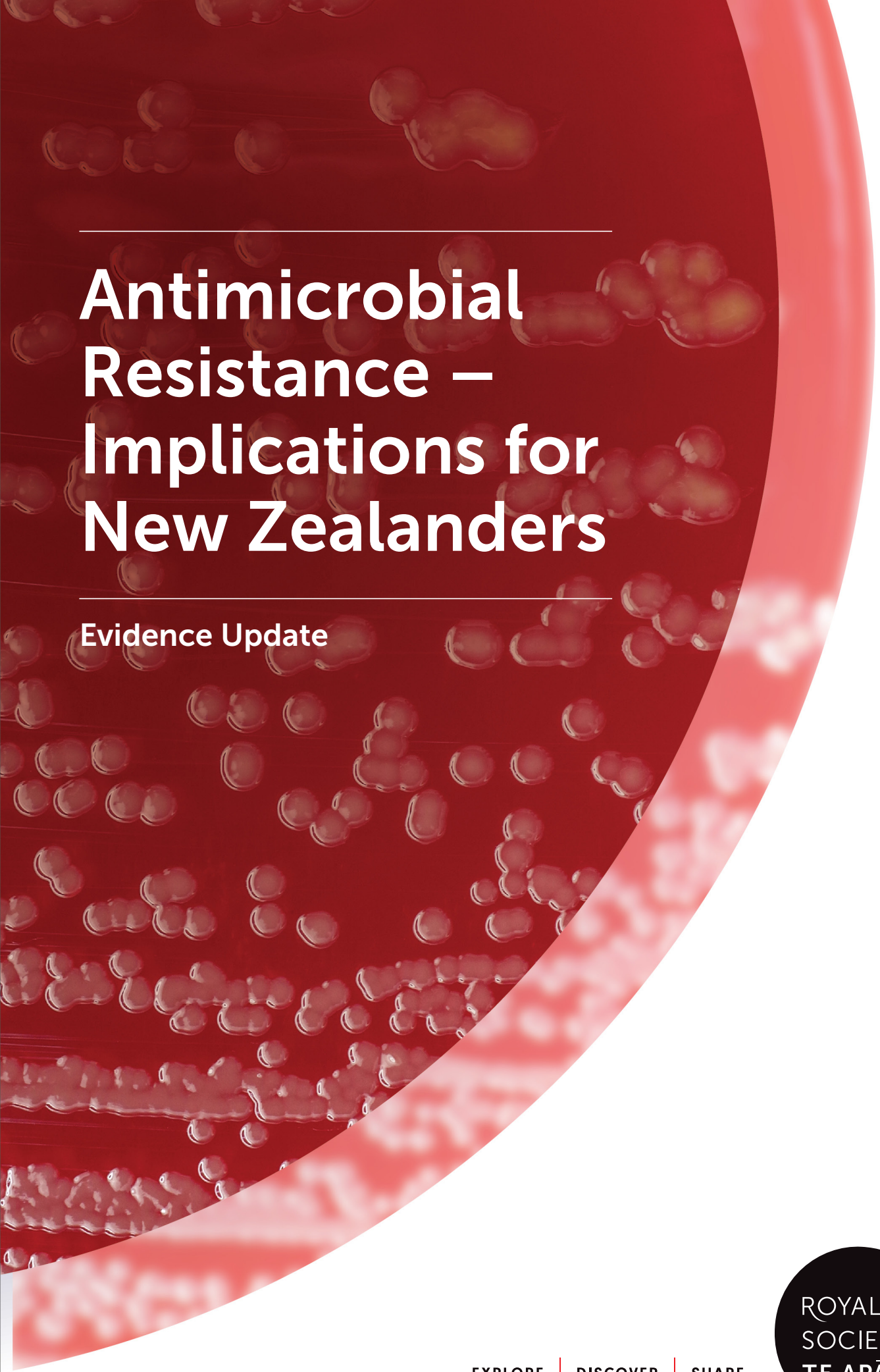


Antimicrobial Resistance – Implications for New Zealanders

Evidence Update

EXPLORE | DISCOVER | SHARE

ROYAL SOCIETY TE APĀRANGI

Summary

Many microbes that commonly cause infectious disease in humans and animals are becoming resistant to the antimicrobial medicines used to treat these diseases.

Antimicrobial resistance is a serious global health problem, especially given the increasing prevalence of antibiotic resistance among common disease-causing bacteria.[1,2]

Estimates suggest that without urgent action infections due to antimicrobial-resistant microbes could kill 10 million people globally per year by 2050.[3,4]

Within New Zealand, use and misuse of antimicrobial medicines, as well as international travel and trade, could accelerate the spread of resistance, increasing morbidity and mortality amongst our community.

Government departments, research institutes, and human and animal health organisations are working together to prepare a national action plan on combating resistance, but this can only delay and reduce the severity of the increasing impact here.

Everyone can help by practicing high standards of hygiene, taking antibiotics only as prescribed, and not insisting on antibiotics if unnecessary.[2,5]

Introduction

Antibiotics and other antimicrobial medicines are important for treating infectious disease in humans, animals and plants. Antimicrobial medicines help combat many common diseases including tuberculosis, malaria, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), sexually transmitted diseases and pneumonia.[1,6] Antibiotics treat and prevent bacterial infections, making possible and improving the safety of chemotherapy, bone marrow or organ transplants, joint replacements and other surgery.[1,7]

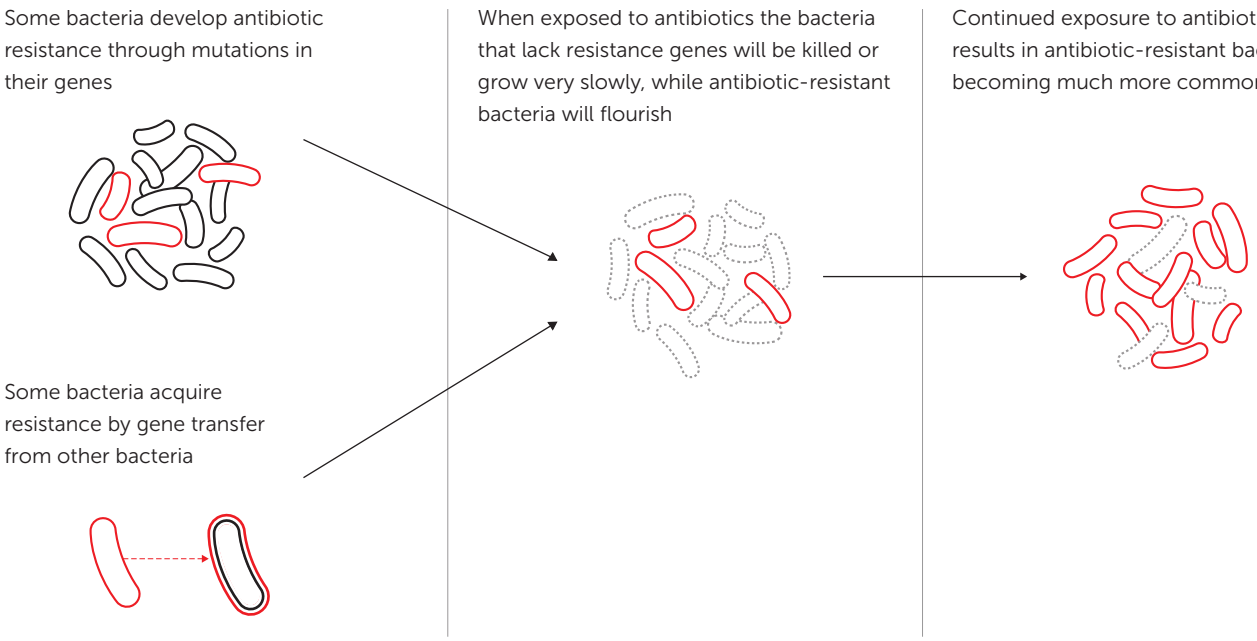
Bacteria are excellent at adapting to their environment. In some cases, bacteria may develop resistance that allows them to survive in the presence of antibiotics (Fig. 1). Other microbes, including fungi, viruses and parasites, can also develop resistance to some of the antimicrobial medicines we use to treat infected people, plants and animals.

Use and misuse of antimicrobial medicines increases the spread of resistance. Antimicrobial-resistant microbes are present in every region of the world, including New Zealand.[1] Of particular concern are high rates of antibiotic resistance among bacteria that cause a number of common infections including skin infections, pneumonia, and urinary tract infections.[1,6] Some bacteria with resistance to multiple classes of antibiotics are now widespread across the world.[1,7]

FIGURE 1

How antibiotic resistance emerges and spreads in bacteria

(Modified from Centers for Disease Control and Prevention[7])



What are microbes and how can they cause infection and disease?

