



OUTBREAK OUTBREAK

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A One Health antimicrobial resistance economic perspective
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OUTBREAK

OUTBREAK is a pioneering transdisciplinary and multi-institutional initiative that is uniquely skilled to solve the growing problem of antibiotic resistance.

The **OUTBREAK** consortium is led by the University of Technology Sydney (UTS) in collaboration with CSIRO, University of Wollongong, University of South Australia, University of Newcastle, NSW Government (Department of Primary Industries, and Department of Health – Illawarra Shoalhaven Local Health District), Sax Institute, Quadram Institute of Biosciences (UK), Southern IML Pathology (now part of Sonic Healthcare Ltd), Microba, MicroGEM (UK), Mimesis and Oracle.

Initially supported by a AUD 1 million Medical Research Future Fund Frontier Health and Medical Research program grant, **OUTBREAK** is comprehensively mapping antimicrobial resistance (AMR) risks by drawing on a diverse range of existing and new datasets – from whole genome sequences of bacteria, census data, patient data and prescribing behaviours through to land use, hospital locations, weather patterns and wastewater-based epidemiology.

At the heart of **OUTBREAK** is the One Health AMR Knowledge Engine – a world-first AI-powered system designed to track, trace and tackle drug-resistant infections. By generating, integrating and analysing data from humans, animals, plants and the environment (One Health approach), the knowledge engine will predict the location-specific and person-specific threat of an antibiotic resistant infection now and in the future. This information can then be overlaid with economic and resourcing data to inform potential mitigation strategies.

The **OUTBREAK** solution straddles public good and commercialisation opportunities, and could be scaled to all of Australia, and potentially the world. In the future, the **OUTBREAK** platform could be used to aggregate and present all the different information that would allow for AI-powered risk-based predictions relating to any pathogen and infectious disease outbreak.

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1

Foreword



In his 1945 Nobel Prize speech, Alexander Fleming noted that penicillin, the antibiotic he discovered, could be rendered ineffective by the evolutionary process of antimicrobial resistance (AMR). “It is not difficult,” he said, “to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them.” Fleming’s words were prescient. Today, AMR is a gathering storm that threatens a century of progress in medicine. Yet the human and economic cost of increased resistance has not been fully recognised.

There are, we suspect, a number of reasons for this. In part, it reflects the intangible nature of AMR and the consequent difficulty in quantifying its impacts. Unlike other infectious agents, AMR represents a phenomenon that spans diverse species of microscopic organisms (the term ‘antibiotic resistance’ refers to resistance of bacteria to antibiotic treatment, whereas the broader concept of AMR also encompasses treatment resistance in viruses, fungi, and other microscopic organisms). Moreover, it has become apparent that resistance can emerge in commensal (non-harmful) microbial populations but can then be transferred to pathogenic microbes.

Another major challenge is the alignment of incentives. From an economic point of view, AMR is a negative externality - the costs of overusing or misusing antibiotics are not borne by those who incur it. Conversely, the benefits of action to mitigate AMR may not immediately be felt by the individuals and organisations that are required to act.

With these challenges in mind, the OUTBREAK team has put together an economics report with the aim of establishing and highlighting the range of socioeconomic impacts of antibiotic resistance in Australia and identifying potential strategies for intervention.

To make the problem tractable, we focus on a specific clinical condition - urinary tract infection (UTI) - and the health and economic sequelae of antibiotic resistance. Although UTIs are typically mild and resolve quickly, they can progress to kidney and bloodstream infection, sepsis, and in some cases, death. The associated costs can also escalate quickly if treatment in the community does not resolve and the patient requires hospitalisation. We provide an estimate of the total cost of UTIs to the Australian healthcare system and model a range of scenarios with antibiotic resistance levels worsening (due to inaction) or reducing via intervention.

Throughout the report, we adopt a ‘One Health’ perspective, recognising the intertwined nature of human, animal, and environmental health. Human exposure to antibiotic resistance can come from our food, domesticated and wild animals, soils, and water. The emergence of antibiotic resistance is driven, not only by inappropriate (overuse, underuse, and untargeted) use of antibiotics in human healthcare but also by its use and misuse in the livestock industry. Pollution in the environment compounds the problem, providing a selection pressure that accelerates the rise of resistance.

This One Health perspective also allows the identification of a broader range of interventions and AMR mitigation strategies. We consider illustrative examples, within the poultry industry and in wastewater treatment. We pay specific attention to new market opportunities that may align the incentives to agriculture and industry with the community good of improved human health. We also introduce the concept of smart prescribing, using One Health data to predict which particular antibiotics will be most effective for a particular individual in a particular location at a particular time.

There remains a high degree of uncertainty in any estimates concerning AMR. As such, one of the most important contributions of this report is to identify gaps in data and knowledge of AMR in the Australian context that will enable a more precise estimation of the costs of AMR and the potential returns on investment of mitigation strategies. It should, nevertheless, be clear that under any scenario, there is a pressing need for action to avert the worst consequences of AMR. This report from the OUTBREAK consortium represents an important step towards that objective.

2

Executive summary



The threat of antimicrobial resistance

Antimicrobial resistance (AMR) occurs when bacteria and other microbes become resistant to the medicines used to kill them allowing them to spread and cause life-threatening infections that are difficult to treat. Left unchecked, AMR could rob us of the ability to treat infections and support life-saving surgeries and therapies. Even common infections such as urinary tract infections (UTIs) will carry a high risk of mortality. According to a 2016 report by British economist Lord Jim O’Neill, commissioned by the UK Government and The Wellcome Trust, deaths related to bacterial infections will increase exponentially from current levels of 700,000 per year to 10 million by 2050, similar to the current number of annual deaths due to cancer and diabetes.

To date, the focus of research and biomedical investment has primarily been on the development and spread of AMR in hospitals. However, there is evidence that the use of antimicrobial drugs in animals can lead to AMR in humans and likely vice-versa. Tackling AMR therefore requires a ‘One Health’ approach that acknowledges the interconnection between human health, animal health, and environmental health.

AMR also represents an international economic crisis. Its effects will be felt globally in hospitals, aged care facilities, prisons and other institutions in which healthcare costs are borne socially. Industries including travel and insurance are likely to be affected with further impacts on labour, productivity, and consumption. AMR will also impact the livestock industry, both directly, through the loss of animals and the costs of treatment, and indirectly via reduced consumer demand and exports.

A number of reports have attempted to estimate the economic burden of AMR at a global level. The aforementioned O’Neill report, for example, concluded that by 2050 AMR infections will place a cumulative USD 100 trillion of economic output at risk. The 2016 World Bank report compared the impact of AMR on gross domestic product (GDP) to the 2008 global financial crisis with no prospect of recovery. However, these reports carry considerable uncertainty. Economic analyses focused on Australia are either limited in scope or group Australia with other countries with very different policies towards antibiotic use.

Economic costs of AMR in the context of urinary tract infections

In the current report we take a more focused approach, looking at the economic costs of UTIs and potential benefits of various mitigation strategies. UTIs are the most common bacterial infections requiring medical attention and a leading justification for antibiotic prescription. Women, babies, and older people are affected disproportionately. Common symptoms include lower abdominal pain, discomfort, and stress that can significantly affect quality-of-life. In many cases, UTIs resolve quickly. However, invasive UTIs that spread to the kidneys or blood can be life-threatening if they are not controlled quickly with an appropriate antibiotic or if the pathogen has drug resistance.

The economic costs of UTIs and AMR are considerable. We illustrate these costs via a patient journey that includes real-world costs provided by the Illawarra Shoalhaven Health District in NSW, Australia as well as national health data. An initial doctor’s (GP) visit and prescription (total average cost AUD 95) escalates to emergency department presentation (total cost AUD 283), hospital admission and transfer to an intensive care unit (ICU, total cost ~AUD 20,000). Most UTI cases will not progress in such a way. However, our analyses indicate that the annual direct cost for UTIs in Australia is approximately AUD 909 million. This does not include the flow-on economic costs when patients with UTIs block other patients from moving through the health system (e.g. from ambulance to emergency department or from ward to ICU). Nor does it include indirect costs to the family of UTI patients or their economic activity.

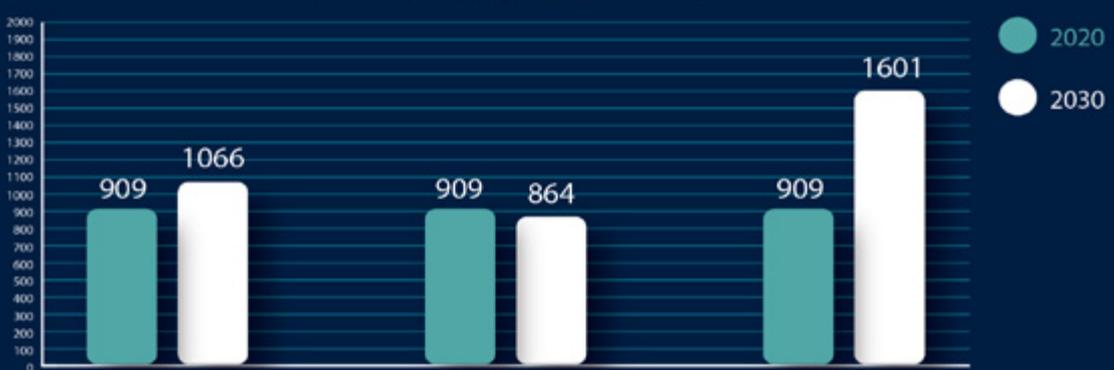
Although the major part (AUD 590 million) of those costs are due to hospitalisation, in many cases, hospital admission will reflect a failure of antibiotic treatment in the community. Resistance to first-line (those initially recommended for treatment) antibiotics is therefore a significant driver of overall costs. We model three different future scenarios, scaled up to the projected population of Australia in 2030. With resistance to first-line antibiotics at its current estimated level of 21% in the Illawarra Shoalhaven region, the cost is AUD 1.1 billion. An increase to 50% resistance sees costs rise to AUD 1.6 billion. Conversely, interventions to reduce resistance to 10% see costs fall to AUD 864 million.

