote research and sustainable investment in new medicines, diagnostic tools, vaccines and other interventions.			
Switzerland[1436]	2015 onwards	Information and education: Knowledge of antibiotic resistance will be improved among experts and the general public so that more responsible decisions are taken	Monitoring: A cross-sector system employing standardised methods will be developed for monitoring humans, animals, agriculture and	Prevention: The need for antibiotics will be reduced to the essential minimum by implementing targeted preventive measures and effective alternatives. Resistance control: The transmission and spread	Appropriate use of antibiotics: Rules on the appropriate use of antibiotics will be defined in accordance with the current state of understanding. These will be binding and	Research and development: Interdisciplinary research and development work on the emergence, transmission, spread and control of resistant bacteria will be intensified. This research will also	Cooperation: Cooperation among the various stakeholders at political, scientific and economic levels will be encouraged and coordinated beyond the	Cooperation: Cooperation among the various stakeholders at political, scientific and economic levels will be encouraged and coordinated beyond the	

[1432] Federal Task Force on Combating Antibiotic-Resistant Bacteria. (2020). *National action plan for combating antibiotic-resistant bacteria 2020–2025*. US Department of Health & Human Services. Retrieved from https://aspe.hhs.gov/sites/default/files/migrated_legacy_files//196436/CARB-National-Action-Plan-2020-2025.pdf

[1433] Ministry of Environment and Food of Denmark, & The Danish Ministry of Health. (2017). *One health strategy against antibiotic resistance*. Copenhagen, Denmark: Retrieved from https://sum.dk/Media/0/D/One%20health%20strategy%20mod%20antibiotikaresistens%20engelsk.pdf

[1434] The Danish Ministry of Health. (2017). *National action plan on antibiotics in human healthcare*. Copenhagen: The Danish Ministry of Health. Retrieved from https://www.who.int/publications/m/item/denmark-one-health-strategy-against-antimicrobial-resistance

[1435] Department of Health. (2017). *Ireland's national action plan on antimicrobial resistance 2017-2020.* Retrieved from https://assets.gov.ie/9519/afcba9bce7c54bf9bcbe9a74f49fdaf2.pdf

[1436] Federal Office of Public Health. (2015). *Strategy on antibiotic resistance Switzerland*. Retrieved from https://www.bag.admin.ch/bag/en/home/krankheiten/infektionskrankheiten-bekaempfen/antibiotikaresistenzen.html

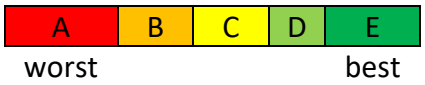
Country/ organisation	Years covered	Objective themes							Notes
		Awareness	Surveillance and research	Infection prevention and control	Antimicrobial stewardship	Investment in new medicines, diagnostics, vaccines etc.	Governance	International collaboration	
		and resistance levels fall.	the environment. Research and development: Interdisciplinary research and development work on the emergence, transmission, spread and control of resistant bacteria will be intensified. This research will also provide the basis for the targeted development of antimicrobial substances and cost-effective diagnostic products.	of resistant organisms will be minimized in order to reduce antibiotic resistance.	implemented consistently.	provide the basis for the targeted development of antimicrobial substances and cost-effective diagnostic products.	boundaries of individual disciplines both nationally and internationally as part of the OneHealth approach. General conditions: General conditions and incentives, whether political, legal or financial in nature, will be created so that effective antibiotics are available and are used in a prudent, sensible manner.	boundaries of individual disciplines both nationally and internationally as part of the OneHealth approach.	
Japan[1437]	2016–2020	1. Improve public awareness and understanding, and promote education and training of professionals	2. Continuously monitor antimicrobial resistance and use of antimicrobials, and appropriately understand the signs of change and spread of antimicrobial resistance	3. Prevent the spread of antimicrobial-resistant organisms by implementing appropriate infection prevention and control	4. Promote appropriate use of antimicrobials in the fields of healthcare, livestock production and aquaculture	5. Promote research on antimicrobial resistance and foster research and development to secure the means to prevent, diagnose and treat the antimicrobial-resistant infections		6. Enhance global multidisciplinary countermeasures against antimicrobial resistance	

[1437] Government of Japan. (2016). *National action plan on antimicrobial resistance (AMR) 2016–2020*. Retrieved from https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf

7.5 Aotearoa New Zealand's AMR self-assessment

Aotearoa New Zealand's self-assessment on progress on AMR as reported to the Tripartite AMR survey.[1438] Note that the assessment process changed in 2019–2020, with this most recent round involving feedback from experts. Prior to this the MoH were doing their self-assessment without expert input. This may explain some of the worsening scores over time.