A microorganism or microbe can refer to bacteria, viruses, fungi or parasites. Microbes occur in every environment including soil, water, air, and plants, as well as in and on humans and other animals. Most microbes are harmless or even beneficial to humans most of the time. While some microbes have adapted to infect and cause disease, even normally harmless or beneficial microbes can cause disease if they multiply in parts of the body where they do not normally reside, or inside someone with a suppressed immune system.

Infection and disease caused by microbes can occur in any organism such as humans, animals and plants. Infections can be transmitted by direct or airborne contact between individuals, through contaminated food or water, by transfer from other surfaces where pathogens (disease-causing microbes) may live, or via insects or animals.[8]

Infectious diseases in New Zealand

Hospital admissions data and annual surveillance reports on notifiable diseases, outbreaks, influenza-like illness and sexually transmitted infections capture some information on the burden of infectious diseases in New Zealand.[9-12] In the year between July 2013 and June 2014, almost 91,000 people had infectious diseases listed as the main reason for why they were hospitalised, accounting for around 8% of all hospitalisations.[13,14] However, the occurrence of infectious diseases in hospitals is even higher as some patients admitted for other illnesses can have secondary complications caused by an infectious disease. Worldwide, up to 10% of patients receiving healthcare develop an infection related to this care.[15] Over two thirds of infectious disease hospitalisations are due to bacterial infections, more than a quarter are due to viruses, and less than 1% are due to fungi and other microbes.[13,14] Hospitalisations are only the tip of the iceberg, and most infectious diseases occur and are managed in the community.

Lower respiratory tract, skin and soft tissue, and gut infections are the most common manifestations of infectious disease in New Zealand.[16] These infections accounted for nearly 60% of all hospital admissions for infectious disease between 2004 and 2008.[16] The rates of skin and soft tissue infections caused by the bacterium *Staphylococcus aureus* are high and increasing.[17]

In 2015, there were 558 outbreaks of infectious disease investigated in New Zealand, consisting of 8,510 individual cases.[9] Hospitalisation occurred in 3.3% of the outbreak cases for which information was available on whether an individual was hospitalised.[9] Microbes infecting the gut were implicated in the majority of outbreaks (90%), with norovirus reported as the cause for over a third of outbreaks, and over half the individual cases.[9]

Everyone is susceptible to infectious disease; however, some groups of people are disproportionally affected. The rates of some infectious diseases in Māori and Pacific peoples are about twice as high as in those of European descent and other ethnic groups.[16] Likewise, the rates are significantly higher than average in the youngest and oldest age groups, and in the most socio-economically disadvantaged New Zealanders.[16]

What are antimicrobial medicines and how do they work?

Antimicrobial medicines treat and prevent infections in humans, animals and plants. Antibiotics are antimicrobial agents that specifically interact with bacteria to either kill them or inhibit their growth.[18]

Substances with known antibacterial properties have been used for many centuries but it was only in the middle of last century that many of the antibiotics, as we know them today, were discovered.[19,20] Along with the discovery of antibiotics came a better understanding of bacterial diseases, and the ability to test bacteria for their susceptibility to antibiotics, so that the most effective medicine can be selected to treat each infection.[21]

How antibiotics treat infection

Exposure of bacteria to antibiotics may either kill* the bacterial cells, or inhibit reproduction.†[22] In patients with a normal immune system, inhibiting the infecting bacteria is often sufficient to cure the disease.[23]

Antimicrobial resistance: how it emerges and spreads

Antibiotic-resistant bacteria

Bacteria are able to evolve rapidly in response to threats from their environment, including threats from antibiotics.[24] Random mutations in a bacterium's genetic material may give bacteria the property of being resistant to some antibiotics (Fig. 1). Alternatively, bacteria may acquire resistance through mechanisms that allow the transfer of genes from other bacteria of the same or a different species (see below). Genes that allow bacteria to be resistant to antibiotics have existed in the environment for over 2 billion years.[25,26] However, the widespread use of antibiotics in recent decades has led to resistance in common disease-causing bacteria becoming much more prevalent.

As resistance becomes more common, new drugs are required to combat the infections. These antibiotics, in turn, have driven a cycle of use leading to resistance to each new drug.

Other microbes can also develop resistance

Mutations in other microbes, such as viruses, fungi and parasites, sometimes give them resistance to antivirals, antifungals and antiparasitic medicines respectively. Exposure to antimicrobial agents can allow resistant microbes to flourish over non-resistant microbes.[1]

Some antivirals are effective at preventing the progression of HIV infection, while other antivirals are used for treating patients with influenza.[1] HIV drug resistance is increasing globally. At least one out of ten patients in Australia, Europe, Japan and the USA starting HIV treatment for the first time is infected with a strain of HIV that is resistant to at least one drug.[1] Vaccination is the preferential method for preventing influenza, however, use of antivirals during influenza epidemics and pandemics is increasing.[1] As a consequence, some viruses develop resistance to these antivirals, with widespread resistance occurring in some influenza viruses.[1] Resistance can develop rapidly. In some cases, viruses have shown a high rate of emerging resistance to the antiviral Tamiflu after a single course of treatment.[27]

* These antibiotics are referred to as 'bactericidal agents'

† These antibiotics are referred to as 'bacteriostatic agents'

Yeasts that are the most common cause of fungal infections (such as *Candida albicans*) are now showing antimicrobial resistance globally.[1] These fungi commonly live in the body without causing disease, however, they can proliferate, especially among people with suppressed immune systems, including those treated with immunosuppressive drugs or when beneficial bacteria in the body are suppressed by broad-spectrum antibiotics.[7]

New Zealand does not have the mosquitoes that transmit parasites that cause malaria. However, people do sometimes acquire the disease while travelling.[10] Resistance to the antiparasitic drugs used to treat malaria has increased in South East Asia and Africa.[1]

The spread of antimicrobial resistance

Once a single microbe has acquired resistance to an antimicrobial drug, the proportion of microbes that are resistant to that drug usually will increase. Exposure to environments with antimicrobial agents increases the preferential growth of antimicrobial-resistant strains (Fig. 1).[24] Genes that give the microbe antimicrobial resistance can be passed on to subsequent generations.

Antibiotic resistance also spreads between bacteria of the same or different species in the local environment through the transfer of genes for resistance. This process allows multiple genes to be shared and resistant bacteria to proliferate, even without the added pressure from antibiotics in the environment. The development of resistance may place a burden on the bacteria but some bacteria can evolve strategies that overcome this burden such as turning off the gene unless it is required.[28]

Globalisation, with the increased rapid movement of people, food, and animals around the world, contributes to the spread of antimicrobial-resistant microbes.[1,6,29] Resistant microbes that arise in one part of the world can spread to others through trade and travel, including movements of food, water, animals and people.[6,30] In the year between July 2015 and June 2016, over 3.3 million overseas visitors came to New Zealand, and there were 2.5 million overseas trips by New Zealanders.[31]

Other causes of antimicrobial resistance

Antimicrobial agents can be found in many consumer products, including soaps, hand lotions, toothpaste, deodorants, cosmetics, cleaning products, pesticides and even integrated into some plastic and fabric materials.[32-35] Just as with pharmaceuticals, there is a risk that the presence of these antimicrobial agents can provide a selective pressure for the development and spread of resistance in bacteria and fungi. Genes conferring resistance to these non-pharmaceutical antimicrobial agents may also induce pharmaceutical antimicrobial resistance.[32,33,35] Under normal household conditions, using antibacterial soaps does not reduce the chance of infections any more than washing with regular soap and water.[36,37]

The presence of antimicrobial agents in the environment also contributes to the emergence and selection of resistant microbes.[38] The majority of antimicrobial medicines ingested by humans and animals are not broken down, but end up in wastewater treatment plants and the environment.[39] Antimicrobial agents in cleaning and personal care products are also washed down the drain and accumulate in the environment.[34] Antimicrobial agents can also enter soil and water via the aquaculture and horticulture industries.[40,41]

Another way antimicrobial agents end up in our environment is through waste from factories where they are manufactured.[42] The majority of antibiotics are manufactured in China and India and there are reports of pharmaceutical manufacturers illegally dumping their waste into rivers and onto nearby land, or burying it in undisclosed locations.[43]