Comparison of the health costs of UTIs in different 2030 AMR scenarios

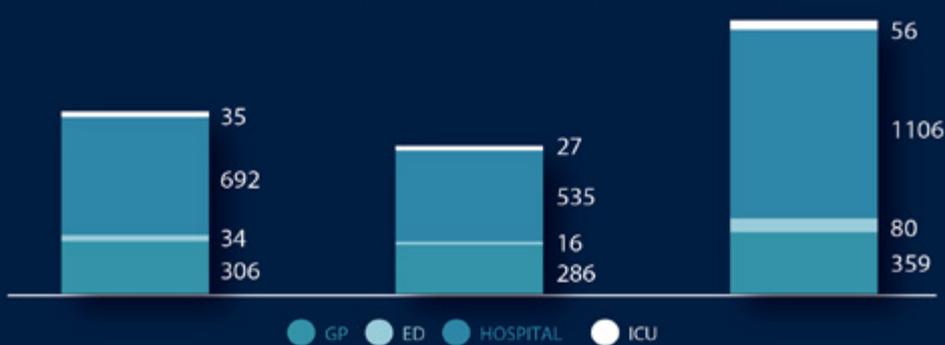
FIRST-LINE ANTIBIOTIC RESISTANCE (%)



TOTAL COSTS (AUD MILLIONS)



PATIENT JOURNEY COSTS (AUD MILLIONS, 2030)



One Health solutions to reducing AMR costs

An important step towards reducing UTI costs is to improve prescribing of antibiotics. Given that resistance rates to different antimicrobials vary seasonally and across geographical locations, we advocate a smart prescribing approach in which GPs and hospital physicians can be guided algorithmically by information about current AMR in the local environment.

We also explore opportunities for reducing AMR in the environment. An important source of AMR infection is meat and fresh produce. We focus on *Escherichia coli* (*E. coli*) bacteria, responsible for the vast majority of UTIs in Australia as well as a significant proportion of food-borne gastroenteritis cases. Like other bacteria, *E. coli* carry plasmids - mobile packets of DNA that can be 'swapped' between bacteria.

One such plasmid, referred to as ColV, can carry genes that enhance the virulence of *E. coli* (i.e. its ability to cause disease) in humans as well as genes that convey antibiotic resistance. It is also highly prevalent in Avian Pathogenic *E. coli* (APEC), a form of *E. coli* that causes the disease colibacillosis in chickens. Addressing APEC could have significant human health benefits by reducing contact with and transmission of ColV-carrying *E. coli*.

A further potential source of AMR exposure is water. One consequence of using antibiotics to treat infectious disease is that human and animal waste contains significant quantities of residual antibiotics which makes its way to wastewater treatment plants. Effective sewage collection significantly decreases a population's exposure to infectious agents but treatment plants have not been optimised to remove antibiotic resistant bacteria or their genes before they re-enter our waterways. We suggest that attempts to improve water treatment in Australia could provide significant economic opportunities, particularly in allowing greater reuse of water for drinking.

Looking forward

Our report has demonstrated the considerable impact of AMR on healthcare costs. But just as importantly, it has also highlighted the gaps in data and knowledge that are critical for improving our understanding of AMR, modelling its costs, and evaluating the potential benefits of different intervention strategies. In particular, the availability of linked data from GPs, emergency departments, and hospitals would reveal how patients can be hospitalised for a UTI, a condition that should be treatable in the community. Breaking down the data silos would also allow researchers and policy makers to measure and predict how changes in the efficacy of treatment by GPs can cascade through the healthcare system.

Our focus has been on the direct monetary costs of AMR to the healthcare system. Future analyses should also include non-monetary metrics such as disability adjusted life years (DALYs) and indicators of sick leave/absenteeism, reduced activity and mental stress and anxiety that help capture the broader impact of AMR and – crucially – the potential benefits of intervention. It will also be important to quantify the impact on groups that are particularly affected by AMR, such as the elderly, and (in the Australian context) members of the Aboriginal and Torres Strait Islander community. Crucially, efforts to access, integrate, and stratify healthcare data will not only help researchers and policy makers but can also directly improve patient care by enabling smarter, personalised prescribing of antibiotics.

Our report illustrates the potential synergies and economic opportunities that arise from a holistic One Health approach. For example, environmental surveillance for AMR will provide an early warning for AMR outbreaks, particularly when targeted at potential hotspots such as hospitals, aged care facilities, and wastewater treatment plants. It can facilitate monitoring of water quality. Such data can also improve smart prescribing, enabling doctors (and veterinarians) to avoid antibiotics with a high risk of resistance in a geographical area. Beyond AMR, this surveillance infrastructure would also enable tracking, tracing and tackling of other infectious agents.

The ongoing COVID-19 pandemic illustrates the intimate connection between the health of national and global economies and the health of the population. Although operating at a slower timescale, AMR may ultimately come at a much greater cost than COVID-19, not least because the loss of antibiotics will amplify the effect of future epidemics and pandemics. The lesson from COVID-19 is that quick and effective responses can save lives, jobs and reduce economic repercussions. Early investment in solutions and mitigation strategies will likely pay for itself many times over.

3

The antimicrobial resistance pandemic



The threat of antimicrobial resistance

Imagine a world without antibiotics – a paper cut could kill you, and routine surgeries, minor health conditions including respiratory and urinary tract infections (UTIs) and even childbirth would carry a high risk of complications and death. This world was a grim reality less than 100 years ago, before the advent of antibiotics. Unfortunately, it's one we're set to face again with the rise of antimicrobial resistance (AMR).

AMR is widely recognised as an international health crisis¹. As Margaret Chan, former Director General of the World Health Organization has argued, resistance to antibiotics could bring “an end to modern medicine as we know it.”² Many procedures that are now commonplace - hip replacements, cancer chemotherapy, intensive care for premature babies - rely on effective antimicrobial drugs. Without them, these procedures will carry a significant risk of intractable infection, complications, and mortality³.

According to a 2016 report commissioned by the UK Government and The Wellcome Trust, deaths related to drug-resistant infections will increase exponentially from current levels of 700,000 per year to 10 million deaths annually by 2050⁴, similar to the number of current annual deaths due to cancer and diabetes combined.

Mechanisms of AMR

AMR happens when microbes become resistant to the medicines used to kill them. Most of our antibiotics, for example, are based on substances naturally produced by microbes that have existed in the environment for millennia. However, over the past century, the mass production of these antibiotics for use in human and veterinary medicine has meant that they are now present in sufficient concentrations in the environment to provide a ‘selection pressure’. Bacteria carrying genes that convey resistance are more likely to survive and reproduce in these environments.

Importantly, antibiotic resistance genes are not only passed from bacteria to their offspring but can also be transferred ‘horizontally’ between bacteria via mobile genetic elements such as plasmids⁵. This means that AMR can arise in populations of bacteria that are otherwise harmless, but can then pass to disease-causing bacteria. Plasmids can also carry virulence genes that cause the drug resistant bacteria to become pathogenic.

Further complicating the picture, antibiotic resistance genes tend to cluster together in complex resistance regions: in plasmids⁶ for example. The implication is that any antibiotic selection pressure will select for comprehensive antibiotic resistance⁷. This phenomenon of co-selection is perhaps the greatest challenge to address in the fight against AMR and the one concept that is most poorly understood.

The One Health approach to AMR

While much of the focus on AMR has been on hospital-acquired infections, for many patients, resistance is acquired in the community⁸ - from other people, from food, from domestic and wild animals, and from our environment, particularly our water and soils. Increasingly, therefore, researchers (including the OUTBREAK team) view AMR as a ‘One Health’ problem.

1 Pathogens and Global Health (2015) 109: 309

2 ‘WHO Director-General addresses G7 health ministers meeting on antimicrobial resistance’ (2015)

3 Infection (2014) 42: 5; Transplant Proc. (2014) 46: 2777; Lancet (2003) 361: 2068

4 ‘Tackling drug-resistant infections globally: Final report and recommendations’. The review on antimicrobial resistance. HM Government and the Wellcome Trust (2016)

5 Mol. Cell (2010) 37: 311

6 Gut Pathog. (2019) 11: 3

7 Trends Microbiol. (2006) 14: 176; Front. Microbiol. (2012) 3: 399; Antimicrob. Agents Chemother. (2018) 62: e02357

8 BioMed Res Int. 2018, Article ID 7656752

One Health is a framework that considers human health to be intimately intertwined with the health of animals (wild and domestic) and the health of the environment⁹. It has been applied successfully to a number of zoonotic diseases (arising in non-human animals) including Ebola, avian influenza¹⁰, rabies¹¹, Brucellosis¹², and Hendra virus¹³. With AMR, the focus is not on a particular pathogen such as a virus or bacterium but on the property of antibiotic resistance and, more specifically, the genes that convey resistance and, in bacteria, the plasmids that carry those genes.

Illustrative of the One Health approach to AMR is our own work on the ColV plasmid, which is carried by human and avian *E. coli* bacteria. ColV has been found to carry genes that convey antibiotic resistance as well as virulence genes that cause disease in humans and in birds (see Box: *E. coli* and the ColV plasmid).

The One Health approach to AMR also emphasises the health of the environment. Antibiotic residues from manufacturing, hospital and animal waste enter our waterways and our soils and provide a strong selection pressure for bacteria holding on to antibiotic resistance genes.

E. coli and the ColV plasmid

E. coli is a common bacterium that exists ordinarily in healthy guts of humans and animals. However, it is capable of causing serious, life-threatening disease. In Australia, for example, *E. coli* is responsible for one third of food-borne gastroenteritis cases and the vast majority of UTIs^a. In estimates of the economic impact of AMR on GDP, almost 50% can be attributed to *E. coli*^b.

There is growing evidence that the ColV plasmid enhances the ability of *E. coli* to cause disease in humans^c. ColV is found in faecal *E. coli* populations in the gut of healthy humans^d and in *E. coli* grown from store-bought fresh produce^e, suggesting a food borne origin. Although its presence in gut bacteria appears to pose no immediate risk to human health, problems can arise when these bacteria enter the urinary tract, a process that occurs with a disproportionate incidence in females^f.

ColV plasmids are also found in avian pathogenic *E. coli* (APEC) which causes colibacillosis^g. In some countries, this is a major concern for the poultry industry. Colibacillosis is characterised by decreased growth rate, reduced egg production, and unusable carcasses and is spread by aerosolisation of fecal dust in poultry sheds.

ColV carriage has also been documented in wildlife. We have observed the presence of ColV containing antibiotic resistance genes in *E. coli* isolated from coastal populations of silver gulls living near major metropolitan and coastal cities in Australia^h. It is currently unclear whether gulls have acquired ColV from their visits to municipal dumping sites and wastewater treatment plantsⁱ or whether ColV has found a natural home in avian species more broadly. Studies are required to understand potential transmission routes for ColV between wildlife and free range poultry operations.

a Emerg Infect Dis. (2005) 11(8): 1257–1264 ; J Infect Dis (2016) ;213(1):6-13.i; PLoS ONE 11(2010): e0164306

b 'Tackling drug-resistant infections globally: Final report and recommendations'. The review on antimicrobial resistance. HM Government and the Wellcome Trust (2016)

c Int. J. Antimicrob. Agents (2018) 52: 430 ; Infection and immunity 78(2005):1931-42 ; mBio (2018) 9: e00470-18

d Microb. Drug Resist. (2018) 24: 411

e Front. Microbiol. (2020) 10: 3050

f J. Infect. Dis. (2016) 213: 6

g Microb. Genom. (2019) 5: e000250

h J. Antimicrob. Chemother. (2016) 71: 63 ; J. Antimicrob. Chemother. (2019) 74: 2566

i Colonial Waterbirds (1993) 16: 9

9 Front. Vet. Sci. (2018) 5:14.

10 NSW Public Health Bull. (2011);22(5-6):123-6

11 The Veterinary Record (2014) 175(8):188-93

12 Preventive Veterinary Medicine (2005) 69: 77

13 Emerging Infectious Diseases (2014) 20(3)

Compounding this problem, pollutants including other pharmaceutical agents and heavy metals such as copper and zinc are also known to select for AMR¹⁴.

