Investigating an alternative regulatory and reimbursement framework for antimicrobials in Australia

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Abstract

Background

The economic risks associated with antimicrobial development, including the emergence of resistance, have contributed to a substantial decline in new antimicrobials marketed by pharmaceutical companies. Antimicrobial resistance increases the risk of treatment failure, prolonged hospitalisation and increased mortality. Interventions to optimise and reduce the use of antimicrobials exerts downward pressure on antimicrobial sales, reducing the economic return for manufacturers. Disinvestment in antimicrobials by the pharmaceutical industry has also resulted in supply chain problems, resulting in frequent global shortages of commonly used antimicrobials. The lack of new antimicrobials in development is considered by the World Health Organization to be a public health crisis, requiring increased public and private investment in the research and discovery of new antimicrobials. Consequently, governments globally are seeking alternative registration pathways and innovative methods of reimbursement to support a sustainable pipeline of these essential medicines into the future.

Aims

The purpose of this research was to explore the feasibility and sustainability of an alternative regulatory and funding model for antimicrobials in Australia, and contextualise that alternative framework within the broader global and national objective of antimicrobial stewardship. Specific aims of this thesis were to (1) determine the unmet need for registered antimicrobials in Australian clinical practice, firstly by quantifying the use of unregistered antimicrobials and secondly by identifying the clinical indications for which they are used; (2) explore the perspective of stakeholders regarding the feasibility of a de-linked reimbursement model in Australia and alternative methods of value assessment for regulatory and funding purposes; and (3) estimate the willingness of health care practitioners to pay for particular attributes of new antimicrobial drugs.

Methods

A sequential, mixed-methods approach was used for this research. A descriptive, pharmaco-epidemiological study, triangulating three data sources, was undertaken to quantify the utilisation of unregistered antimicrobials in clinical practice. To determine the clinical indications where there is an unmet need, a retrospective review of applications submitted to the Therapeutic Goods Administration from two principal referral hospitals over a two-year period was conducted. These studies, together with a review of the literature, informed a qualitative study involving semi-structured interviews of stakeholders. Finally, a discrete choice experiment was conducted, to investigate which attributes of a new antimicrobial are preferred by infectious disease specialists and pharmacists, and to determine their willingness-to-pay for narrow-spectrum agents.

Results

Analysis of three different data sources indicated that the usage of antimicrobials not registered for use in Australia is increasing. A high proportion of unregistered antimicrobials dispensed from public hospitals are used in the outpatient setting. The most common clinical justification for utilising an unregistered antimicrobial was that the pathogen was resistant to registered antimicrobials or treatment with registered options had failed. Dominant themes from stakeholder interviews included: funding silos are a barrier to de-linking reimbursement from sales; the evidence required for public funding varies depending upon the setting; and funding status or cost is used as a stewardship tool. Policymakers were uncertain about how to incorporate future resistance into economic evaluations of new antimicrobials without a systematic method to capture costs avoided due to good stewardship. Results of the discrete choice experiment showed that price and spectrum of activity were the attributes with the main influence on the antimicrobial choice of health practitioners with expertise in antimicrobial stewardship. Patient co-payment, whether an antimicrobial was federally funded on the Pharmaceutical Benefits Scheme, and the route of antimicrobial administration also significantly impacts antimicrobial choice at the point of care.

Conclusions:

Overall these findings provide empirical evidence on the economic factors that impact on the appropriate use of antimicrobials in Australia. The price, the source of public or private funding and the cost to the patient all impact the selection of antimicrobials at the point of care. Federal funding of all antimicrobials, delinked from usage, could address unmet need, improve security of access and better facilitate efforts to ensure the effective stewardship of antimicrobials. From a policy perspective, this thesis highlights a number of challenges including the substantial legislative reform that would be required to support a centralised framework that de-links funding from sales and subsidises the cost of antimicrobials based on the appropriateness of use.

"Pull the string and it will follow wherever you wish.

Push it, and it will go nowhere at all."

— Dwight D. Eisenhower

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree. I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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Nadine Therese HILLOCK

25 May 2022

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Finally, to my beloved husband Richard – you have been my rock. Thank you for your unconditional love, patience and support. I could not have done this without you.