Antimicrobial resistance extends beyond ecological boundaries

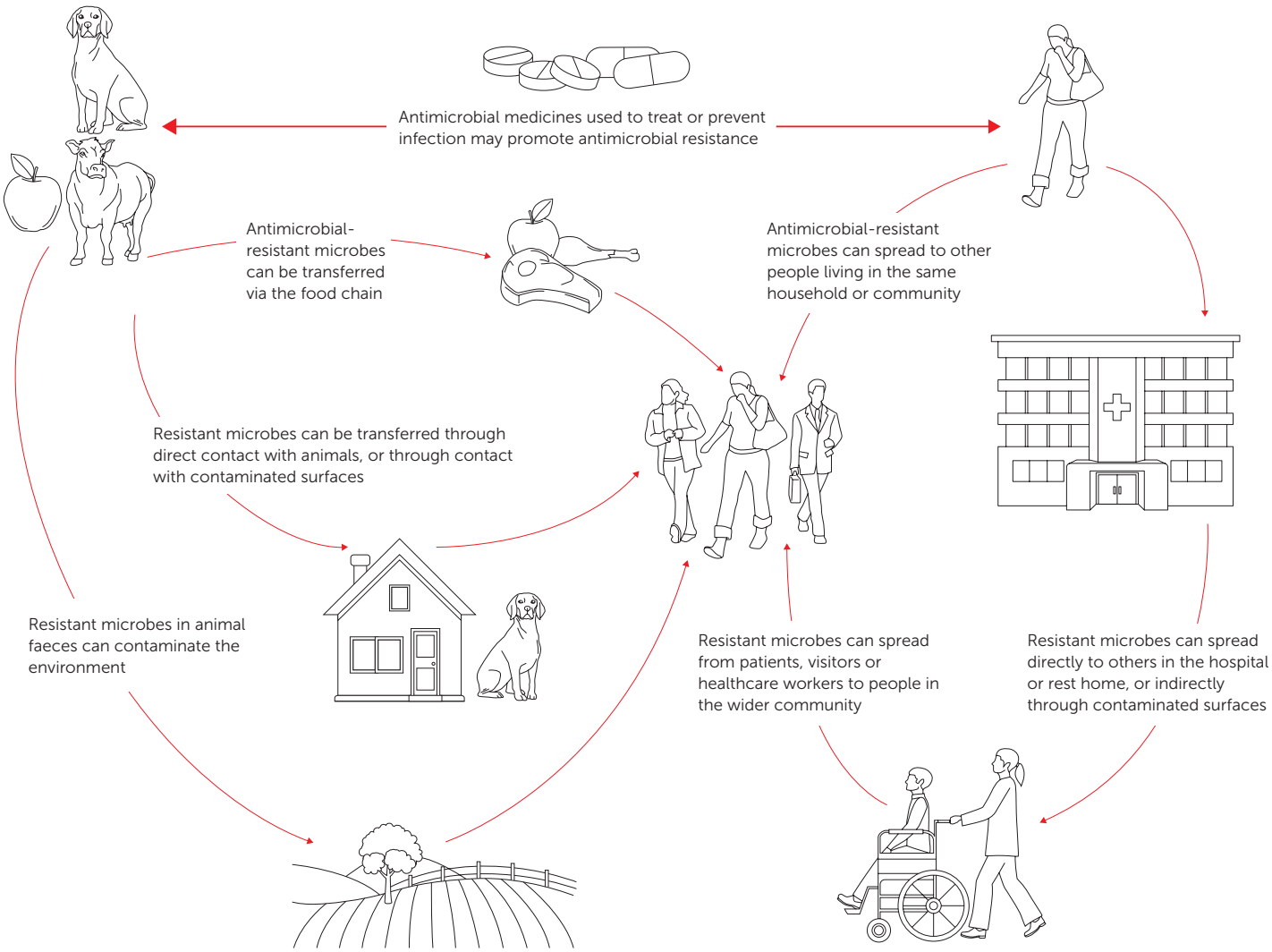
Antimicrobial agents, especially antibiotics, are frequently used to treat infections in both humans and animals. In animals, including livestock and pet animals, antimicrobial medicines are used for the treatment and prevention of infectious diseases, which, if uncontrolled, could result in production losses, severe disease and welfare concerns. In some countries, antimicrobial agents are also used as growth promoters. As with use for humans, use of antimicrobial agents for animals can lead to the emergence of new resistant microbes, or the proliferation of already resistant microbes.

Antimicrobial resistance can spread between animals, humans, food and the environment.[38] The One Health concept recognises that animals, humans and the environment are interconnected and experts across these sectors can work together to tackle disease that can spread between people and animals.[44] Resistance can spread between animals to humans via a number of pathways, including food, water and direct contact (Fig. 2). The spread of antibiotic resistance can occur through either transfer of genes encoding resistance or transfer of bacterial strains.[45-47] There is also evidence that this resistance can pass in the other direction, from humans to animals.[48]

FIGURE 2

How antimicrobial resistance can spread in New Zealand

(Modified from Centers for Disease Control and Prevention[7])



Use and misuse of antimicrobial medicines can accelerate the spread of resistant microbes in the community

Use of antimicrobial medicines in New Zealand

Within the community

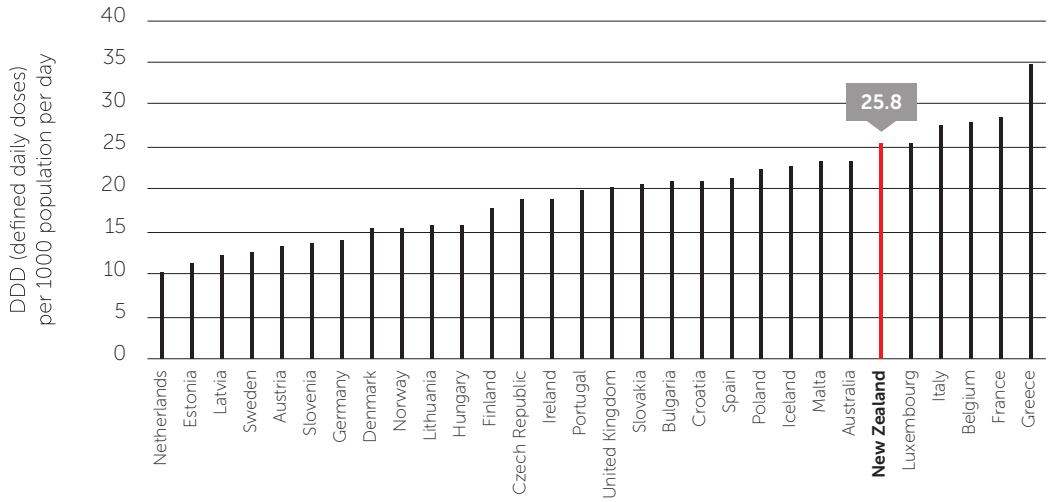
New Zealand has a high rate of antibiotic use for human medicine compared to the rate of use in many other countries (Fig. 3).[49,50] Levels of antibiotic use in the community in recent years are comparable with those in European countries that are widely considered to have profligate use of antimicrobial medicines, and that have, as a consequence, high levels of antimicrobial resistance.[51] In New Zealand, approximately 95% of the antibiotics intended for human consumption are dispensed by community pharmacies.[52] Sometimes these prescriptions are of nil or trivial benefit.[51] For example, most upper respiratory tract infections are caused by viruses and therefore cannot be cured with antibiotics. Antibiotic dispensing increases dramatically each winter, for example during 2014 there was a 40% increase between summer and winter.[49]

There is a marked variation in the total amount of community antibiotic dispensing, and in the quality of antibiotic prescribing, between the different District Health Board regions in New Zealand.[49,51] Regional differences in the incidence of infection and demographics (age, ethnicity, socio-economic status, geography) may account for some of this variation. A study of the antibiotic consumption by over 5500 children enrolled in the Growing Up in New Zealand study showed that, on average, each child had been dispensed 9.5 antibiotic courses by the age of five years.[53] The study showed more antibiotic courses were dispensed to a higher proportion of Māori and Pacific children than other ethnicities.[53] Children living in areas with a high incidence of socio-economic deprivation also received more antibiotics than other children.[53] Both these findings are consistent with a higher occurrence of infectious disease within these groups.[16] Only 3% of the children in the study had not received a single antibiotic course from community pharmacies during their first five years of life.[53]

High levels of use of topical antibiotic creams in New Zealand have led to high levels of resistance.[54,55] Resistance intensified with increased dispensing,[55] driven, in part, by over-the-counter availability of the antibiotic Mupirocin (without the need for a prescription) between 1991 and 2000.[54]

FIGURE 3

Rates of antibiotic use in the community*, 2014



* Prescriptions in the community only. Hospital prescriptions excluded.