The economic costs of AMR

Costs associated with AMR

The most immediate costs of AMR are in relation to healthcare. AMR results in more and longer hospital stays and increased mortality. Patients with AMR may require additional, and potentially more exotic and expensive, treatments. They also place further pressure on already stretched medical personnel and facilities. As risk of AMR-related complications increases, patients and doctors may avoid or postpone elective surgery.

Beyond human healthcare, AMR poses risks to food production, particularly in the meat industry. Food producers face the immediate costs of AMR-affected animals needing to be treated or dying. Concerns about AMR could affect prices and consumer demand and exports could be affected as countries put up trade barriers to shield themselves from more resistant bacteria.

Several factors combine for AMR to cost far more in the future than it does now. Not least is the compounding of lives lost to, and otherwise harmed by AMR as well as the growing public expenditure, often unattributed, to tackling AMR. Global population may be smaller than otherwise due to AMR, impacting labour demand as well as supply. Tied to the healthcare points above, the quality of work and workers are also likely to be affected, as both physical health and changed behaviour impact productivity. Finally, it is important to consider how long-term trends such as the ageing population and climate change interact with AMR.

International analyses of AMR costs

Numerous attempts have been made to estimate the economic costs associated with AMR. For example, in the United States, costs associated with drug-resistant bacterial infections are estimated at USD 20 billion a year and annual productivity losses are USD 35 billion¹⁵. In Europe, costs attributed to drug-resistant bacterial infections amount to EUR 1.5 billion per year¹⁶. In the Western Pacific, the estimated economic cost of drug-resistant bacterial infections over the next 10 years is USD 1.35 trillion¹⁷.

The most comprehensive global economic analysis of AMR is the 2016 O'Neill report, commissioned by the Wellcome Trust and the UK Government. It concluded that AMR infections will place a cumulative USD 100 trillion of economic output at risk by 2050 (see Box: The O'Neill Report).

The World Bank, meanwhile, has estimated that AMR will cause GDP to fall by 1.1-3.8% annually by 2050¹⁸, which is comparable to the 2008 global financial crisis occurring every year (see Box: The World Bank report). However, in attempting to gauge the cost/benefit of acting on AMR, the report found that 'action on AMR constitutes one of the highest-yield development investments available to countries today'.

Similar conclusions were reached by a 2018 report from the Organization for Economic Cooperation and Development (OECD)¹⁹. It calculated that investing as little as two US dollars per person per year could avert three out of four deaths caused by 'superbug infections'. The comprehensive public health measures include handwashing and more prudent prescription of antibiotics and the 'benefits so great that investments are likely to pay for themselves'²⁰.

14 Antimicrob. Agents Chemother. (2018) 62: e02357

15 'Antibiotic resistance threats in the United States', CDC (2013)

16 'Averting the AMR crisis', OECD (2019)

17 'Antimicrobial resistance in the Asia Pacific region: a development agenda', WHO (2017)

18 'Drug-resistant infections: a threat to our economic future', World Bank (2016)

19 'Stemming the superbug tide: Just a few dollars more', OECD (2018)

20 'No time to wait: Securing the future from drug-resistant infections. Report to the Secretary-General of the United Nations', Interagency Coordination Group on antimicrobial resistance (2019)

Given that these reports differ in their focus and analytical approach to calculating economic impact, a direct comparison or synthesis of their conclusions is not possible. Nonetheless, there are some consistent patterns in their results. The reports agree that AMR will result in significant economic losses at a global scale. They also consistently show that the extent of those projected losses is highly sensitive to the AMR scenario that actually plays out. It follows that the greater our understanding of AMR, the tighter the modelling can become, allowing policy makers to operate with greater certainty. More importantly, perhaps, it demonstrates how efforts to mitigate (and potentially reverse) AMR can bring huge economic returns.

Australian analyses of AMR

While the above-mentioned reports have testified to the extraordinary economic burden of AMR at a global level, much less has been reported about the impact of AMR on Australia specifically. This means that resource and investment decisions to combat AMR lack a comprehensive evidence base.

The KPMG analysis in the O'Neill report included analyses dividing the world into six regions. Australia was included in a region referred to as 'Southern, South-Eastern and Eastern Asia, together with Oceania'. According to KPMG's projections, GDP in this region will decrease by 5% to 10% by 2050 at the worst-case AMR scenario (i.e. 100% resistance rate). Projecting Australia's current GDP²¹ to 2050 at an average growth rate of 1.3%²², the estimated annual impact of AMR on Australia's economy by 2050 will be between AUD 142 billion and AUD 283 billion²³.

However, grouping Australia in this region is problematic not least because it is an island. Import restrictions and stringent controls on antibiotic prescribing in Australia provide some level of protection. Furthermore, Australia has a conservative approach to the use of antimicrobials in food producing animals²⁴ with federal policies banning the use of certain antibiotics that are important for human health. Similar policies do not exist or are not enforced elsewhere in the region, significantly affecting the types and levels of antibiotic resistances.

There remain significant gaps in Australian AMR data²⁵. In their 2018 report, the OECD notes that more than 50% of observations for the drug-bug combinations were missing. AMR is also not captured as a cause of death on death certificates, leading to a severe under-estimation in patients with comorbidities such as diabetes and cancer.

In terms of cost estimates, a 2006 report²⁶ from the Expert Advisory Group on Antimicrobial Resistance (EAGAR), estimated that AMR-related morbidity and mortality cost the Australian economy AUD 250 million annually. However, this figure is extrapolated from 1992 US hospital data and it does not include the economic effects of lost productivity due to prolonged hospital stays. EAGAR also reports that Australia spends in excess of AUD 500 million a year on antimicrobials for infections treated in the community.

Other studies have taken a more focused approach to the costs of AMR in Australia. A 2019 study using Queensland Department of Health data²⁷ found that hospitals likely spend more than AUD 11 million per year treating just two kinds of AMR out of the many clinically relevant drug-bug combinations: Ceftriaxone-resistant *E. coli* bloodstream infections and Methicillin-resistant *Staphylococcus aureus* (MRSA). Patients with resistant infections spend on average 4.9 days longer in hospital than patients with susceptible infections.

21 'Key economic indicator', Australian Bureau of Statistics (2019)

22 The estimate is from PwC The World at 2050 report

23 'Superbugs to trigger our next global financial crisis', OUTBREAK consortium (2020)

24 <https://www.amr.gov.au/about-amr/amr-australia/amr-and-animal-health-australia>

25 *Infect Dis Health* (2018) 23:54

26 A comprehensive integrated surveillance program to improve Australia's response to antimicrobial resistance, Australia: National Health and Medical Research Council (2006).

27 *Infection control and hospital epidemiology* (2019) Volume 40 (3), pp. 320-327

The O'Neill report

Led by the British economist Lord Jim O'Neill, The Review on Antimicrobial Resistance was commissioned in July 2014 and supported by the Wellcome Trust and UK Government. Its final report^a was published in May 2016 and summarised 19 months of consultation and eight interim papers.

Two consultancy teams, KPMG^b and RAND Europe^c, were tasked with undertaking detailed scenario analyses. Both teams considered three bacterial pathogens - *E. coli*, *K. pneumoniae*, and *S. aureus* - in their analyses that also focused on three major diseases - tuberculosis, HIV, and malaria. However, the teams applied different economic models as described below.

RAND Europe

RAND modeled low (5%), medium (40%) and high (100%) rates of AMR for the three pathogens, estimating annual global GDP losses of USD 188 billion, USD 1.65 trillion, and USD 3.93 trillion respectively by 2050. The team also modeled an 'absolute resistance' scenario in which infections were rendered effectively untreatable. This differs from the 100% resistance scenarios where some effective therapies are still available leading to lower mortality rates. This resulted in annual losses of USD 9.8 trillion by 2050 and cumulative GDP losses of USD 125 trillion over the preceding 40 years.

However, the Computable General Equilibrium approach adopted by RAND is controversial. It is often used in disease modelling at the national and global level to calculate macroeconomic effects, which are aggregate changes across several sectors of the economy. Ultimately, this changes the GDP which is a measure of the size and growth rate of an economy. Critics argue that the models may not reflect real world economies given the myriad assumptions that have to be made^d. They also exclude indirect consequences such as altered decision-making due to increased perceived risks. For example, patients may forego elective surgeries and tourists may reduce their travel if they are concerned about AMR risks.



a 'Tackling drug-resistant infections globally: Final report and recommendations'. The review on antimicrobial resistance. HM Government and the Wellcome Trust (2016)

b 'The global economic impact of anti-microbial resistance', KPMG (2014)

c 'Estimating the economic costs of antimicrobial resistance: Model and results', RAND (2014)

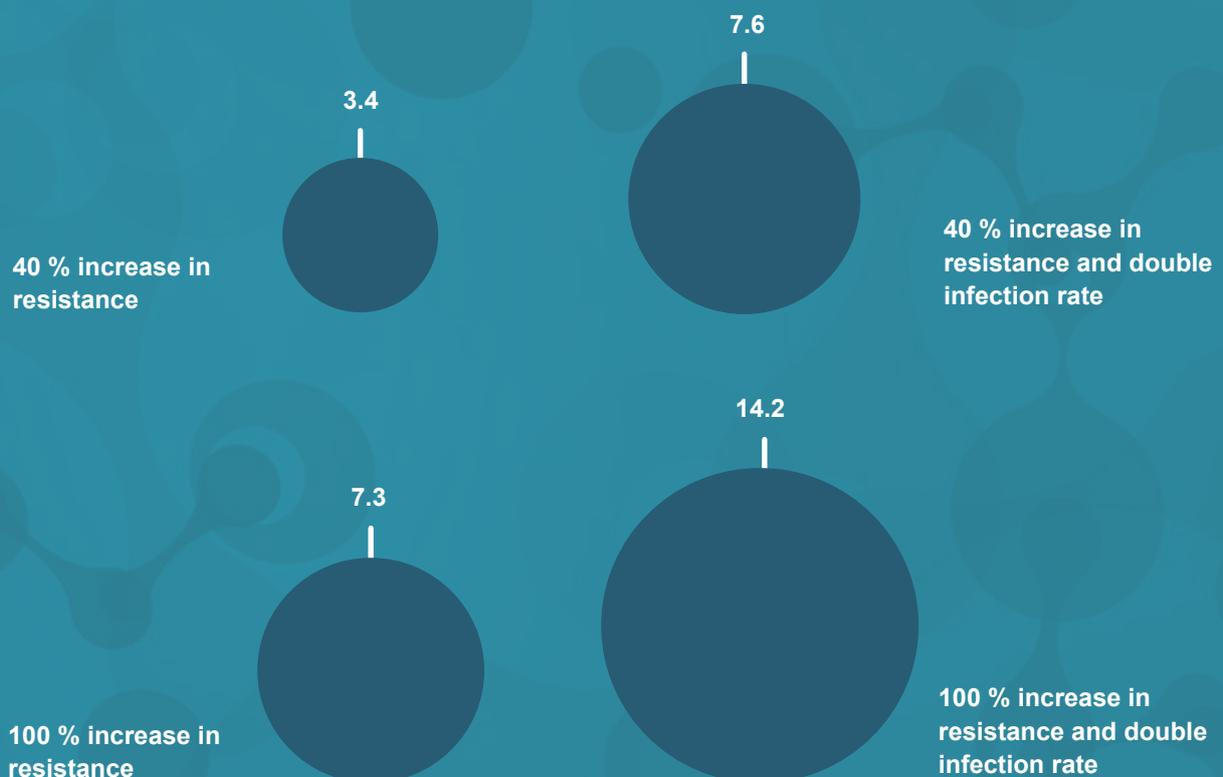
d Lancet Infect Dis. (2019) 19: e392–98

The O'Neill report (continued)