Abbreviations and acronyms

AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
ARTG	Australian Register of Therapeutic Goods
AURA	Antimicrobial Use and Resistance in Australia
CAR	Critical Antimicrobial Resistances
CDC	Center for Disease Control and Prevention (US)
DCE	Discrete Choice Experiment
DDD	Defined Daily Dose
DRG	Diagnosis Related Group
eTG	Electronic Therapeutic Guidelines®
FDA	Food and Drug Administration
HREC	Human Research Ethics Committee
HTA	Health Technology Assessment
MSD	Merck Sharp & Dohme
NAUSP	National Antimicrobial Utilisation Surveillance Program
NDM-1	New Dehli metallo-β-lactamase 1
NPV	Net Present Value
OBD	Occupied Bed Day
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
QUM	Quality Use of Medicines
R & D	Research and Development
RCT	Randomised controlled trial
RWE	Real World Evidence
SAS	Special Access Scheme
TGA	Therapeutic Goods Administration
US	United States (of America)
WHO	World Health Organization
WTP	Willingness to pay

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Manuscripts contributing to thesis

1. Hillock NT, Karnon J, Turnidge J, Merlin TL. (2020). Estimating the utilisation of unregistered antimicrobials in Australia. *Infection, Disease & Health*. 25(2): 82-91

2. Hillock NT, Paradiso L, Turnidge J, Karnon J, Merlin TL. (2020) Clinical indications treated with unregistered antimicrobials: The regulatory challenges of antimicrobial resistance and access to effective treatment for patients. *Australian Health Review*. 44(2): 263-9 doi: 10.1071/AH18240

3. Hillock NT, Merlin TL, Karnon J, Turnidge J, Eliott J (2020). Feasibility of de-linking reimbursement of antimicrobials from sales: the Australian perspective as a qualitative case study. *JAC-Antimicrobial Resistance*. 2(2) doi.org/10.1093/jacamr/dlaa023

4. Hillock NT, Merlin TL, Karnon J, Turnidge J, Eliott J (2020). Value assessment of antimicrobials and the implications for development, access and funding of effective treatments: Australian stakeholder perspective. *International Journal of Technology Assessment in Health Care*. 37(1): 1-7

5. Hillock NT, Merlin TL, Turnidge J, Karnon J (2022). Modelling the future clinical and economic burden of antimicrobial resistance: the feasibility and value of models to inform policy. *Applied Health Economics and Health Policy*. https://doi.org/10.1007/s40258-022-00728-x

6. Hillock NT, Chen G, Louise J, Turnidge J, Merlin T, Karnon J. Is it worth the money? Healthcare practitioners' willingness to pay for narrow-spectrum and other attributes of antimicrobials (unpublished manuscript)

Conference presentations arising from thesis

Oral presentations

- Hillock NT, Turnidge J, Karnon J, Merlin TL. Antimicrobial drugs and the Special Access Scheme: an anomaly or a marker of a system in crisis? National Medicines Symposium, Canberra. 30th May – 1st June, 2018.

- Hillock NT, Merlin TL, Turnidge J, Karnon J. Feasibility of implementing a Commonwealth-funded delinked reimbursement model for antimicrobials in Australia: the What, the Why, and the How? 11th Health Services and Policy Research Conference, HSRAANZ, Auckland. 4th – 6th December, 2019.

Poster presentations

- Hillock N, Turnidge J, Karnon J, Merlin T (2017) *Investigating the utilisation of unregistered antimicrobial drugs in Australia*. Poster presented at the 11th Annual Florey Postgraduate Research Conference, Adelaide. 20th September, 2017.