How the Tripartite scoring system works:



Assessment item	2016-17	2017-18	2018-19	2019-20
Multisectoral approach to addressing AMR	B	C	C	C
Country progress with development of a national action plan on AMR	B	D	D	D
Raising awareness and understanding of AMR risks and response	B	C	C	C
Training and professional education on AMR in the human health sector	D	C	C	C
Training and professional education on AMR in the veterinary sector	E	C	D	D
Training and professional education on AMR in farming sector (animal and plant), food production, food safety and the environment	n/a	B	B	B
Progress with strengthening veterinary services	E	E	E	E
National monitoring system for consumption and rational use of antimicrobials in human health	D	D	C	A
National monitoring system for antimicrobials intended to be used in animals (terrestrial and aquatic) (sales/use)	E	C	D	D
National monitoring system for pesticide use in plant production including antimicrobial pesticides such as bactericides and fungicides	n/a	D	A	A
National surveillance system for antimicrobial resistance (AMR) in humans	C	C	C	C

[1438] World Health Organization. (2020). Global database for the tripartite antimicrobial resistance (AMR) country self-assessment survey (TrACSS). Retrieved 4 August 2021 https://amrcountryprogress.org/

Assessment item		2016-17	2017-18	2018-19	2019-20
National surveillance system for antimicrobial resistance (AMR) in animals (terrestrial and aquatic)		C	D	D	D
National surveillance system for antimicrobial resistance (AMR) in food (animal and plant origin)		C	not answered	D	D
Is the country using relevant antimicrobial consumption/use and/or antimicrobial resistance data to amend national strategy and/or inform decision making, at least annually?	Human health including WASH	n/a	n/a	No	No
	Animal health (terrestrial and aquatic)	n/a	n/a	Yes	Yes
	Plant health	n/a	n/a	n/a	Yes
	Food production	n/a	n/a	n/a	Yes
	Food safety	n/a	n/a	n/a	Yes
	Environment	n/a	n/a	n/a	No
National AMR Laboratory network in animal health and food safety sectors	Effective integration of laboratories in the AMR surveillance	n/a	n/a	C	C
	Level of the standardization and harmonization of procedures among laboratories included in the AMR surveillance system	n/a	n/a	D	D
	Relevance of diagnostic (bacteriology) techniques used by laboratories included in the AMR surveillance system	n/a	n/a	D	D
	Technical level of data management of the laboratory network in the AMR surveillance system	n/a	n/a	D	D
Infection Prevention and Control (IPC) in human healthcare		D	D	D	D
Good health, management and hygiene practices to reduce the use of antimicrobials and minimize development and transmission of AMR in animal production (terrestrial and aquatic)		C	B	B	B
Good management and hygiene practices to reduce the development and transmission of AMR in food processing		C	not answered	B	B
Optimizing antimicrobial use in human health		E	D	C	C
Adoption of “AWaRe” classification of antibiotics in the National Essential Medicines List		n/a	n/a	n/a	A
Optimizing antimicrobial use in animal health (terrestrial and aquatic)		E	C	C	C
Optimizing antimicrobial pesticide such as bactericides and fungicides use in plant production		E	n/a	n/a	C
Legislation and/or regulations to prevent contamination of the environment with antimicrobials		E	D	n/a	n/a