KPMG

KPMG also made projections to 2050, considering scenarios in which infection rates as well as AMR rates varied. They found that in high-income countries, 100% resistance led to a projected decrease in GDP of 0.95% to 1.95% if infection rates are constant. GDP is reduced by 2.2% to 4.0% if infection rates doubled at the same time as resistance rates increased^f.

Health costs were primarily calculated by a change in expected mortality under each scenario. These estimates were transformed into adjusted labour force projections for each country using a Total Factor Productivity model. This assumes the same amount of inputs – including labor, human and physical capital, and materials - and assesses how efficiently the resources are used in the production process in terms of changes to GDP. However, in an AMR scenario, a reduction in labour supply is expected, violating the assumption that labor is a fixed input. Results may therefore be an underestimation of the potential cost of AMR because, like Computable General Equilibrium analyses, broader healthcare, social and indirect costs are excluded.



^f 'The global economic impact of anti-microbial resistance', KPMG (2014)

The World Bank report

In 2016, the World Bank^a modelled the impacts of AMR as shocks to labor supply and livestock productivity. They deemed this to be a conservative approach that would underestimate AMR's full economic effects. The report indicates that by 2050:

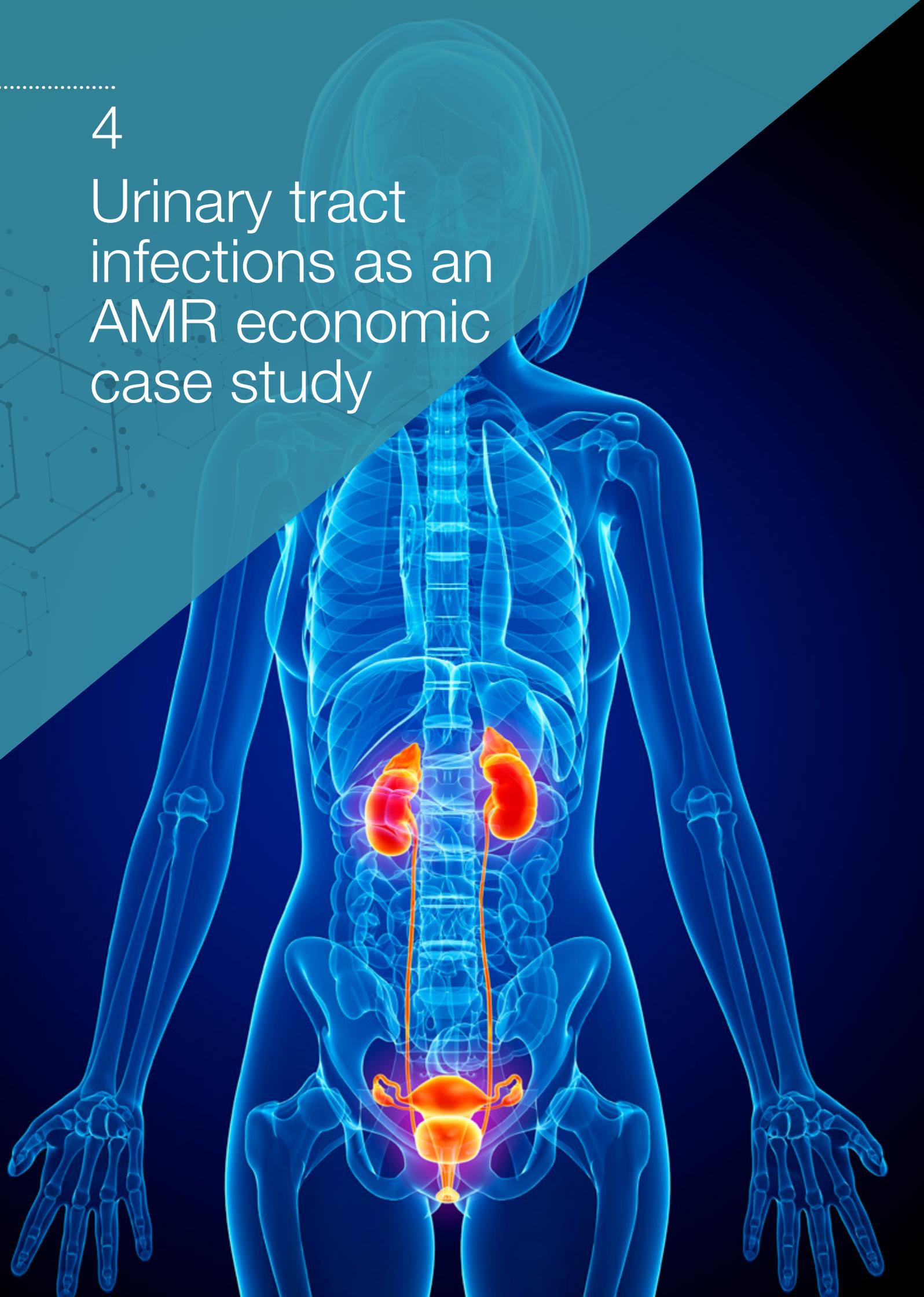
- GDP will shrink by 1.1% to 3.8%
- Global livestock production could fall by 2.6%-7.5%
- An additional 28.3 million people will have fallen into extreme poverty
- Global healthcare costs may increase from USD 300 billion to more than USD 1 trillion per year

However, the report found that the benefits of acting on AMR significantly outweigh the costs. Even if the required investments in veterinary and human health is greater than their estimated USD 0.2 trillion, and only 50% of the cumulative costs are avoided, the net present value of action is between USD 9.8 trillion and USD 26.8 trillion by 2050.

The report also found the largest absolute and per capita gains will flow through to middle- and high-income countries. If only 10% of the costs of AMR are avoided, high-income countries would still see a benefit of between USD 0.9 trillion and USD 2.7 trillion over the course of their projections.

4

Urinary tract
infections as an
AMR economic
case study



What are the costs?

Urinary tract infections (UTIs) are the third most common human infection (after respiratory and gastrointestinal infections) and the most common bacterial infections resulting in hospital admissions¹. They affect an estimated 12–15% of women annually and 50% of women by 32 years of age². Babies and older people are also at relatively high risk of UTIs. As with many conditions, UTIs lead to poorer health outcomes if the patient is also suffering from other conditions such as diabetes³.

Common symptoms of UTIs include lower abdominal pain, discomfort, and stress that can significantly affect quality-of-life. In many cases UTIs resolve quickly. However, invasive UTIs that spread to the kidneys (pyelonephritis) or blood (bloodstream infections/bacteremia) can be life-threatening if they are not controlled quickly.

UTIs are primarily caused by pathogenic *Escherichia coli* (*E. coli*), and they are the most frequent source of bloodstream infections (sepsis)⁴, accounting for over 40% of cases in Australia in 2018⁵. Treatment for UTIs is primarily via antibiotics. UTIs are one of the leading clinical indications resulting in antibiotic prescription in primary care⁶. In the United Kingdom (UK), trimethoprim and nitrofurantoin remain the first-line antibiotics for UTIs⁷. In Australia, trimethoprim is also routinely prescribed empirically for uncomplicated cases⁸. However, resistance to these and other antibiotics used to treat UTIs is growing⁹. Modelling in the EU, Iceland, and Norway found resistance added between six and eleven days to hospital stays for UTIs¹⁰.

The economic costs associated with UTIs are considerable. A 2002 study estimated the annual economic burden in the USA to be approximately USD 2 billion¹¹. In the UK, in 2013-2014, the National Health Service spent GBP 434 million in treating 184,000 patients with unplanned admissions relating to UTIs¹².

To understand the economic costs of AMR in an Australian context, we can follow the case of a fictional patient named Sarah (see Box: A patient journey) who develops a UTI. This patient-centric approach is increasingly being adopted in order to more efficiently allocate health services and provide value-based care.

Sarah's journey illustrates the considerable resource burden that AMR places on the Australian healthcare system. In addition to the direct medical costs associated with our patient, there are a number of other flow-on costs. These include ambulance ramping and bed blocking (See Box: Hidden AMR costs).

1 Indian J Nephrol. (2009) 19: 129 ; Infect Dis. (2016) 213(1): 6–13

2 Can Pharm J CPJ Rev Pharm Can RPC (2017) 150: 298 ; Can Pharm J CPJ Rev Pharm Can RPC (2018) 151: 305

3 Clin J Am Soc Nephrol (2006) 1: 327

4 Int. J Antimicrobial Agents (2007) 30: 390-397

5 'Third Australian report on antimicrobial use and resistance in human health' AURA (2019)

6 Scand J Prim Health Care (2017) 35: 162

7 Lancet (2018) 391: 1966

8 'Empirical treatment of bacterial urinary tract infections (adults). Clinical Guideline.' SA Health (2017)

9 PLoS ONE (2016) 11: e0164306

10 'Health at a Glance: Europe 2018' OECD/EU (2018)

11 Am J Med. (2002) 113:5S

12 'Reducing unplanned admissions to hospital due as a result of urinary incontinence.' Unplanned Admissions Consensus Committee (2016)

A patient journey

Sarah is a 68-year-old grandmother living in Wollongong NSW. During the day, Sarah provides care for her grandchildren so that her daughter, a single mother, can attend work in the local high school. Sarah has Type 2 diabetes which is being managed by her general practitioner (GP). After a week with her grandchildren, including several trips to the local beach, she falls ill with what she believes to be a UTI.