Source data from ESR,[49] ECDC[56] and ACSQHC[57]

Within hospitals

Hospital prescriptions accounted for approximately 5% of antibiotics dispensed for human use in New Zealand in 2015.[52] Antimicrobial resistance rates in microbes isolated from patients in hospitals are influenced not only by use of antimicrobial medicines, but also by the efficacy of preventing transmission of microbes and the vulnerability of the patient population to developing infections. Hospitals also manage the care of some people with antimicrobial-resistant infections, for example, in travellers returning to the country carrying infections caused by bacteria resistant to a vital last-resort antibiotic, carbapenemase-producing Enterobacteriaceae (CPE).

Antimicrobial stewardship uses processes designed to measure use of antimicrobial medicines and optimise appropriate practices. Stewardship is used in many large New Zealand hospitals.[58,59] Some District Health Boards in New Zealand have dedicated antimicrobial stewardship pharmacists.[60] There are also some national initiatives that promote prudent use of antimicrobial medicines in the community and in hospitals.[60]

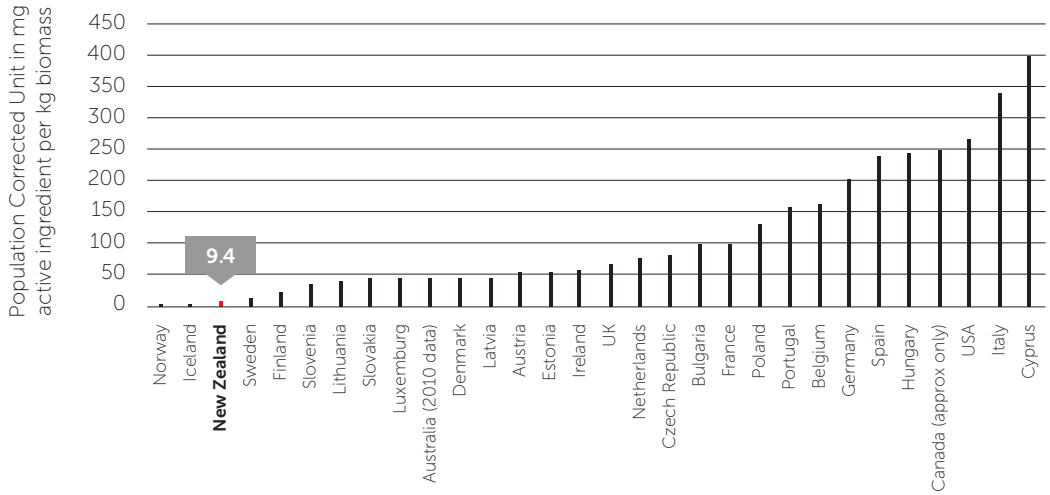
Use of antimicrobial agents as veterinary medicines and horticultural treatments

Overall, use of antimicrobial medicines across the farming sector in New Zealand is considered very low by international standards (Fig. 4).[61,62] This reflects, in part, the abundance of pasture-based farming practices when compared with more intensive agricultural practices in some other countries.[63] In some countries, high levels of use of antimicrobial medicines in animals is exacerbated by the use of antimicrobial agents as growth promoters in food producing animals. This practice is not permitted in New Zealand.[61]

The pig, poultry and dairy cattle industries consume the majority of antibiotics used by animals in New Zealand.[64] These industries use antibiotics to treat sick animals as well as to prevent common infections spreading quickly between animals growing in close proximity. These diseases, if left unchecked, may lead to high mortality and hence poor animal welfare outcomes. Situations in which this preventative treatment may be used include the intensive rearing of pigs and poultry, and controlling mastitis disease in dairy herds.[64]

FIGURE 4

Rates of animal antibiotic use in 2012



Source data from Hillerton et al. 2017[61]

One antibiotic, zinc bacitracin, accounts for over a third of agricultural antibiotic sales in New Zealand.[64] This antibiotic is used predominately in feed on poultry farms, and, to a lesser extent, in the pig industry, to prevent outbreaks of disease.

Cephalosporins are another type of antibiotic used in veterinary medicines in New Zealand.[64] The 3rd and 4th generation cephalosporins are considered high priority and critically important for use in human medicine; their use in veterinary medicine is tightly controlled and used only for therapeutic purposes.[65] Cephalosporins for veterinary use (1st to 4th generation) contribute between 3 and 4% of total antibiotic sales and sales of 3rd and 4th generation cephalosporins have doubled between 2010 and 2014.[64] The dairy industry uses a large proportion of antibiotics in this class[64] and the New Zealand Veterinary Association has released guidelines advising a more prudent and appropriate use of these drugs for dairy cows, horses, cats and dogs.[66-68]

The horticulture sector also uses antibiotics to combat bacterial disease. There are two antibiotic products registered for horticultural use in New Zealand. These products are registered for certain crops including tomatoes, kiwifruit, and pip and stone fruit.[64] The outbreak of kiwifruit vine disease caused by the bacterium *Pseudomonas syringae* pv. *actinidiae* (Psa) resulted in increased sales of antibiotics for horticultural use between 2011 and 2014.[64] Sales for antibiotics used in horticulture make up 0.9–1.5% of the total antibiotic sales in veterinary medicines and horticulture treatments combined.[64]

Antimicrobial resistance in New Zealand

New Zealand has relatively low rates of antimicrobial resistance compared with many other countries. However, this situation could easily change with the spread of emerging and existing resistant microbes.

Case study 1: Antibiotic resistance of MRSA

Infections with methicillin-resistant *Staphylococcus aureus* (known as MRSA) are common in many hospitals and some communities across the world.[1] MRSA can cause common skin infections such as boils, school sores and cellulitis, blood infections and pneumonia, and is resistant to penicillin-based antibiotics.[7,42]

In contrast to the situation in other high-income countries such as Australia and the UK, these MRSA bacteria have not become widely established in New Zealand hospitals.[69-71] However, the prevalence of detection of MRSA in New Zealand communities and hospitals has increased significantly in recent years. Between 2006 and 2015 the rate of disease caused by these bacteria increased by 77%, from 14.3 to 25.3 per 100,000 population over the 1-month testing period, although most of this increase occurred before 2011.[72]

Although MRSA infections were once mostly restricted to hospital-acquired infections, the global characteristics of MRSA has changed with the emergence and spread of bacterial strains known as community-associated MRSA (CA-MRSA).[1] These bacteria have spread around the world, most notably the type known as "USA 300 CA-MRSA" from North America,[73] which was first reported in New Zealand in the mid-2000s.[74]

In 2014, about one in ten of the *S. aureus* strains causing infection in New Zealand were MRSA.[75] During a 1-month period in 2015, MRSA was isolated from over 800 people with a staphylococcal skin and/or soft tissue infection.[72] The widespread use of topical antibiotics may have driven the spread of MRSA in New Zealand.[55]

The proportion of staphylococcal disease caused by MRSA in New Zealand remains low compared with UK, USA and France.[42] Within New Zealand, there is a considerable variation between regions, with the highest rates of MRSA isolated from patients in the top half of the North Island.[72]

Case Study 2: Antibiotic resistance in the bacterial family Enterobacteriaceae

Enterobacteriaceae are a family of bacteria including *E. coli* and *Klebsiella pneumoniae* that commonly live in the intestines and can cause infections of the bladder and kidneys (cystitis and pyelonephritis). These bacteria may produce proteins, known as extended-spectrum beta-lactamases (ESBL), which destroy penicillin and related antibiotics. These ESBL-producing Enterobacteriaceae (ESBL-E) were first identified in New Zealand in the early 1990s.[76,77] However, it was not until the mid-2000s that the incidence of people diagnosed with these infections increased significantly, in both hospital and community settings.[77,78]

Within New Zealand, the spread of ESBL-E has occurred in healthcare and residential care facilities,[79] and ESBL-E is now endemic[‡] in the New Zealand community. The proportion of infections due to ESBL-E remains lower in New Zealand than in North America and some parts of Europe.[42] Data from a multinational antimicrobial resistance survey reported low but increasing rates of ESBL-E in the South Pacific.[80-82]

Levels of antimicrobial resistance in animals are not routinely monitored in New Zealand.[60] A baseline survey from 2009 to 2010 did not detect ESBL-E in the animal groups (calves, pigs and poultry) tested.[83] However ESBL-E has been isolated from pets.[63]