7.6 Technology and innovation to combat AMR and infectious disease

Approach	Description of approach	Example(s)
Antimicrobial surfaces and coatings	Antimicrobial coatings could reduce AMR by lowering use of antimicrobial drugs and by lowering the amount of antimicrobial compounds used when disinfecting surfaces. Lab studies show promising results but they are not routinely replicated in real life situations.[1439] Testing in real life situations is challenging because of the risk of allowing infection and variable factors such as traffic volume, extent of contamination, and extent of contact resulting in cross-contamination. Further research is needed to determine the effectiveness, longevity and cost benefits of antimicrobial surface coatings under different use scenarios.	A collaboration between NZ Company Resene paints, who market a silver-based antimicrobial paint[1440], and Victoria University of Wellington demonstrated high efficacy of antimicrobial paints to disinfect surfaces experimentally loaded with multidrug resistant strains of *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Evaluation of these paints in clinical settings for reducing microbial load is currently being investigated. NZ start-up company, Inhibit Coating, is developing a silver-based antimicrobial coating that retains silver nanoparticles within the coating polymer matrix, preventing leaching.[1441] Preventing leaching improves the effective life of the coating as well as reducing potential environmental contamination. Coatings containing titanium dioxide particles are not directly antimicrobial but the photocatalytic properties of the particles generate reactive oxygen species in the presence of light, which damage microbes.[1442] A research group at the University of Canterbury[1443] is investigating the direct attachment of titanium dioxide nanoparticles to metal surfaces.[1444] Other coatings are being investigated for their ability to reduce medical implant infection, including strategies for inhibiting biofilm growth on orthopaedic implants.[1445]
Rapid diagnostics / point-of-care testing	New technologies can speed up diagnosis of infectious diseases and identification of resistant strains. This helps aid use of the correct antimicrobial and dose, prevents over-prescription of broad-spectrum antibiotics and prescriptions where the antibiotic is ineffective. Point-of-care diagnosis is where the equipment used to make the diagnosis is easy to use and generally cheap	In NZ Mastatest has been developed for rapidly diagnosing mastitis on dairy farms – it indicates the pathogen and its susceptibility within 24 hours.[1446] Researchers in NZ have investigated methods to quantify pathogen load using rapid bacterial DNA quantification by PCR, the use of *Pseudomonas fluorescens*, and a transient reporter eclipse assay for assessing resistance conferred by isolated bacterial avirulence genes.[1447] These methods can allow rapid identification of resistant cultivars and facilitate resistance gene discovery for plant breeding programs.

[1439] Dunne, S.S., Ahonen, M., Modic, M., *et al.* (2018). Specialized cleaning associated with antimicrobial coatings for reduction of hospital-acquired infection: Opinion of the COST Action Network AMiCI (CA15114). *Journal of Hospital Infection, 99*(3), 250-255. https://doi.org/10.1016/j.jhin.2018.03.006

[1440] Resene. (2011). Wall protection. Retrieved 15 November, 2021, from https://www.resene.co.nz/comn/whtsnew/wall_protection.htm

[1441] Inhibit Coatings. (n.d.). Inhibit Coatings. Retrieved 15 November, 2021, from https://www.inhibitcoatings.com/

[1442] Foster, H.A., Ditta, I.B., Varghese, S., *et al.* (2011). Photocatalytic disinfection using titanium dioxide: spectrum and mechanism of antimicrobial activity. *Applied Microbiology and Biotechnology, 90*(6), 1847-1868. https://doi.org/10.1007/s00253-011-3213-7

[1443] University of Canterbury. (2019, 20 February). *Shape-changing element holds key to anti-bacterial coating* [Press release]. Retrieved from https://www.canterbury.ac.nz/news/2019/shape-changing-element-holds-key-to-anti-bacterial-coating.html

[1444] Krumdieck, S.P., Boichot, R., Gorthy, R., *et al.* (2019). Nanostructured TiO_2 anatase-rutile-carbon solid coating with visible light antimicrobial activity. *Scientific Reports, 9*(1), 1883. https://doi.org/10.1038/s41598-018-38291-y

[1445] Li, J., Mutreja, I., Hooper, G.J., *et al.* (2020). Combined infection control and enhanced osteogenic differentiation capacity on additive manufactured Ti-6Al-4V are mediated via titania nanotube delivery of novel biofilm inhibitors. *Advanced Materials Interfaces, 7*(7), 1901963. https://doi.org/10.1002/admi.201901963

[1446] Bates, A., Laven, R., Bork, O., *et al.* (2020). Selective and deferred treatment of clinical mastitis in seven New Zealand dairy herds. *Preventive Veterinary Medicine, 176*, 104915. https://doi.org/10.1016/j.prevetmed.2020.104915; Mutreja, I., Warring, S.L., Lim, K.S., *et al.* (2019). Biofilm inhibition via delivery of novel methylthioadenosine nucleosidase inhibitors from PVA-tyramine hydrogels while supporting mesenchymal stromal cell viability. *ACS Biomaterials Science & Engineering, 5*(2), 748-758. https://doi.org/10.1021/acsbiomaterials.8b01141

[1447] Jayaraman, J., Chatterjee, A., Hunter, S., *et al.* (2021). Rapid methodologies for assessing *Pseudomonas syringae pv. actinidiae* colonization and effector-mediated hypersensitive response in kiwifruit. *Molecular Plant-Microbe Interactions®, 34*(8), 880-890. https://doi.org/10.1094/MPMI-02-21-0043-R; ibid.