Presentation to GP

Sarah visits her GP (AUD 73.95) who prescribes a course of trimethoprim (AUD 38.84). After five days, her symptoms have not improved. She returns to her GP (AUD 73.95) who prescribes cephalexin (AUD 21.06) and takes a urine sample (AUD 20.55).

Total cost: AUD 228.35



Emergency Department

Whilst waiting for her test results to return, Sarah's worsening symptoms force her to present to the emergency department at her local hospital. There, she is administered a third course of antibiotics, ampicillin (AUD 8.80) and gentamicin (AUD 4.60), through an intravenous cannula. She also undergoes a number of diagnostics tests (AUD 266.60).

Total cost: AUD 279.40



Admission to ward and subsequent admission to ICU

Sarah is admitted to hospital, initially for three days (AUD 3,747). However, her condition deteriorates and she is sent to the intensive care unit (ICU) with sepsis, where she stays for a further three days (AUD 11,529).

Whilst in the ICU, Sarah undergoes a further suite of diagnostic tests. These include: Venous Blood Gas (AUD 31.75); Full Blood Count (AUD 15.97); Urea, Electrolytes & Creatinine (AUD 18.56); C-Reactive Protein (AUD 9.14); Liver Function Test (AUD 20.44); two Blood Cultures (AUD 57.94); Chest X-Ray (AUD 44.42); and Patient Episode Initiation (AUD 17.80). Sub total AUD: 216.02

Results of her earlier tests indicate that she is resistant to standard antibiotic therapies. She is prescribed a fourth course of antibiotics - a ten-day course of meropenem (AUD 180.00), a broad-spectrum antibiotic that is only called upon when standard antibiotic therapy does not work.

Her condition improves, so she returns to the ward where she stays for a further seven days for observation (AUD 8,743).

Total cost: AUD 24,415

After 13 days in hospital and four courses of antibiotics, Sarah is well enough to return home.

GRAND TOTAL COST: AUD 25,139

Hidden AMR costs



Sarah's journey illustrates the direct costs associated with a drug-resistant UTI. However, this patient-centric approach does not capture the indirect costs of a rise in the incidence of drug-resistant infections to the healthcare system or to the wider economy.

Ambulance ramping

For example, Sarah's eight hours in the emergency department could have contributed towards a phenomenon known as ambulance ramping. This occurs when the emergency department reaches its capacity limit, meaning that ambulances are forced to wait with patients rather than discharge them into the care of the hospital. The ambulance crew are therefore prevented from responding to other emergencies.

The economic costs associated with ambulance ramping are difficult to quantify. However, NSW Ambulance receives at least AUD 768 (2019 full cost emergency call-out fee excluding per kilometre charge^a), and up to several thousand dollars, from the patient (or their insurance company). In the year ending February 2020, the four emergency departments of hospitals in the Illawarra Shoalhaven saw 47,082 presentations of patients who were brought in by ambulance.

Scaling these figures up by population to the whole of Australia gives a total of about 2.9 million arrivals by ambulance with a total value of at least AUD 1 billion. A small adverse variation to these figures in percentage terms can clearly have a large impact on the revenue stream in absolute terms, as well on the health outcomes for patients whose ambulance is delayed.

Emergency demand in Australian hospitals has been increasing 5-10% annually for well over a decade^b. An outbreak of AMR could result in emergency wards and ICUs exceeding their capacity with flow-on impacts for the rest of the health service.

Bed blocking

Sarah's transfer to the ICU represents another step where capacity problems can arise, limiting the movement of patients within the hospital or health system. Australia currently has 1485 ICU beds in public hospitals and 538 ICU beds in private hospitals^c. In the Illawarra Shoalhaven district, average occupancy of the 27 ICU beds ranged from 76% to 92% in the 12 months to February 2020. Although, the economic costs associated with bed blocking are difficult to quantify, it is clear that any adverse variation to AMR rates will have a large impact on the availability of ICU beds.

Wider economic costs

Our analyses also do not account for the disruption caused by an individual's illness and hospitalisation in terms of their own activity and that of their relatives. In Sarah's case, her illness meant that she could not provide childcare for her grandchildren. As a result, her daughter was forced to take time off work and the school where she works needed to engage a casual supply teacher at the rate of between AUD 339 and AUD 409 per day.

a 'Account and fees', NSW Ambulance (2020)

b Med. J. Aust. (2009) 190: 364 ; (2019) position statement on access block: <https://acem.org.au/Content-Sources/Advancing-Emergency-Medicine/Better-Outcomes-for-Patients/Access-Block>

c 'Crunching global coronavirus ICU data will save lives in 'swamped' Australian hospitals, says expert.' ABC News (2020)

Health costs of UTIs in Australia

Sarah's journey is not one experienced by every patient presenting to the GP with a UTI. Only a fraction of UTI patients are admitted to hospital and most of these do not require intensive care. Nonetheless, our analyses (model inputs described in detail online, see Appendix for details) show that the current direct economic costs of UTIs for the Australian healthcare system approximate AUD 909 million per year in 2020.

GP consultations and pathology

UTIs represent ~1.8% of all GP presentations¹³ which is approximately 2.62 million per year. According to the Medicare Benefits Schedule for May 2020, GP consultations cost between AUD 17.50 and AUD 108.85, depending on their duration. We take AUD 50 as an average cost for a consultation. We assume that most UTI consultations result in prescription of an antibiotic (either trimethoprim or cephalexin) and, based on data from the Illawarra Shoalhaven region, that pathology tests are ordered following one third of UTI-related GP consultations. The total annual costs of these consults and pathology tests amount to AUD 244 million in 2015.

Emergency Department

According to the Australian Institute of Health and Welfare (AIHW)¹⁴, UTIs result in approximately 94,400 ED presentations per annum. With a cost of AUD 283 for initial pathology tests and intravenous antibiotics, these ED costs amount to approximately AUD 27 million per year in 2015.

Hospitalisation

The AIHW also records 75,617 hospitalisations for UTIs in 2015-16¹⁵. Based on data from the Illawarra Shoalhaven region, approximately 2.9% of these have ICU involvement and cost around AUD 20,130 each. Cases that do not involve ICU treatment cost around AUD 7,294 including antibiotic and pathology costs. Our estimate for the total annual cost for hospitalisation due to UTIs is therefore AUD 552 million in 2015.

Total costs

According to our analyses, in 2015, the cost to the Australian healthcare system of UTIs at the GP, ED, and hospital admission totals AUD 850 million. This figure does not include knock-on effects such as ambulance ramping and bed blocking. Nor does it include indirect costs of UTIs to the economy.

Our analyses are based on data from 2015. According to the Australian Bureau of Statistics, since December 2015, the Australian population has grown from 23.6 million to 25.6 million in 2020. Correcting for this change in population, the estimated total cost for 2020 is AUD 909 million compared with AUD 850 million in 2015. This correction is conservative because it does not account for increasing infection rates and the aging Australian population which is associated with an increase in the likelihood of UTIs and UTI-related complications¹⁶.

It also assumes that resistance rates in 2020 are comparable to those in 2015. An increase in resistance to antibiotics prescribed by GPs will reduce the success of treatment by GPs, resulting in increased presentation at the ED and - most importantly in terms of the costs - an increase in hospital admissions for UTIs. These costs will continue to grow as resistance rates increase.

Costs of UTIs under future AMR scenarios

By 2030, the Australian population is forecast to be 30 million¹⁷. With all else being equal, our estimate of the cost of UTIs to the Australian healthcare system in 2030 is AUD 1.1 billion.

Again, this assumes that resistance rates remain at 2015 levels. In Australia, resistance to trimethoprim in

13 General practice activity in Australia 2015-16. General practice series no. 40. Sydney: Sydney University Press (2016)

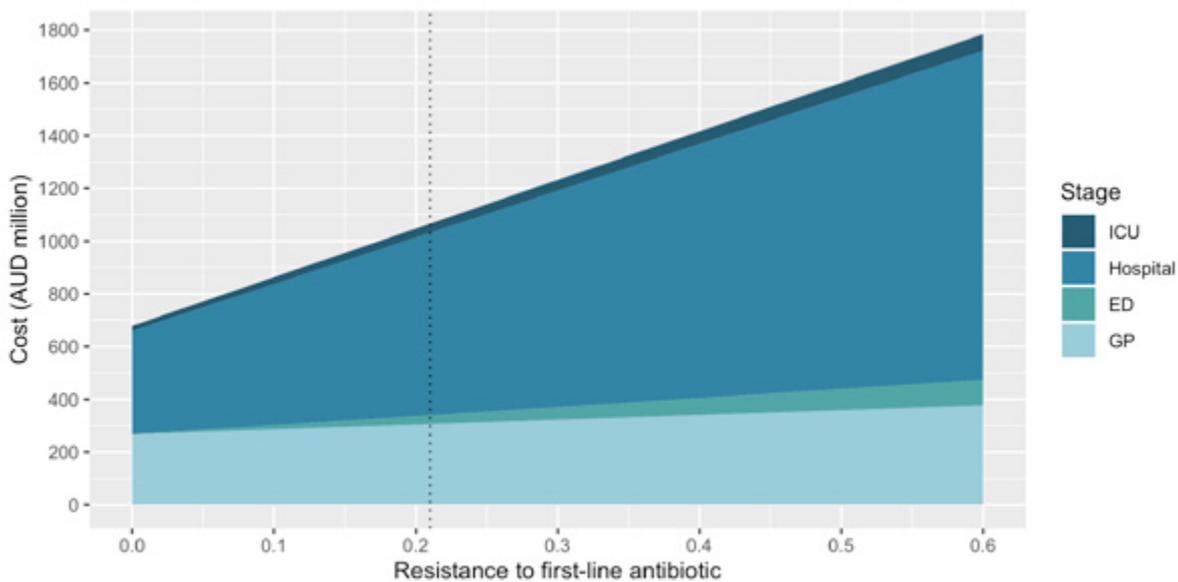
14 'Emergency department care 2015-16: Australian hospital statistics' AIHW (2016)

15 'Admitted patient care 2015-16: Australian hospital statistics' AIHW (2017)

16 Ther Adv Urol; 11: 1756287219832172 (2019)

17 'Population Projections, Australia.' Australian Bureau of Statistics (2018)

E. coli isolates from urine samples is currently 21-24%¹⁸. Our modelling (see Box: Modelling the impact of changing resistance on UTI-associated costs) suggests that the cascading effects of an increase to 50% resistance would increase the costs to AUD 1.6 billion in 2030. This is not a far-fetched scenario given UK resistance rates to trimethoprim were 34% in 2016¹⁹.