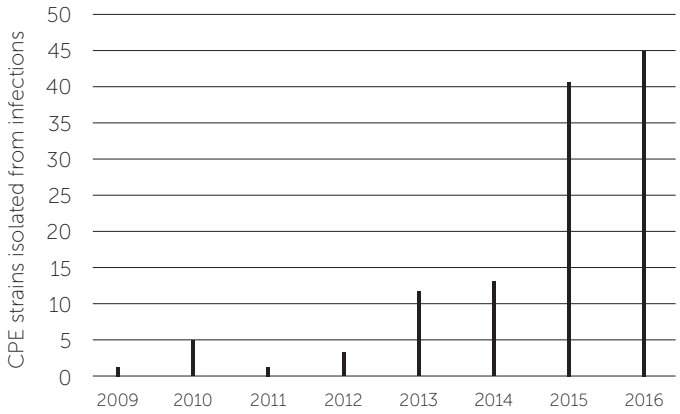
Case study 3: Resistance to last-resort antibiotics

The emergence of carbapenemase-producing Enterobacteriaceae (CPE) is of great concern as carbapenems are a last-resort antibiotic that can be used to treat ESBL-E.[84] Carbapenemase-producing Enterobacteriaceae tend to be resistant to multiple antibiotics. Colistin is one of the last-resort antibiotics to treat patients with CPE. However, in September 2016 a woman in the USA died after being infected with a strain of CPE resistant to 26 different antibiotics, including colistin.[85] Infections such as this are essentially untreatable, and can lead to the death of the patient. The World Health Organization (WHO) classified CPE as a top priority for research and development to find new and effective antibiotic treatments.[86]

While still rare in New Zealand, CPE are becoming widespread around the world, especially in India.[42,87] However, the number of CPE strains isolated in New Zealand has increased in recent years (Fig. 5).[88-90] Most of the cases seen in New Zealand are in patients who had travelled to India.[88-90] Many patients seem to have acquired the resistant bacteria during hospitalisations in other countries.[88,89,91] In 2015, transmission of CPE was identified for the first time between patients in two New Zealand hospitals.[89]

FIGURE 5

CPE in New Zealand



Source data from ESR[88-90]

[‡] An endemic disease is one that is consistently present in a community or region.

Other resistant microorganisms of concern in New Zealand

The Institute of Environmental Science and Research conducts national surveillance of antimicrobial resistance among pathogenic microbes of concern in New Zealand.[72,77,89,92-96] Some antibiotic-resistant strains are widespread in New Zealand healthcare and community settings,[71] whereas others are uncommon but are of great concern elsewhere in the world.[1,7,42]

Antimicrobial-resistant strains can become endemic in healthcare settings. Enterococci are bacteria found in our gut. Some enterococci are intrinsically resistant and can readily acquire resistance to many antibiotics including vancomycin, but resistance to vancomycin is not common in many disease-causing bacteria.[97,98] There is concern that vancomycin resistance will spread from vancomycin-resistant enterococci to common pathogenic bacteria.[98] Unfortunately, infection with vancomycin-resistant enterococci is widespread in patients in the USA[7] and has become prevalent in some Australian hospitals.[99] Similar outbreaks have occurred in New Zealand hospitals from time to time, but fortunately, rigorous infection prevention and control measures have curtailed these outbreaks.[94]

People visiting or returning to New Zealand sometimes import resistant bacteria after receiving medical care overseas.[88]

Societal impact of antimicrobial-resistant infections

Antimicrobial resistance can affect people's lives and contribute to rising healthcare utilisation[1] and costs to society through loss of labour in the workforce.[3] Antibiotic resistance makes it more dangerous to use medical treatments that carry a significant risk of infection, including invasive surgery, cancer therapy and dialysis.[1,3,7] For more virulent bacteria, resistance may result in the death of the patient. For less virulent bacteria, it may mean that treating the infection becomes more complicated, requiring the use of antibiotics that may be less effective and/or more toxic to the patient.[1,7] It could mean further costs and treatments to mitigate the undesirable side-effects of these more toxic drugs. It may also result in the need for other interventions to control the infection, such as surgery.[100,101]

In New Zealand, 302 cases of tuberculosis (TB) were reported during 2014, including three cases that were identified as multidrug resistant.[93] A study into a multidrug-resistant case estimated the total cost of treatment was nearly NZ$327,000.[102] Extended hospital stays, outpatient treatment and more expensive second-line drug treatment accounted for most of this cost.[102]

Internationally, most economic studies have focused on the costs to society of specific infections.[103] A study investigating the costs from all antibiotic-resistant infections sampled 1,391 high-risk hospitalised adult patients from a single, large, urban public teaching hospital in Chicago, USA.[104] In this sample, 13.5% had antibiotic-resistant infections. The total medical and societal cost associated with antibiotic-resistant infections in this study was calculated to be between US$13.35 million and 18.75 million.[104] If health-related quality of life could be adequately measured, and included, the estimated societal burden would have been higher.

The UK government commissioned former Goldman Sachs chief economist Jim O'Neill to review and estimate the future global costs of antimicrobial resistance.[3] The extent of losses to the world economy caused by decreases in the supply of labour resulting from three resistant bacterial infections (caused by *E. coli, K. pneumoniae,* and *S. aureus*) and three major infectious diseases (HIV, TB, and malaria) was projected.[3] The results of the study highlighted that antimicrobial resistance is a serious threat to health and the global economy. There could be a broader effect on the economy through changes in tourism and global trade.[3]

Currently, 700,000 people per year are estimated to die globally from antimicrobial-resistant infections.[3] By 2050, this death toll is projected to increase to 10 million people annually if the rate of increase in antibiotic resistance remains unchecked.[3] To put this in perspective 8.8 million deaths were attributed to cancer in 2015.[3,105] The broad-brush estimate for antimicrobial resistance fatalities by 2050 should be interpreted with caution due to limited data availability and the general assumptions necessary for such long-term forecasts.[106]

In the short period since the O'Neill review started in 2014, new forms of resistance have emerged that were not expected to occur so soon. Emerging issues include transmission between different bacterial strains of resistance to colistin, an antibiotic of last resort in human medicine.[4]

Combating antimicrobial resistance

International approach

The World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) are collaborating to address antimicrobial resistance across the sectors spanned by these agencies.[6] The foundation for this collaboration is a One Health approach that recognises that antibiotic resistance extends beyond the borders between humans, animals and the environment. To assist in strategic planning, WHO and OIE have classified some antibiotics as critically important for human[65] and animal health[107] respectively.

WHO identified five key strategies for tackling the growing problems caused by antimicrobial resistance:[6]

- Increase global awareness and understanding about antimicrobial resistance
- Use surveillance and research to strengthen knowledge on antimicrobial resistance
- Reduce the incidence of infections through hygiene, sanitation and other preventative measures
- Optimise the use of antimicrobial agents
- Increase investments in countering antimicrobial resistance

Reducing unnecessary use of antimicrobial agents in agriculture has been recommended to help reduce the emergence and spread of resistant microbes.[4] Recommendations include avoiding using antimicrobial agents considered critically important for treating infections in humans[65] and avoiding using them to prevent infection in groups of animals, particularly where alternative approaches exist. Such alternatives include the use of vaccination, more targeted application of antimicrobial agents, improved biosecurity, infection control, improved animal welfare by providing good housing and appropriate nutrition, and by breeding robust animals. Reducing the use of antimicrobial agents in livestock farming has been shown to reduce the levels of resistant organisms in animals,[108] although this is not always the case.[109,110] It has been difficult to demonstrate a link between reducing use in animals and a reduction in the prevalence of resistant bacteria in humans.[111]

New Zealand's antimicrobial resistance plan

There have been a number of initiatives to monitor and address antimicrobial resistance in New Zealand. In a recent initiative, the Antimicrobial Resistance Strategic Action Plan Development Group was formed to prepare a national antimicrobial resistance plan, due by mid-2017.[112] The group consists of members from relevant government agencies and professional organisations across the human and animal health sectors.