Approach	Description of approach	Example(s)
	enough to be used at the bedside or in the doctor's office, as well as being rapid. DNA/RNA approaches to rapidly detect genes/microbes is an active area of research.	ESR has been actively developing point-of-need sequencing devices (using nanopore devices) that have potential to detect AMR genes and microbes across a variety of applications. Development of a loop-mediated isothermal implication (LAMP) assay has scope to make it easier and cheaper to detect *Phytophthora agathidicida* (the cause of kauri dieback) as well as being more accurate than culture-based techniques.[1448]
Vaccines	Vaccines can be used to reduce the prevalence of many diseases (including ones with drug resistance). Development of vaccines requires significant time and investment. New technologies including mRNA-based and viral vectors have been widely used during the COVID-19 pandemic. Vaccines have the potential to reduce microbial loads and transmission, however some vaccines may require regular updating in response to 'vaccine escape'.	While in recent years vaccine development and research has focused on COVID-19, there are many other vaccines being developed. This includes for pathogens such as *Staphyloccous* species, *Streptococcus* species, and infections including tuberculosis, chlamydia, and gonorrhoea.[1449] mRNA-based vaccines have been heralded as a 'game changer' as they can be rapidly generated and adapted.[1450] Many countries are investing in mRNA-based technologies due the rapid response and flexibility that the platform provides.
Host modulation	Host modulation looks at how to help the host (patient) fight bacteria, particularly how the immune system can be supported to eliminate bacteria.[1451] There are a number of approaches to host-directed therapy including modulating innate immune cell function, modulating adaptive immune responses, programmed cell death, and metabolism.[1452]	An area of focus for the use of host modulation is in the treatment of periodontal diseases. In periodontal disease, gram negative bacteria form a biofilm that causes a host inflammatory response.[1453] Host modulation is an important emerging treatment strategy. The Malaghan Institute in NZ undertakes research on host modulation for cancer, allergic and other diseases, though not for bacterial infections.[1454]
Bacteriophage therapy	Bacteriophages are a type of virus that infects bacteria.[1455] They have been used therapeutically since their discovery in the early 1900s but have not been used systematically in infection management since antibiotics became widely used in the 1940s.[1456] Globally, robust trials are few and mostly	In NZ there are bacteriophages approved as processing aids in food, for example, to eradicate or reduce the presence of *Listeria monocytogenes* and *Escherichia coli*. A recent trial in Australia used bacteriophage therapy in patients with severe *Staphylococcus aureus* infections to assess safety, though further trials are needed to assess efficacy.[1458]

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Approach	Description of approach	Example(s)
	unsuccessful thus far, and coordinated effort is needed to define the role and likely candidates for bacteriophage therapy.[1457] Bacteriophage therapies can be used alone or in conjunction with antibiotics.	Work has been undertaken in NZ on a bacteriophage that is a potential biocontrol agent for kiwifruit phytopathogen PSA.[1459]
Lysins / Bacteriophage endolysins	Bacteriophage endolysins (lysins) are enzymes produced by bacteriophages that can kill bacteria by breaking through the bacterial cell wall.[1460] As the lysins structurally damage the bacterial cell wall, it is hard for the bacteria to gain resistance to the lysins.	The majority of research into the use of lysins has been against *S. aureus,* though the use of lysins against gram-negative bacteria is also being explored.[1461] Work underway at Massey has investigated the suitability of use of endolysins to use prophylactically against pathogenic bacteria in hospital settings.[1462] In the University of Canterbury, work is underway to expand the range of bacteria that can be attacked by lysins.[1463]
Monoclonal antibodies	Antibodies target bacteria, so could be used as an alternative to antibiotics.[1464] A key challenge is to enable antibodies to target a range of bacteria rather than limited spectrum. There are large upfront costs and scaling costs, but there have been some success stories in clinical trials.[1465]	There are multiple companies currently pursuing these therapies and are in various stages of development.[1466] These include for *S. aureus*, Psa and *E. coli* (ST131).
Microbiome therapy/probiotics	Our microbiome (i.e. the microorganisms within our body) and our immune system (which fights off infections) have a two-way relationship.[1467] This offers potential to leverage this relationship to prevent and mitigate the emergence of AMR. The microbiome can be manipulated by the introduction of collectives of microbes, whole communities of microbes, nutrients or other growth factors that may	NZ company BLIS Probiotics has developed the world's first advanced oral probiotics for throat and skin health based on technology developed at Otago University.[1468] The Gut bugs team at the Liggins Institute, University of Auckland is performing clinical trials on microbiome transfers for the restoration of microbiomes. This is a transferrable technology that is important for treatment of recurrent vancomycin resistant *Clostridioides difficile* infections.