Projected costs of patient journey stages as antibiotic resistance rates rise (2030)

The other side of these analyses is that substantial savings can be achieved by improving the success rates for initial treatment by GPs. Using our patient journey as an example, if more (personalised and localised) information was available, Sarah could have been prescribed an effective antibiotic at the time of her initial GP appointment, the whole sequence of failed treatments, tests, and hospital admissions would have been prevented.

Our modelling suggests that even reducing resistance rates from 21% to 10% could reduce the 2030 costs associated with UTIs from AUD 1.1 billion to AUD 864 million - a saving of AUD 202 million per annum. Of course, UTIs represent only a part of the total healthcare burden caused by AMR. The total cost for the Australian healthcare system is likely a large multiple of the numbers presented here.

¹⁸ 'Second Australian report on antimicrobial use and resistance in human health.' AURA (2017)

¹⁹ 'Antibiotic-resistant UTIs increasing in England.' Prescriber (2017)

Modelling the impact of changing resistance on UTI-associated costs

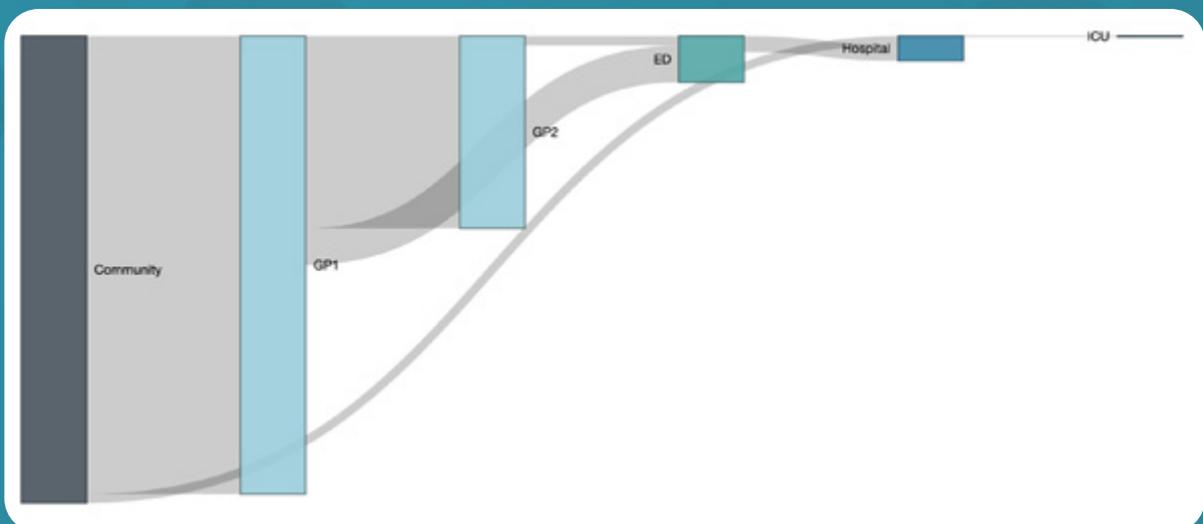
Our estimates of the costs associated with UTIs to the Australian healthcare system are based on real-world patient journey data indicating the number of UTI patients presenting at GP surgeries and ED, the number admitted to hospital and the proportion requiring ICU treatment.

To model how these costs change under different AMR scenarios, we have made the following assumptions:

- The majority of patients initially present at the GP and are treated with first-line antibiotics.
- Some of the patients with resistance proceed directly to the emergency department.
- The remainder return to their GP where they receive a different antibiotic. The probability of failure depends on the resistance to the second-line antibiotic. Unsuccessfully treated patients also present at the emergency department.
- At the emergency department, a certain proportion of patients are admitted to hospital. This proportion remains constant even if the absolute number of patients presenting at the emergency department changes.
- Some patients are hospitalised directly (i.e. without passing through the emergency department). We assume that these patients have also not seen their GP and so their numbers are not affected by changing resistance.
- Of those patients admitted, a proportion result in transfer to the ICU. Again, this proportion does not change.



The Sankey diagram below shows the flow of patients through the healthcare system in our 2030 scenario with 50% resistance to first-line antibiotics and 5% resistance to second-line antibiotics.



Australian Institute of Health and Welfare

A recent AIHW²⁰ report put the total health expenditure for UTIs in 2015-2016 at AUD 962 million. This includes costs for admitted patients, ED, outpatient clinics as well as the costs of medicines and tests (under Australia's Pharmaceutical Benefits Scheme and the Medicare Benefits Schedule). The estimate is slightly higher than our own 2015-2016 analysis for UTI-related costs of AUD 850 million.

There are a number of differences in the assumptions and approach of these two analyses. In particular, the AIHW estimate included costs associated with three codes within the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10)²¹ - 'Cystitis' (N30), 'Urethritis and urethral syndrome' (N34), and 'urinary tract infection, site not specified' (N39). In contrast, our analyses relied on data sources for which only the numbers for N39-coded patients were provided. Thus, although our estimates are conservative in this respect, they are within 15% of the official government statistics.

The non financial impacts of UTIs

The AIHW data also contains disability adjusted life years (DALYs) for infectious diseases - UTIs broken down by Australian States and Territories²². One DALY represents one lost year of 'healthy life' due to premature death, or living with ill health or disability or a combination of these factors. In 2015, the UTI DALY age-standardised rate (ASR/1,000 population) ranged from 0.2 (Australian Capital Territory) to 0.6 (Northern Territory). Overall, ASR-DALYs for UTIs appear to be increasing with a national average of 0.3 in 2011 and 0.35 in 2015.

A recent European web survey-based study assessed almost 2,000 responses from women who suffer from recurrent UTIs across five countries (GESPRIT study)²³. The researchers report a mean of 3.09 days sick leave, 3.45 days of limited activities, and mental stress due to UTIs. This is in addition to the average of 2.7 GP visits/year and 2.17 to 3.36 prescriptions/year. This suggests future assessments of the health and economic impacts of UTIs should be designed to include quality of life metrics in order to determine the full impact of AMR.

²⁰ 'Disease expenditure in Australia', Australian Institute of Health and Welfare (2019)

²¹ 'International Statistical Classification of Diseases and Related Health Problems', 10th Revision (ICD-10)-WHO Version (2019)

²² 'Australian burden of disease study 2015: interactive data and disease burden', Australian Institute of Health and Welfare (2020)

²³ 'Social and economic burden of recurrent urinary tract infections and quality of life: a patient web-based study (GESPRIT)', Expert Review of Pharmacoeconomics & Outcomes Research, 18:1 (2018)

5

One Health solutions to AMR



Addressing the AMR challenge

As our economic analysis indicates, antimicrobial resistance (AMR) has a dramatic impact on the economic burden of urinary tract infections (UTIs). It reduces the likelihood of successful treatment by GPs and increases the probability of hospitalisation. Without action to mitigate AMR, the healthcare costs will inevitably increase further. But what action should be taken to address this problem?

The One Health perspective provides some answers to that question. Resistance to antibiotics is usually detected in patients when they are in the hospital - but healthcare-associated (also referred to as hospital-acquired) infections can be distinguished from those that are community-acquired.

Our patient story is illustrative. Sarah had previously been treated successfully with trimethoprim. This time, however, it was ineffective. We suspect she has been infected with a trimethoprim-resistant strain of *Escherichia coli* (*E. coli*) for which there are a number of possible sources - eating contaminated food, swimming at the local beach, feeding birds at the park with her grandchildren, or gardening.

One approach is to try and reduce people's exposure to AMR in the community and environment. Later in this section, we consider two specific examples - the poultry industry and wastewater management - where concerted action could have a significant impact on AMR. Critically, we also explore ways in which addressing AMR presents economic opportunities to those industries, potentially increasing their presence and position in the marketplace.

However, even if action were to be taken now, the resultant benefits in terms of reduced environmental exposure to AMR may take many years to become apparent. These longer term objectives need to be complemented by action with more immediate results. In the following section, therefore, we consider the potential benefits of smart prescribing, whereby the prescription and treatment is informed by inferences about the patient's likely resistance to different antibiotics, increasing the likelihood of successful treatment.

Ultimately, we argue that this dual approach of reducing exposure to AMR in the environment and making smarter use of available antibiotics is not only complementary but synergistic.

Smart prescribing

GPs and emergency doctors are flying blind

Looking back at our patient story, a critical event was the initial prescribing of an ineffective antibiotic by Sarah's GP. This is not an unusual occurrence. According to the latest report on Antimicrobial Use and Resistance in Australia (AURA), 23.5% of the 26.5 million antimicrobial prescriptions in Australia were inappropriate¹. A 2017 study in the Medical Journal of Australia found that for acute respiratory tract infections, between 80% and 90% of the prescribed antibiotics fall outside the antibiotic prescribing guidelines². Emergency doctors face similar pressures. A study of a large public tertiary emergency department in Queensland³ estimated that 22% of antibiotic prescriptions relating to urinary conditions were inappropriate.

This is not a reflection on the capabilities or professionalism of GPs and emergency doctors. In the absence of rapid diagnostic tests, they have to prescribe antibiotics empirically based on the patient's symptoms rather than an understanding of the underlying infection. Typically, this means prescribing a broad-spectrum (effective against a large variety of bacteria) antibiotic to cover off the different possibilities.

Even if an appropriate antibiotic is prescribed for the underlying infection, it may be ineffective due to antibiotic resistance. For example, in the Illawarra Shoalhaven region of NSW, resistance rates of urine *E. coli* to trimethoprim, commonly prescribed for UTIs, are now around 18-21% having increased from 13% ten

¹ Third Australian report on antimicrobial use and resistance in human health. Australian Commission on Safety and Quality in Healthcare (2019)

² Med J Australia (2017) 207: 65

³ J Antimicrob Chemother. (2019) 74: 515

years ago (Illawarra Shoalhaven Local Health District, unpublished data). The likely consequences are further GP consults, additional pathology testing, and further antibiotic treatment.

One way of ensuring that patients receive an appropriate antibiotic that is likely to be effective is by ordering pathology tests for a sample specimen (faecal, urine, blood, throat swab, etc.). This involves *in vitro* laboratory tests and may include bacterial cultures that are exposed to various antibiotics at different concentrations. Unfortunately, this process can take several days or even weeks which in many cases is too slow to be useful. As a result, antibiotic treatment resembles a trial and error process in which the patient's failure to recover (or the escalation of their symptoms) is the first indication that the antibiotic is ineffective.

Smart prescribing enables rapid, accurate prescribing that reduces the risk of AMR

Anecdotally, infectious disease clinicians make prescribing decisions by including personal knowledge of resistance based on the location of a patient's primary residence. Smart prescribing supports this decision-making process, combining local AMR data and algorithms to estimate the likelihood that a particular patient in a particular location will carry resistance to a particular antibiotic. Unlike *in vitro* testing, results can be provided to the prescriber instantly, increasing the likelihood that their initial prescription is appropriate.