The New Zealand Veterinary Association aims to eliminate the use of antibiotics in the maintenance of animal health by 2030.[113] It has also released a statement aspiring to replace the use of the antibiotic preventative treatment known as Dry Cow Therapy with non-antibiotic based management practices by 2020.[114]

Research in New Zealand

Further research is required to improve our understanding of resistance and to develop alternative methods for treating and preventing antimicrobial-resistant infections. Some New Zealand scientists are working on the following projects:[115]

- Developing new or better vaccines
- Searching for novel antimicrobial agents in New Zealand fungi and from bacteria in soil
- Exploring new drugs for tuberculosis
- Discovering and investigating how to control a subset of viruses that specifically target certain bacteria
- Using a One Health approach to tackle human, animal and plant diseases
- Designing surfaces that are resistant to microbe
- Studying mechanisms of antimicrobial resistance with the intention to re-engineer antibiotics and improve their efficiency

How everyone can help combat resistance

Unnecessary use and misuse of antibiotics contribute to the spread of antibiotic resistance. WHO provides advice and summarises actions that individuals, policy makers, health professionals and the agriculture sector can take to help mitigate the spread of resistance.[2,5]

Antibiotics are not effective against viral infections such as influenza and common colds. WHO recommends only taking antibiotics prescribed by a certified health professional, and to never demand antibiotic treatment against their professional medical advice.[2,5] WHO recommends following directions to complete the full prescription when using antibiotics and never sharing or using leftover antibiotics.[2,5]

To prevent infections occurring in the first place, WHO recommends regular hand washing, following good hygiene practices when preparing food, and keeping relevant vaccinations up to date.[2,5]

Our Experts

Royal Society Te Apārangi prepared this paper under the guidance of the following experts:

Professor Gregory Cook FRSNZ, Professor Nigel French FRSNZ, Professor Gary Hawke FRSNZ, Professor Jack Heinemann, Dr Heather Hendrickson, Professor Richard Le Heron FRSNZ, William Leung, Dr Sally Roberts, Dr Trudy Sullivan, Associate Professor Mark G. Thomas, Dr Siouxsie Wiles and Dr Deborah Williamson.

Professor Kiaran Kirk and Dr Stephen Page provided independent international review of the paper.

The Society would also like to thank the following experts for their valuable contributions and commenting on the paper:

Professor Richard Beasley FRSNZ, Professor John Brooks, Dr Bryce Buddle FRSNZ, Associate Professor Brent Copp, Helen Heffernan, Dr Allen Petrey, Dr James Ussher, Australasian Society for Infectious Diseases, Māori Health Review, The New Zealand College of Public Health Medicine, New Zealand Medical Association, New Zealand Veterinary Association, Public Health Association of New Zealand, The Royal Australasian College of Physicians and The Royal New Zealand College of General Practitioners.

References

1. WHO. Antimicrobial resistance: global report on surveillance. Geneva, Switzerland: World Health Organization; 2014.

2. WHO. October 2016. Antibiotic resistance: fact sheet. World Health Organization <http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/>.

3. O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. UK: Welcome Trust and HM Government; 2014.

4. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. UK: Welcome Trust and HM Government; 2016.

5. WHO. October 2016. Posters on human health: world antibiotic awareness week. World Health Organization <http://www.who.int/campaigns/world-antibiotic-awareness-week/posters/en/>.

6. WHO. Global action plan on antimicrobial resistance. Geneva, Switzerland: World Health Organization; 2015.

7. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Atlanta, Georgia, USA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2013.

8. Bonita R, Beaglehole R, Kjellström T. Basic epidemiology. Geneva Switzerland: World Health Organization; 2006.

9. Institute of Environmental Science and Research Limited. Annual summary of outbreaks in New Zealand 2015. Wallaceville, New Zealand: Institute of Environmental Science and Research Limited; 2016. Report nr FW16009.

10. Institute of Environmental Science and Research Limited. Notifiable diseases in New Zealand: annual report 2015. Porirua, New Zealand: Institute of Environmental Science and Research Limited; 2016. Report nr FW16017.

11. Institute of Environmental Science and Research Limited. Sexually transmitted infections in New Zealand: annual surveillance report 2014. Porirua, New Zealand: Institute of Environmental Science and Research Limited; 2015. Report nr FW15023.

12. Institute of Environmental Science and Research Limited. Influenza surveillance in New Zealand 2015. Wellington, New Zealand: Institute of Environmental Science and Research Limited; 2016. Report nr FW16018.

13. Wiles S. 2016. InfectedNZ: the state of the nation. InfectedNZ. <http://www.tepunahamatatini.ac.nz/infectednz-the-state-of-the-nation/#post_content2016>.

14. Ministry of Health. 2016. Publicly funded hospital discharges–1 July 2013 to 30 June 2014. <http://www.health.govt.nz/publication/publicly-funded-hospital-discharges-1-july-2013-30-june-2014>.

15. WHO. Report on the burden of endemic health care-associated infection worldwide. Geneva, Switzerland: World Health Organization; 2011.

16. Baker MG, Barnard LT, Kvalsvig A, Verrall A, Zhang J, Keall M, Wilson N, Wall T, Howden-Chapman P. Increasing incidence of serious infectious diseases and inequalities in New Zealand: a national epidemiological study. The Lancet 2012;379(9821):1112–1119.

17. Williamson DA, Zhang J, Ritchie SR, Roberts SA, Fraser JD, Baker MG. *Staphylococcus aureus* infections in New Zealand, 2000–2011. Emerging Infectious Diseases 2014;20(7):1156–1161.

18. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiology and Molecular Biology Reviews 2010;74(3):417–433.

19. Eliopoulos GM, Moellering, C. R. Principles in anti-infective therapy. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed. Philadelphia, PA, USA: Churchill Livingstone, Elsevier; 2015.

20. Lewis K. Platforms for antibiotic discovery. Nature Reviews Drug Discovery 2013;12(5):371–387.

21. Turnidge JD. Susceptibility testing methods: general considerations. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Warner DW, editors. Manual of Clinical Microbiology. 11 ed. Washington, DC. USA: ASM Press; 2015. p 1246–1252.

22. Kohanski MA, Dwyer DJ, Collins JJ. How antibiotics kill bacteria: from targets to networks. Nature Reviews Microbiology 2010;8(6):423–435.

23. Nemeth J, Oesch G, Kuster SP. Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy 2015;70(2):382–395.

24. Opal SM, Pop-Vicas A. Molecular mechanisms of antibiotic resistance in bacteria. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8 ed. Philadelphia, PA, USA: Churchill Livingstone Elsevier; 2015. p 235–251.

25. Hall BG, Barlow M. Evolution of the serine β-lactamases: past, present and future. Drug Resist Update 2004;7(2):111–123.

26. Risso VA, Gavira JA, Mejia-Carmona DF, Gaucher EA, Sanchez-Ruiz JM. Hyperstability and substrate promiscuity in laboratory resurrections of Precambrian β-lactamases. Journal of the American Chemical Society 2013;135(8):2899–2902.

27. Moscona A. Oseltamivir resistance – disabling our influenza defenses. New England Journal of Medicine 2005;353(25):2633–2636.

28. Patel JB, Richter SS. Mechanisms of resistance to antibacterial agents. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, W. WD, editors. Manual of Clinical Microbiology. 11 ed. Washington, DC, USA: American Society of Microbiology; 2015. p 1212–1245.

29. MacPherson DW, Gushulak BD, Baine WB, Bala S, Gubbins PO, Holtom P, Segarra-Newnham M. Population mobility, globalization, and antimicrobial drug resistance. Emerging Infectious Diseases 2009;15(11):1727–1732.

30. FAO. The FAO action plan on antimicrobial resistance 2016–2020. Rome, Italy: Food and Agriculture Organization of the United Nations; 2016.

31. Statistics New Zealand. Global New Zealand – International trade, investment, and travel profile: Year ended June 2016. Wellington, New Zealand: Ministry of Foreign Affairs and Trade, and Statistics New Zealand; 2016.

32. Levy SB. Antibacterial household products: cause for concern. Emerging Infectious Diseases 2001;7(3 Suppl):512–515.

33. Yueh MF, Tukey RH. Triclosan: a widespread environmental toxicant with many biological effects. Annual Review of Pharmacology and Toxicology 2016;56:251–272.

34. Bedoux G, Roig B, Thomas O, Dupont V, Le Bot B. Occurrence and toxicity of antimicrobial triclosan and by-products in the environment. Environmental Science and Pollution Research 2012;19(4):1044–1065.

35. Kurenbach B, Marjoshi D, Amábile-Cuevas CF, Ferguson GC, Godsoe W, Gibson P, Heinemann JA. 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 2015;6(2):e00009-15.

36. Aiello AE, Larson EL, Levy SB. Consumer antibacterial soaps: effective or just risky? Clinical Infectious Diseases 2007;45 Suppl 2:S137–147.

37. US Food and Drug Administration. 2016. Antibacterial soap? You can skip it—use plain soap and water. FDA Consumer Update: <www.fda.gov/forconsumers/consumerupdates/ucm378393.htm>.

38. Woolhouse M, Ward M, van Bunnik B, Farrar J. Antimicrobial resistance in humans, livestock and the wider environment. Philosophical Transactions of the Royal Society of London. Series B. Biological Sciences 2015;370(1670):20140083.