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Approach	Description of approach	Example(s)
	resist dysbiosis/disease by strengthening or restoring beneficial functions or otherwise exclude invasive or antibiotic-resistant strains and species. More research is needed in this area.	
Air handling and UV lamps	In-room air sterilization can be enhanced by portable air filtration units that contain HEPA filtration and other air sterilization technology. New designs can deliver much higher clean air delivery rates than older ones, providing up to 10+ air changes per hour for small or medium sized rooms. Additionally, airflow control can limit spread throughout a facility. Specialised wall-mounted lamps that emit UV-C light to the upper, unoccupied zone of a room can rapidly destroy infectious particles. The effect of upper room UV-C irradiation is additive to any existing room ventilation.	New Zealand company NanoLayr (formerly Revolution Fibres) produces electrospun nanofibers that can be impregnated with active additives to trap and neutralise particles.[1469] In NZ, the Infection Prevention Control service and Building and Property have sourced an appropriate product from Philips NZ (Signify).
Pharmaceutical antimicrobial drugs	Development of new pharmaceutical antimicrobial drugs has been decreasing over time but efforts to discover new drugs continue, with antibiotics with novel modes of action being a particular priority.	While a review in 2016 found 47 different schemes globally looking to incentivise the development of new antimicrobials, there are still few new drugs being brought to market.[1470] NZ research includes a programme to develop new treatments for drug-resistant tuberculosis and other antimicrobial compounds,[1471] research considering compounds from NZ fungi,[1472] lipopeptide antibiotics,[1473] and compounds from soil bacteria[1474] for new antimicrobial compounds.[1475] Other research considers the development of new antibiotic compounds for agricultural use,[1476] and work on modifying a new antibiotic isolated from a soil bacterium to make it more easily produced.[1477]

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Approach	Description of approach	Example(s)
		An anthelmintic drug (used to treat infections of animals with parasitic worms) is being investigated for its antibiotic properties.[1478] Development of antiviral drugs has had particular focus in recent years due to the COVID-19 pandemic and the University of Otago is leading a project to develop new classes of antivirals.[1479] The Ferrier Institute, based at Victoria University of Wellington, is one of the leading research groups in the development of antiviral nucleoside analogues.[1480]
Artificial intelligence	Artificial intelligence can be used to interrogate and combine large data sets such as those generated from antimicrobial susceptibility testing and WGS to assist in prescription decisions, drug and vaccine discovery and development, and effective combinations of antimicrobials.	This is a new area where data can be collected to build clinical decision support systems and design new antibiotics and develop synergistic drug combinations.[1481]
Prodrugs	Prodrugs are molecules with little to no pharmacological activity that can be converted into an active drug inside the body.	In NZ, prodrug antimicrobials that activate in the presence of infection are being developed for livestock.[1482]
Surveillance	A variety of biological substrates (e.g. wastewater or surface swabs) could be used to screen for high-risk microbes and/or AMR genes. This surveillance could assist in building a risk-framework at a given location.	Research at the University of Auckland is looking to establish methods to identify the appearance of novel antibiotic resistance genes in the NZ microbiome. While in the early stages of implementation, if combined with routine wastewater screening these methods could be used to identify the emergence of potential problematic resistant organisms within the NZ community. Wastewater-based epidemiology (WBE) programs, focused on genomic techniques, are underway at ESR.
Public awareness of prevention methods	Innovation in the space of public awareness and education of infection control measures could significantly improve infectious disease outcomes.	COVID-19 has shown many regulators and organisations using new approaches to education to spread messaging around control measures (hand sanitation, cough etiquette, masks, etc.). NZ's early approach to clear COVID-19 messaging and branding was highlighted as a positive example of effective communication around the world.[1483]

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7.7 A rangatahi hui on AMR

In June 2021, we ran a hui about AMR for rangatahi at Aorere College in Tāmaki Makaurau Auckland. After a session explaining what AMR was, led by science teacher Chloe Innes, groups of students had a facilitated discussion with a member of the OPMCSA team based on one of two AMR scenarios. Students were also given the opportunity to provide their top challenges and solution at the end of the session.

Scenario one:

In recent days several people have been admitted to hospital with very serious abdominal cramps, diarrhoea, fever, headache, nausea and vomiting. It is discovered that these people have become sick from bacteria called *Salmonella* (*Salmonella enteritidis*) and they have been exposed to this from eating eggs and chicken from some chicken farms in Aotearoa New Zealand.