The potential utility of algorithms to support decision-making by prescribers is highlighted by a recent study⁴ involving 9,455 women in the greater Chicago area. Algorithms that combined information about previous AMR, prior prescription data, and patient place of residence were found to raise the rate of successful treatment of uncomplicated urinary tract infections from 87.5% to 92.2%.

Smart prescribing for AMR will benefit from the inclusion of multiple streams of data, from hospitals, GPs, and pathologists, as well as farms, sewage treatment plants, waterways and other sites that may be sources or vectors of AMR. Combining artificial intelligence and machine learning with scientific knowledge about AMR transmission will provide an ability to 'forecast' the risk that particular microbes will be resistant to a particular antimicrobial at a particular time and place so that effective preventive action can be taken.

Smart prescribing can slow the advance of AMR

The prescribing of ineffective antibiotics and the indiscriminate use of broad spectrum antibiotics compounds the problem of AMR by introducing unnecessary antibiotics into patients and their environment. An improvement in prescribing practices through smart prescribing would reduce the volume of antibiotics that are used inappropriately and limit the rate of evolution of new resistant strains.

Smart prescribing can therefore be seen as a novel approach to antimicrobial stewardship. It is well-established that stewardship programmes are effective in reducing the incidence of AMR in a hospital setting, especially when carried out in conjunction with infection control measures such as hand-hygiene interventions⁵. Indeed, an analysis of hospital service utilisation data from the Illawarra Shoalhaven Local Health District over the last ten years provided us with evidence for the effectiveness of stewardship programs as indicated by a significant reduction in resistance rates.

However, other studies have provided less cause for optimism. A 2010 study in Sweden⁶, for example, found that decreasing use of trimethoprim-containing drugs by 85% had only a marginal effect on trimethoprim resistance, which remained high. More recently, a British study found a complex relationship between antibiotic use and resistance⁷. Reduced use of amoxicillin and trimethoprim was associated with reduced resistance. Nevertheless, resistance to cefalexin and co-amoxiclav increased.

4 Urology (2020) 137: 72

5 Lancet Infect. Dis. (2017) 17: 990

6 J Antimicrob Chemother. (2010) 65: 350

7 PLoS ONE (2020) 15: e0232903

One interpretation of these conflicting findings is that stewardship programs may have more impact on resistance rates to some antibiotics than to others. Indirect evidence to support this view comes from our ongoing analyses of *E. coli* antibiotic sensitivity in the Illawarra-Shoalhaven region. For ampicillin, resistance rates were significantly higher in winter versus summer, which may reflect increased prescribing of ampicillin for upper respiratory tract infections in colder months. However, seasonality effects were not observed for trimethoprim.

Quantifying the exact relationships between antibiotic usage and resultant resistance rates is critically important for informing prescription policies that will ensure antibiotics keep playing their life-saving role.

Tackling AMR in food

Evidence for a link between UTIs and *E. coli* infection from poultry

Reducing antibiotic consumption may not be sufficient in itself to reverse antibiotic resistance. It is therefore important to consider other strategies for reducing human exposure to AMR.

There is now a well-established link between UTI infections, extraintestinal pathogenic *E. coli* (ExPEC) and contamination of meat products, particularly pork and chicken⁸. For example, a 2018 study⁹ conducted in Arizona, USA studied isolates from poultry meat and from human clinical samples in the same geographically isolated community. Notably, ST131-H22, a poultry-adapted strain of *E. coli* was found in both human and poultry meat isolates.

The Arizona study also looked at carriage of ColV plasmids. As noted earlier (see Box: *E. coli* and the ColV plasmid), ColV in Avian Pathogenic *E. coli* (APEC) carry a number of genes that affect the virulence of APEC including its ability to attach to and colonise target tissues sites, produce toxins, and evade the immune system^{10 11}. The researchers found that ColV was present in 84% of meat source and 25% of human clinical source ST131-H22 isolates. Carriage of ColV was associated with greater drug resistance and increased likelihood that the *E. coli* would carry resistance-conferring genes.

Vaccinating poultry against colibacillosis could reduce AMR exposure in humans

APEC is a significant concern for the poultry industry in many countries. It is responsible for colibacillosis, which results in decreased growth rate, reduced egg production, and unusable carcasses. International studies suggest that it accounts for between 3.3% and 10% of mortality due to disease¹². Vaccinating chickens against colibacillosis could be an effective and economic strategy for improving the health of chickens¹³ that would also reduce AMR exposure in humans.

In Australia, colibacillosis is considered less of a problem than in other countries. Transmission is largely managed by improving housing conditions (cleaning and ventilation) to reduce the risk that chickens are exposed to aerosolized APEC in fecal dust. However, it is important to recognise that APEC is still present in the guts of poultry and, potentially, in poultry meat. So while vaccination of poultry may not be deemed necessary in terms of addressing colibacillosis, it could still bring significant health benefits for humans.

Consumption of chicken meat in Australia now exceeds other livestock food sources. Most of Australia's chicken consumption is produced domestically¹⁴ and exports are now valued at AUD 75 million¹⁵. Addressing AMR in Australian poultry therefore provides an opportunity to expand these markets and meet

8 Microbiology (2005) 151: 2097 ; Foodborne Pathog Dis. (2010) 7: 537 ; Emerg Infect Dis. (2010);16: 88 ; J Infect Dis (2005) 191: 1040; Scientific Reports (2020) 10: 906 ; Emerg Infect Dis. (2007) 13: 838 ; Canada. Emerg Infect Dis. 18: 415– 421 (2012) ; J Med Microbiol. (2011) 60:1502–1511

9 mBio (2018) 9: e00470-18

10 Microb. Genom. (2019) 5: e000250.

11 Appl. Environ. Microbiol. (2009) 75: 6955

12 Preventive Veterinary Medicine (2013) 109: 354 ; Avian Diseases (2010) 54: 1241-1250

13 Tijdschrift voor Diergeneeskunde (2002) 127: 582

14 'Meat consumption'. Department of Agriculture Water and the Environment (2020)

15 'Australian Industry Facts & Figures', Australian Chicken Meat Federation (2020)

the increasing consumer demand for safe and economically sustainable meat protein production¹⁶.

Livestock manure is a potential source of AMR

Another means by which resistant bacteria can transfer from livestock to humans is via manure. Waste from livestock is a rich source of nitrogen and phosphorus and is typically composted and then sold or directly pumped back onto farmland. However, faeces of pigs¹⁷ and poultry¹⁸ are an important source of *E. coli* with resistance to trimethoprim. Holding ponds become hotspots for the selection of AMR and the swapping of plasmids that can give resistance to otherwise benign bacteria. When manure is used as a fertilizer, it introduces a risk of human exposure to resistant bacteria via fresh produce such as fruit and vegetables or via run-off into waterways. Strategies such as vaccination for addressing AMR in livestock also reduces environmental exposure to AMR via animal manure.

Wastewater treatment

Wastewater treatment plants are an AMR hotspot

The inevitable consequence of using antibiotics to treat infectious disease is that human and animal waste contains significant quantities of residual antibiotics. In Australia, most human waste makes its way to one of several hundred wastewater treatment plants. These treatment plants are also an aggregation point for various wastewater-borne pollutants including heavy metals that provide a selection pressure for AMR¹⁹. As such, wastewater treatment plants are now recognised as an important 'hotspot' for the development of AMR.

Effective sewage collection significantly decreases a population's exposure to infectious agents, including resistant bacteria²⁰. However, treated effluents discharged to the environment almost invariably contain some amounts of AMR markers (resistant organisms and/or genes)²¹. Leaking pipes and sewer overflows can also lead to untreated wastewater containing resistant bacteria and antibiotic resistance genes entering the environment.

In the Australian and international water sectors, health and environmental regulators recognise that they currently lack the data and knowledge needed to effectively regulate and manage environmental releases of resistant bacteria and genes. However, there is currently no agreed parameter or compliance requirement related to the presence of antibiotic resistant bacteria or their genes in treated effluents, and wastewater treatment plants have not been designed or optimised for the removal of these new contaminants.

Water recycling presents new challenges and opportunities

Recycling of water is now the norm in many Australian states, particularly Victoria, South Australia, and Western Australia. The focus of water recycling today is on agricultural reuse applications, metropolitan reuse (dual reticulation and urban green space irrigation) and as a water source for environmental flows. Water recycling for drinking-water production, while practiced internationally and technologically feasible, is not a priority for most of the Australian water sector due to the widespread rollout of seawater desalination.

Nonetheless, with Australia likely to face significant future droughts and water shortages under a changing climate, concerted efforts are being made to find new ways to improve the quality of treated wastewater so that it can be reused in more high value applications such as horticulture or even as a climate-independent drinking-water supply²². The cost of advanced treatment technologies such as membrane filtration, membrane bioreactors, and advanced disinfection and oxidation processes like ultraviolet irradiation and

16 'Ethical foods: international situation assessment, opportunities and threats' Australian Government, Rural Industries and Research and Development Corporation. (2012) ; Meat Science (2018) 137: 123

17 Antibiotics (2016) 5: 37

18 PLoS ONE (2017) 12: e0185326

19 Water Environment Research (2017) 89: 921

20 'Scientists around the world are already fighting the next pandemic', The Conversation (2020)

21 Crit. Rev. Environ. Sci. Technol. (2019) 49: 1623

22 'Drinking water through recycling: The benefits and costs of supplying direct to the distribution system.' Australian Academy of Technological Sciences and Engineering (2013)

ozone with peroxide for treating wastewater and producing high-quality recycled water has progressively reduced over recent years as their adoption rises.

The Australian water industry relies on the ongoing safety and public acceptance of its recycled water. Consumers are increasingly educated and discerning about food quality, and changing consumer preferences for healthy food of quality provenance are already impacting conventional food production practices and supply chains. Recycled water has the potential for significant AMR carriage and exposure within the food and agriculture sector. Therefore, it is imperative that the associated risks are properly understood in order to safeguard food security and consumer health, as well as the sector's reputation, productivity, and growth.

6

The future of infectious disease surveillance



COVID-19 highlights the need for outbreak surveillance

The current COVID-19 pandemic can leave no doubt about the societal costs associated with untreatable infectious disease. We have seen how a sudden outbreak can overwhelm a healthcare system and have a cascading impact on treatment of other health conditions such as cancer, heart disease, and other infectious diseases such as tuberculosis, malaria, and HIV. We have witnessed the fragility of economies to sudden shock, and the effect that national and international travel bans and stricter biosecurity measures have had on tourism, trade, supply chains, and access to labour.