39. Michael I, Rizzo L, McArdell CS, Manaia CM, Merlin C, Schwartz T, Dagot C, Fatta-Kassinos D. Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: a review. Water Research 2013;47(3):957–995.

40. Cabello FC. Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment. Environmental Microbiology 2006;8(7):1137–1144.

41. Shah SQ, Cabello FC, L'abée-Lund TM, Tomova A, Godfrey HP, Buschmann AH, Sørum H. Antimicrobial resistance and antimicrobial resistance genes in marine bacteria from salmon aquaculture and non-aquaculture sites. Environmental Microbiology 2014;16(5):1310–1320.

42. Center for Disease Dynamics, Economics & Policy. State of the world's antibiotics, 2015. Washington, D.C., USA: CDDEP; 2015.

43. European Public Health Alliance. 2016. Drug resistance through the back door: how the pharmaceutical industry is fuelling the rise of superbugs through pollution in its supply chains. <http://epha.org/wp-content/uploads/2016/08/DRUG-RESISTANCE-THROUGH-THE-BACK-DOOR_WEB.pdf>.

44. One Health Initiative. Accessed May 2017. <http://www.onehealthinitiative.com/about.php>.

45. Lazarus B, Paterson DL, Mollinger JL, Rogers BA. Do human extraintestinal *Escherichia coli* infections resistant to expanded-spectrum cephalosporins originate from food-producing animals? A systematic review. Clinical Infectious Diseases 2015;60(3):439–452.

46. Shen Z, Wang Y, Shen Y, Shen J, Wu C. Early emergence of mcr-1 in *Escherichia coli* from food-producing animals. The Lancet Infectious Diseases 2016;16(3):293.

47. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, Doi Y, Tian G, Dong B, Huang X and others. 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 2016;16(2):161–168.

48. Grøntvedt CA, Elstrøm P, Stegger M, Skov RL, Skytt Andersen P, Larssen KW, Urdahl AM, Angen Ø, Larsen J, Åmdal S and others. Methicillin-resistant *Staphylococcus aureus* CC398 in humans and pigs in Norway: A "One Health" perspective on introduction and transmission. Clinical Infectious Diseases 2016;63(11):1431–1438.

49. Williamson DA, Roos RF, Verrall A. Surveillance report: antibiotic consumption in New Zealand, 2006–2014. Porirua, New Zealand: The Institute of Environmental Science and Research Limited; 2016.

50. Center for Disease Dynamics, Economics & Policy. Resistance map. Accessed May 2017. <http://resistancemap.cddep.org/AntibioticUse.php>.

51. Thomas MG, Smith AJ, Tilyard M. Rising antimicrobial resistance: a strong reason to reduce excessive antimicrobial consumption in New Zealand. New Zealand Medical Journal 2014;127(1394):72–84.

52. Duffy E, Ritchie S, Metcalfe S, Van Bakel B, Thomas MG. Antibacterials dispensed in the community comprise 85–95% of total human antibacterial consumption. Manuscript in preparation.

53. Hobbs MR, Grant CC, Ritchie SR, Chelimo, C., Morton SMB, Berry S, Thomas MG. Antibiotic consumption by New Zealand children: exposure is near universal by the age of 5years. Journal of Antimicrobial Chemotherapy 2017(dkx060. doi: 10.1093/jac/dkx060).

54. Upton A, Lang S, Heffernan H. Mupirocin and *Staphylococcus aureus*: a recent paradigm of emerging antibiotic resistance. Journal of Antimicrobial Chemotherapy 2003;51(3):613–617.

55. Williamson DA, Monecke S, Heffernan H, Ritchie SR, Roberts SA, Upton A, Thomas MG, Fraser JD. High usage of topical fusidic acid and rapid clonal expansion of fusidic acid-resistant *Staphylococcus aureus*: a cautionary tale. Clinical Infectious Diseases 2014;59(10):1451–1454.

56. European Centre for Disease Prevention and Control. Antimicrobial Consumption Interactive Database (ESAC-Net). Accessed May 2017. <http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial-consumption/esac-net-database/Pages/database.aspx>.

57. Australian Commission on Safety and Quality in Health Care. AURA 2016: First Australian report on antimicrobial use and resistance in human health. Sydeny, Australia: Australian Commission on Safety and Quality in Health Care; 2016.

58. Duffy E, Gardiner S, du Plessis T, Bondesio K, Morar B. A snapshot of antimicrobial use in New Zealand hospitals – a comparison to Australian and English data. New Zealand Medical Journal 2015;128(1421):82–84.

59. Ticehurst R, Thomas M. Antimicrobial consumption at Auckland City Hospital: 2006–2009. New Zealand Medical Journal 2011;124(1332):9–20.

60. Ministry of Health, Ministry for Primary Industries. Antimicrobial Resistance: New Zealand's current situation and identified areas for action. Wellington: Ministry of Health and Ministry of Primary Industries; 2017.

61. Hillerton JE, Irvine CR, Bryan MA, Scott D, Merchant SC. Use of antimicrobials for animals in New Zealand, and in comparison with other countries. New Zealand Veterinary Journal 2017;65(2):71–77.

62. O'Neill J. Antimicrobials in agriculture and the environment: reducing unnecessary use and waste. UK: Welcome Trust and HM Government; 2015.

63. Toombs-Ruane LJ, Benschop J, Burgess S, Priest P, Murdoch DR, French NP. Multidrug resistant Enterobacteriaceae in New Zealand: a current perspective. New Zealand Veterinary Journal 2017;65(2):62–70.

64. Ministry for Primary Industries. 2011–2014 Antibiotic Sales Analysis. Wellington, New Zealand: ACVM Group, Systems Audit, Assurance & Monitoring Directorate, Ministry for Primary Industries; 2016.

65. WHO. Critically important antimicrobials for human medicine. Geneva, Switzerland: World Health Organization; 2016.

66. New Zealand Veterinary Association. Antibiotic judicious use guidelines for the New Zealand veterinary profession: Dairy. Wellington, New Zealand: New Zealand Veterinary Association; 2016.

67. New Zealand Veterinary Association. Antibiotic judicious use guidelines for the New Zealand veterinary profession: Equine. Wellington, New Zealand: New Zealand Veterinary Association; 2016.

68. New Zealand Veterinary Association. Guidelines for the clinical use of antimicrobial agents in the treatment of dogs and cats. Wellington, New Zealand: New Zealand Veterinary Association; 2016.

69. Humble MW. Imported methicillin-resistant *Staphylococcus aureus* infection: a case report. New Zealand Medical Journal 1976;84(578):476–478.

70. Martin DR, Heffernan HM, Davies HG. Methicillin-resistant *Staphylococcus aureus*: an increasing threat in New Zealand hospitals. New Zealand Medical Journal 1989;102(872):367–369.

71. Williamson DA, Heffernan H. The changing landscape of antimicrobial resistance in New Zealand. New Zealand Medical Journal 2014;127(1403):41–54.

72. Heffernan H, Bakker S. Annual survey of methicillin-resistant *Staphylococcus aureus* (MRSA), 2015. Porirua, New Zealand: Nosocomial Infections Laboratory, Institute of Environmental Science and Research Ltd; 2016.

73. Klein EY, Sun L, Smith DL, Laxminarayan R. The changing epidemiology of methicillin-resistant *Staphylococcus aureus* in the United States: a national observational study. American Journal of Epidemiology 2013;177(7):666–674.

74. Institute of Environmental Science and Research Limited. Annual survey of methicillin-resistant *Staphylococcus aureus* (MRSA), 2006. Porirua, New Zealand: Institute of Environmental Science and Research Limited.

75. Heffernan H, Bakker S, Woodhouse R, Dyet K, Williamson D. Demographics, antimicrobial susceptibility and molecular epidemiology of *Staphylococcus aureus* in New Zealand, 2014. Porirua, New Zealand: Antibiotic Reference and Nosocomial Infections Laboratories, Health Group, Institute of Environmental Science and Research Limited; 2015. Report nr FW15002.

76. Institute of Environmental Science and Research Limited. Extended-spectrum β-lactamases (ESBLs) in Enterobacteriaceae confirmed in 2002. Porirua, New Zealand: Institute of Environmental Science and Research Limited.

77. Heffernan H, Woodhouse R, Blackmore T. Prevalence of extended spectrum β-lactamases among urinary *Escherichia coli* and *Klebsiella* in New Zealand in 2006. Porirua, New Zealand: Communicable Disease Group, Institute of Environmental Science and Research Limited; 2006.

78. Heffernan H, Woodhouse R. Annual survey of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, 2009. Porirua, New Zealand: Institute of Environmental Science and Research Limited.