Doctors want to treat some patients who have become very ill with antibiotics. The first antibiotic they try doesn't work.

Researchers say that the use of antibiotics on the chicken farm to prevent diseases in the flock may have led to the development of this resistant strain.

Scenario two:

A person who was playing their weekly basketball game tripped and grazed their knee. After a few days pass, the graze appears to be infected. They make a trip to the doctor and get a course of antibiotics.

After taking the antibiotics for three days, the infection doesn't seem to be getting any better. The person returns to the doctor, who then takes a swab and sends it off for testing. The results come back that the infection is caused by a drug-resistant strain of the Staph (*Staphylococcus aureus*) bacteria, called MRSA. The antibiotic being taken will not heal the infection.

Also living in their house is a whānau member They are particularly worried because one of their whānau members recently had surgery and if they become infected, it could lead to severe infections of internal organs or sepsis.

Prompts for facilitators:

- Impact – what are the implications of this?
- What might this mean for your whānau or community?
- What might this mean for Aotearoa New Zealand?
- What are some potential solutions?

Outcomes

We were impressed with the breadth and depth of ideas generated by the students, many of which were the same as those posed by the experts on our panel and reference group. The COVID-19 response appeared to play a role in their understanding of health issues such as AMR, inspiring some of their solutions.

Current and future challenges identified included:

- Social issues
    - People most affected are likely to be from lower socioeconomic areas and under-resourced communities.
    - AMR could lead to the loss of the public's faith in the medical system if medicines stop working.

- Broader impacts
    - Negative impacts on the agriculture industry.
    - Possible impacts on biodiversity.
    - Potential disruption to food chain – loss of animals, increased costs of affected foods, could cause a famine.
- Growing impacts over time
    - Resistant infections can spread within households and communities
    - Might need higher doses of antibiotics to treat infections, but this contributes to AMR
    - Could lead to another pandemic
- Limitations in the healthcare system
    - Barriers to accessing healthcare
    - Overwhelmed healthcare system if increasing number of outbreaks
- Having sufficient research and resource to address the issues
    - Might not have enough resource to create new antibiotics or the knowledge to do so
    - Need to decide where to put resources – on new drugs vs preventative methods like vaccines

Potential solutions identified included:

- Keep the public informed and involve them
    - Transparency around the problem existing now and efforts to address it.
    - Public surveys to get ideas about how to solve it.
    - Public messaging in schools and the media about the problem of AMR and how to prevent it (e.g. social media campaigns, raising awareness of the importance of personal and food hygiene).
    - Educating farmers on how to treat or prevent diseases.
    - More education around symptoms for certain illnesses and when to get checked.
- Prevention
    - Prescribe fewer antibiotics, stop selling them online in America, require a second opinion from doctors for antibiotic prescription.
    - Develop vaccines.
    - Changes to farming systems so you don't need antibiotics, e.g. improved nutrition, stop cage farming, testing on farms, test animal feed and the environment that farmed animals are surrounded by to see if these introduce diseases.
    - Increase food safety testing.
    - Wear more protective gear in situations where people might be injured (e.g. sports).
    - Annual check-up for staff to make sure they aren't spreading resistant bacteria.
- Target the bacteria
    - Developing new antibiotics or improving existing ones.
    - Research new non-antibiotic treatments.
    - Look for and be open to innovative solutions/interventions.
    - Probiotics – use good bacteria to get rid of bad bacteria.
    - Bacteriophages.
    - Transfusions to filter blood and get rid of bacteria.
    - Reminders/charts to take medicine so that the whole antibiotic course is taken.
- Response to outbreaks
    - Prioritise protecting the more vulnerable.

    - Have better prepared hospitals in case of serious issues and pandemics, or even specific facilities.
    - Improve the health workforce and remove barriers to entry (e.g. high costs of training).
    - Isolate the infected person and their close contacts.
    - Take precautions for family members of someone with e.g. MRSA – sanitising, covering up infected area.
    - Rely on different countries for food supply.
    - Kill off diseased flocks/herds and repopulate with new healthy animals.
    - Use the greater good theory.
- Research
    - Collect data on how AMR is caused and spread.
    - Further study into diseases and in the animal setting.
    - Understand the genetics of the host (e.g. chickens) and whether that affects the resistance of the bacteria.
    - Better researchers.
    - Have funding for this research.

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