The parallels with antimicrobial resistance (AMR) are obvious. Scientists have been warning about the health consequences of growing AMR for decades and, more recently, economists have also begun to sound the alarm. COVID-19 makes those warnings all the more tangible. Indeed, the longer term societal and economic impacts of AMR are likely to be much greater than COVID-19¹. AMR is not a single disease but reflects our inability to treat infections caused by a wide range of bacteria and other microorganisms. Strategies such as isolation and social distancing that have proven successful in reducing transmission of SARS-CoV-2 will have little or no impact. There are no simple methods to separate a population into AMR carriers and non-carriers or to determine if an AMR carrier (human or animal) will succumb to a drug-resistant infection.

AMR will also intersect with and amplify future epidemics and pandemics. Viral respiratory infections often lead to bacterial pneumonia². Secondary infections such as these are thought to have been responsible for 95% of deaths during the Spanish flu pandemic³ and the ability to treat them with antibiotics explains in part the lower excess mortality during more recent flu pandemics⁴. According to early data, 50% of COVID-19 deaths have been associated with secondary bacterial infection⁵. Given that the majority of hospitalised COVID-19 patients are likely to be given antibiotics,⁶ increasing resistance would have made the death toll even higher than it already is.

Counting the costs of AMR

Addressing AMR begins with a thorough accounting of cost and benefit. We need to ask where the areas and sectors of greatest antibiotic use are? How much does AMR currently cost, and to whom? How stretched are hospital resources and what is the impact of AMR? What are the benefits to agriculture and trade, and how does that compare not only to the status quo but into the future? What are the returns on investment in different solutions?

Previous reports from KPMG and RAND (included in the O'Neill report) and those from the World Bank and OECD have focused on the whole-of-economy impacts of AMR at a global or regional level. While these have succeeded in highlighting the huge scale of the AMR problem, their broad scope makes it difficult to estimate the costs and benefits of concrete actions to address specific problems affecting countries.

Our approach has been to make the problem narrower and more tractable, focusing on AMR within the context of urinary tract infections (UTIs) and their health and economic costs in Australia. We used data from 2015-2016, estimating that UTIs account for around 2.62 million GP consultations each year, 94,400 emergency department presentations and 75,617 hospitalisations. The total estimated cost for 2015 was AUD 850 million.

We also modelled the costs of UTIs by 2030 under different AMR scenarios. Allowing for population increase, costs will reach AUD 1.1 billion per year even if AMR rates are unchanged from 2015. This is likely to be a conservative estimate as it does not account for the aging of the Australian population

1 'AMR may be worse'. AMR Insights (2020)

2 Front. Microbiol. (2017) 8: 1041

3 J. Infect. Dis. (2008) 198: 962

4 Lancet Infect Dis (2020), 20: E238

5 Lancet (2020) 395: 1054

6 N. Engl. J. Med. (2020) 382: 1708 ; Clin. Infect. Dis. (2020) 2:ciaa530

in that time period. And in the absence of action to address AMR, rates will almost certainly increase. Our modelling suggests that an increase in resistance to GP-prescribed first-line antibiotics from 21% to 50% could see annual costs escalating to AUD 1.6 billion by 2030.

Our analyses also enable a breakdown of current and future costs. They show that the major cost burden of UTIs lies in hospitalisation events - even though these only affect a minority of patients. Hospitalisation costs are also most sensitive to AMR changes because failure to treat in the community means more patients presenting at the emergency department and more being admitted to hospital. Indeed, our modelling is arguably conservative in this respect because we only consider the effect of AMR on the number of hospitalisation events and not the length of stay or the likelihood that intensive care will be required.

Our modelling shows the significant cost savings that can be achieved by addressing resistance to antibiotics prescribed by GPs. If, for example, resistance to first-line antibiotics is reduced from 21% to 10%, the projected cost by 2030 falls from AUD 1.1 billion to AUD 864 million. Again, this saving arises primarily because fewer patients are hospitalised.

Mind the gaps

Our modelling of UTI-related healthcare costs has demonstrated the importance of factoring AMR into cost projections. It is important, however, to acknowledge the limitations of the data we are currently working with. Indeed, one of the main outcomes of this report has been to identify gaps in data and knowledge that are critical for improving our understanding of AMR, modelling its costs, and evaluating the potential benefits of different intervention strategies. The challenge is not only to access relevant datasets but to integrate different sources of data.

To give one example, in attempting to estimate the costs of UTIs under varying AMR scenarios, we relied on separate GP and hospital patient datasets. As a consequence, our modelling of future AMR scenarios required us to make a number of inferences and assumptions about the flow of patients between community and hospital care. One of our goals, therefore, is to access linked data that would allow these assumptions and inferences to be tested and the modelling to be improved. Of particular value would be data concerning the number of times patients present to their GP before presenting at the emergency department. We are also seeking more information about the patients who are hospitalised for a UTI but are not admitted via the emergency department.

Better data are also required to fully evaluate the costs and benefits of different AMR mitigation strategies. Our analyses have focused on the monetary costs of UTIs to the healthcare system. To capture the difference between the current health status of the population and future scenarios, it will be necessary to include non-monetary metrics such as disability adjusted life years (DALYs), sick leave/absenteeism, reduced activity and mental stress and anxiety⁷.

We also need to think about how interventions will affect specific groups within the population. Our modelling assumes a homogeneous population but we know that UTIs affect women more than men and the elderly more than the young. And AMR affects certain communities more than others. For example, in Australia, AMR represents a rising and deeply concerning health burden on the Indigenous population. Almost half of children in the Aboriginal and Torres Strait Islander community have had at least six antibiotic prescriptions before their first birthday⁸ and the rate of potentially preventable hospitalisations for Indigenous Australians is almost three times the rate for non-Indigenous Australians⁹. Of course, better data will not only provide richer and more accurate evidence for researchers and policy makers but is also critical to improving patient care.

⁷ Expert Rev Pharmacoecon Outcomes Res. (2018) 18: 107

⁸ Aust NZ J Publ Heal. (2019) 43: 149

⁹ 'Aboriginal and Torres Strait Islander Health Performance Framework 2010: detailed analyses', AIHW.(2011)

AMR is a One Health problem with One Health solutions

The second part of our report has focused on solutions. Having identified initial treatment failure as a significant driver of costs, the question then becomes how to reduce antibiotic resistance and improve treatment outcomes. Antibiotic stewardship has an important role to play here. More judicious use of antibiotics means lower selection pressure for genes that convey antibiotic resistance. However, while stewardship programs can reduce the rate of AMR increase, it remains unclear how easy it will be to reverse AMR. A key issue here is co-selection. Even if a particular antibiotic is removed from the environment, the relevant resistance genes may be retained by bacteria because they are neighbours of genes that convey resistance to other antibiotics or to heavy metals, antiseptics and pharmaceuticals that are still present in the environment. We must therefore consider alternative AMR mitigation strategies.

Applying a One Health framework, we have considered a number of potential solutions. One such strategy is smart prescribing. The critical insight here is that, while AMR is a global problem, resistance of particular pathogens to particular treatments varies by place and by individual patient history. It should not, therefore, be necessary to blacklist particular antibiotics. Instead, armed with One Health data and an understanding of how resistance spreads through individuals and their environments, it becomes possible to forecast the probability of resistance for a given patient (or community) at a particular time and place.

As our analyses of UTI-related costs has demonstrated, a healthcare system that implemented smart prescribing could realise significant cost savings. But further market opportunities may also arise. For example, as we learn more about the gut microbiome and the options to manage and manipulate it, possibilities emerge to offer probiotics and other products that clear AMR-carrying bacteria from the body or increase resilience by favouring the colonisation of commensal or beneficial bacterial species. In this low AMR scenario, being able to give the right drug, to the right patient, at the right time, and at the right dose to resolve infection first time becomes one step closer.

Another broad class of strategies is to address the potential routes by which humans come into contact with antibiotic resistance. Motivated by the growing body of evidence that links *Escherichia coli* (*E. coli*) from meat - particularly poultry - to UTIs in humans, our first case study focused on the poultry industry. We suggest that vaccination of chickens against the disease colibacillosis, caused by pathogenic *E. coli*, could reduce the potential for transmission of AMR to humans, either through consumption of chicken meat or via the use of chicken manure as a fertiliser. In countries where colibacillosis is a significant problem, vaccination would carry significant economic benefits for farmers in terms of reduced morbidity and mortality for their bird flocks. It could also open new market opportunities for premium meat in countries like Australia where colibacillosis is relatively rare.

We also considered wastewater treatment as a focus for addressing AMR in the environment. As with our poultry case study, we highlighted the economic opportunities that may be provided by AMR mitigation efforts. Specifically, demand for recycled (or reclaimed) water will likely increase as the price of water increases along with the drive to reduce environmental impacts. Applications include crop and irrigation water that can help to maintain and increase agricultural productivity so that Australia can maintain a strong trade position, simultaneously protecting and leveraging its reputation as the 'food bowl of Asia'. Research, development, and investment in new water treatment technologies that can remove antibiotic resistance genes and the DNA vehicles on which they travel, represent a huge opportunity, particularly as water re-use moves from agricultural applications to drinking water.

Our case studies also illustrate the potential synergies and economic opportunities that arise from a holistic One Health approach. For example, smart prescribing of antibiotics can be guided by environmental surveillance, monitoring the risk of AMR exposure in different geographical locations. Routine sample collection and analysis is an increasingly important aspect of the developing field of wastewater-based epidemiology. AMR could also be monitored via remote and/or autonomous sensing systems that can be

inserted at numerous points in the One Health AMR data collection pipeline such as sentinel locations in wastewater treatment networks that target hospital wastewater or aged care facilities. This infrastructure will provide a capacity and agility that is valuable for AMR and for tracking, tracing and tackling other infectious agents, including whatever pandemic the world faces next.

The case for One Health economics

AMR represents one of the great challenges facing humanity in the 21st century. Efforts to mitigate the AMR problem will improve human health, reduce the incidence of untreatable infections, and ensure that hard-won advances in medicine that rely on antibiotics remain viable. However, in proposing and evaluating potential solutions, it is essential that we also consider the wider social and economic impacts of action - and of inaction.

Perhaps the most important economic lesson from COVID-19 is that national and global economies are intimately tied to the health of the population. Just as the One Health perspective recognises that human health cannot be separated from the health of other animals and of our environment, our economies are intimately related to human health. Quick and effective responses to disease outbreaks can save lives and jobs and reduce economic repercussions. Early investment in solutions and mitigation strategies will likely pay for itself many times over.

Appendix

Tables, calculations and assumptions and the OUTBREAK Shiny app, can be found online at outbreakproject.com.au/antimicrobial-resistance-publications.

Where ACT AIHW data was unavailable, estimates were scaled proportionally based on national population data.

Glossary

AMR	antimicrobial resistance
APEC	avian pathogenic <i>E. coli</i>
DALY	disability-adjusted life year
ED	emergency department
GDP	gross domestic product
GP	general practitioner
ICU	intensive care unit
UTI	urinary tract infection



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NO SWIMMING
NO WADING
NO SURFING
NO BODY SURFING

OUTBREAK