79. Moor CT, Roberts SA, Simmons G, Briggs S, Morris AJ, Smith J, Heffernan H. Extended-spectrum β-lactamase (ESBL)-producing enterobacteria: factors associated with infection in the community setting, Auckland, New Zealand. Journal of Hospital Infection 2008;68(4):355–362.

80. Morrissey I, Hackel M, Badal R, Bouchillon S, Hawser S, Biedenbach D. A review of ten years of the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2002 to 2011. Pharmaceuticals (Basel) 2013;6(11):1335–1346.

81. Sheng WH, Badal RE, Hsueh PR, Program S. Distribution of extended-spectrum β-lactamases, AmpC β-lactamases, and carbapenemases among Enterobacteriaceae isolates causing intra-abdominal infections in the Asia-Pacific region: results of the study for Monitoring Antimicrobial Resistance Trends (SMART). Antimicrobial Agents and Chemotherapy 2013;57(7):2981–2988.

82. Hawser SP, Bouchillon SK, Hoban DJ, Badal RE, Hsueh PR, Paterson DL. Emergence of high levels of extended-spectrum-β-lactamase-producing Gram-negative bacilli in the Asia-Pacific region: data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program, 2007. Antimicrobial Agents and Chemotherapy 2009;53(8):3280–3284.

83. Heffernan H, Wong TL, Lindsay J, Bowen J, Woodhouse R. A baseline survey of antimicrobial resistance in bacteria from selected New Zealand foods, 2009–2010. Wellington, New Zealand: Ministry of Agriculture and Forestry; 2011. Report nr 2011/53.

84. Blakiston M, Heffernan H, Roberts S, Freeman J. The clear and present danger of carbapenemase-producing Enterobacteriaceae (CPE) in New Zealand: time for a national response plan. New Zealand Medical Journal 2017;130(1454):72–79.

85. Chen L, Todd R, Kiehlbauch J, Walters M, Kallen A. Notes from the field: pan-resistant New Delhi metallo-beta-lactamase-producing *Klebsiella pneumoniae* – Washoe County, Nevada, 2016. Morbidity and Mortality Weekly Report 2017;66(1):33.

86. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva, Switzerland: World Health Organization; 2017.

87. Johnson AP, Woodford N. Global spread of antibiotic resistance: the example of New Delhi metallo-β-lactamase (NDM)-mediated carbapenem resistance. Journal of Medical Microbiology 2013;62(Pt 4):499–513.

88. Institute of Environmental Science and Research Limited. Enterobacteriaceae with acquired carbapenemases, 2009–2014. Porirua, New Zealand: Institute of Environmental Science and Research Limited.

89. Institute of Environmental Science and Research Limited. Enterobacteriaceae with acquired carbapenemases, 2015. Porirua, New Zealand: Institute of Environmental Science and Research Limited.

90. Institute of Environmental Science and Research Limited. Enterobacteriaceae with acquired carbapenemases, 2016. Porirua, New Zealand: Institute of Environmental Science and Research Limited.

91. Heffernan H, Dyet K, Munroe S, Creighton J, Chan S, Taylor S, Mansell C. First cases of KPC-type carbapenemase-producing bacteria in patients in New Zealand hospitals. Journal of Global Antimicrobial Resistance 2014;2(4):330–333.

92. Heffernan H, Woodhouse R, Williamson D. Antimicrobial resistance and molecular epidemiology of *Neisseria gonorrhoeae* in New Zealand, 2014–15. Porirua, New Zealand: Institute of Environmental Science and Research Limited; 2015. Report nr FW15061.

93. Institute of Environmental Science and Research Limited. Surveillance report: tuberculosis in New Zealand 2014. Porirua, New Zealand: Health Intelligence Team, Institute of Environmental Science and Research Limited; 2015. Report nr FW15062.

94. Institute of Environmental Science and Research Limited. Vancomycin-resistant enterococci, 2015. Porirua, New Zealand: Institute of Environmental Science and Research Limited.

95. Dyet K, Woodhouse R, Heffernan H. Annual survey of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, 2014. Porirua, New Zealand: Antibiotic Reference Laboratory, Institute of Environmental Science and Research Limited; 2014.

96. Institute of Environmental Science and Research Limited. Antimicrobial Resistance. Accessed May 2017. <https://surv.esr.cri.nz/antimicrobial/antimicrobial_resistance.php>.

97. Arias CA, Murray BE. The rise of the Enterococcus: beyond vancomycin resistance. Nature Reviews Microbiology 2012;10(4):266–278.

98. Cetinkaya Y, Falk P, Mayhall CG. Vancomycin-resistant enterococci. Clinical Microbiology Reviews 2000;13(4):686–707.

99. Karki S, Houston L, Land G, Bass P, Kehoe R, Borrell S, Watson K, Spelman D, Kennon J, Harrington G and others. Prevalence and risk factors for VRE colonisation in a tertiary hospital in Melbourne, Australia: a cross sectional study. Antimicrobial Resistance and Infection Control 2012;1(31).

100. Sartelli M, Catena F, di Saverio S, Ansaloni L, Coccolini F, Tranà C, Kirkby-Bott J. The challenge of antimicrobial resistance in managing intra-abdominal infections. Surgical Infections (Larchmt) 2015;16(3):213–220.

101. Madansein R, Parida S, Padayatchi N, Singh N, Master I, Naidu K, Zumla A, Maeurer M. Surgical treatment of complications of pulmonary tuberculosis, including drug-resistant tuberculosis. International Journal of Infectious Diseases 2015;32:61–67.

102. McNaughton A, Blackmore T, McNaughton H. Comprehensive cost of treating one patient with MDR/pre-XDR-TB in Wellington, New Zealand. The European Respiratory Journal 2016;48(4):1256–1259.

103. Smith RD, Coast J. The economic burden of antimicrobial resistance: why it is more serious than current studies suggest. London, UK: London School of Hygiene and Tropical Medicine; 2012.

104. Roberts RR, Hota B, Ahmad I, Scott RD, Foster SD, Abbasi F, Schabowski S, Kampe LM, Ciavarella GG, Supino M and others. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clinical Infectious Diseases 2009;49(8):1175–1184.

105. WHO. February 2017. Cancer: factsheet. World Health Organization <http://www.who.int/mediacentre/factsheets/fs297/en/>.

106. de Kraker ME, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? PLoS Medicine 2016;13(11):e1002184.

107. OIE. OIE list of antimicrobial agents of veterinary importance. Paris, France: World Organisation for Animal Health; 2015.

108. Agersø Y, Aarestrup FM. Voluntary ban on cephalosporin use in Danish pig production has effectively reduced extended-spectrum cephalosporinase-producing *Escherichia coli* in slaughter pigs. Journal of Antimicrobial Chemotherapy 2013;68(3):569–572.

109. Agersø Y, Jensen JD, Hasman H, Pedersen K. Spread of extended spectrum cephalosporinase-producing *Escherichia coli* clones and plasmids from parent animals to broilers and to broiler meat in a production without use of cephalosporins. Foodborne Pathogen and Disease 2014;11(9):740–746.

110. Manson JM, Smith JM, Cook GM. Persistence of vancomycin-resistant enterococci in New Zealand broilers after discontinuation of avoparcin use. Applied Environmental Microbiology 2004;70(10):5764–5768.

111. Manson JM, Keis S, Smith JM, Cook GM. A clonal lineage of VanA-type *Enterococcus faecalis* predominates in vancomycin-resistant enterococci isolated in New Zealand. Antimicrobial Agents and Chemotherapy 2003;47(1):204–210.

112. Ministry of Health. October 2016. Antimicrobial resistance strategic action plan development group. <http://www.health.govt.nz/our-work/diseases-and-conditions/antimicrobial-resistance/antimicrobial-resistance-strategic-action-plan-development-group>.

113. New Zealand Veterinary Association. 25 April 2017. NZ vets taking on one of the biggest health issues facing the planet. <http://www.nzva.org.nz/news/342324/NZVA-media-release-NZ-vets-taking-on-one-of-the-biggest-health-issues-.htm>.

114. New Zealand Veterinary Association. 2016 NZVA position on DCT. <http://nzva.site-ym.com/?page=drycowtherapy&terms=%22dry+and+cow%22>.

115. Wiles S. Antibiotic Resitance – the end of modern medicine? Wellington, New Zealand: Bridget Williams Books Ltd; 2017. 136 p.

For further information, please contact **info@royalsociety.org.nz** or visit the Royal Society Te Apārangi webpage **royalsociety.org.nz/antimicrobial**

ISBN: 978-1-877264-25-2

May 2017