- Hillock N, Paradiso L, Turnidge J, Karnon J, & Merlin T (2019) *Special Access Scheme Category C and antimicrobial drugs - a policy solution or a temporary fix?* Poster presented at the annual meeting of Australian Society for Antimicrobials, Sydney. 21st-23rd February, 2019

- Hillock N, Turnidge J, Karnon J, & Merlin T (2019) *Policy incentives for a sustainable antibiotic market: the perspective of Australian stakeholders - a qualitative study*. Poster presented at the annual meeting of Australian Society for Antimicrobials (ASA 2019), Sydney. 21st-23rd February, 2019

- Hillock N, Chen G, Louise J, Turnidge J, Merlin T, Karnon J (2022). *Is it worth the money? Healthcare practitioners' willingness to pay for narrow spectrum and other attributes of antimicrobials.* Accepted as poster presentation at the 32nd International Congress of Antimicrobial Chemotherapy, Perth. 27th – 30th November, 2022.

Media coverage

- [Interviewed](#) by *Australian Doctor* (1st June 2018) at the National Medicines Symposium in Canberra regarding access to unregistered antimicrobials.
- Interviewed and [quoted](#) by *The Medical Republic* regarding the economic reasons for antibiotic shortages.

Other collaborations and awards

Collaborations

Engaged to provide expert advice to Acil Allen®, an independent economics, policy and strategy advisory firm, to assist with an antimicrobial pricing scoping study funded by the Australian Government Department of Health and Aged Care.

Awards

Recipient of the Neville Derrington Hicks PhD scholarship in 2019, a merit-based prize awarded on the basis of academic achievement and the potential of the research to influence Public Health Policy.

This doctoral thesis is presented as a Thesis by Publication, in accordance with the University of Adelaide Academic Program Rules and Specifications for Higher Degrees Research.

The aim of this thesis was to investigate an alternative regulatory and funding framework for antimicrobial medicines in Australia to support and maintain a sustainable supply of effective medicines, and in a manner that was supportive of the principles of antimicrobial stewardship.

The body of knowledge that constitutes this thesis is a series of studies presented as five published papers and one unpublished manuscript (see Figure 1.5). The text of each manuscript is identical to that submitted for publication however the formatting has been aligned with this thesis, and the tables and figures renumbered for continuity within the thesis itself.

CHAPTER ONE
Introduction

Background

Antimicrobials are medicines that are designed to prevent or treat infections caused by bacteria, viruses, fungi and other pathogens. "Antimicrobial resistance" (AMR) is the natural adaptation of pathogenic micro-organisms to resist those medicines designed to inhibit their growth.[1]

There is an evolutionary drive for bacteria to evolve to be resistant to new antibiotics[1]. When an antibiotic kills or inhibits the growth of sensitive strains of a bacteria, any resistant strains are then able to grow in a competitor-free environment, creating strong selection pressure for these resistant strains.[2] Bacteria can acquire resistance via spontaneous mutational adaptation, transfer of mobile genetic material between bacteria and bacterial species, and alterations in gene expression.[3-5] The overuse and inappropriate use of antibiotics in humans, animals and the environment, in addition to poor infection prevention and control, are considered the key drivers for the spread of antibiotic resistance.[6-9] Inappropriate use of an antimicrobial is defined as usage that is suboptimal for treatment of a suspected or proven infection or is non-compliant with evidence-based guidelines. Reasons for inappropriateness include incorrect dose or frequency of administration, spectrum of activity is too broad or too narrow, or incorrect or prolonged duration of treatment.[10] Bacteria can acquire resistance to multiple antibiotics, and can be defined as "multidrug-resistant" if they acquire resistance to three or more classes of antibiotic, where all antibiotics in those classes have been tested.[11]

Global antibiotic consumption increased by an estimated 65% between 2000 and 2015.[12] Overuse of antibiotics across all settings, especially antibiotics with activity against a broad spectrum of bacterial species, has led to a rapid increase in the global incidence of multidrug-resistant bacteria in the past few decades.[8, 11] Antimicrobial consumption in food-producing animals comprises approximately 73% of total antimicrobial sales globally, and is increasing due to the global demand for meat and fish.[13] In human healthcare, excessive prescribing in clinical practice stems from a combination of factors, including pressure by the patient, the prescribing behaviour of the doctor and their desire to offer treatment, and a paucity of rapid diagnostic tests that can inform the clinician of the nature of an infection quickly and accurately.[14] In Australia, point prevalence data suggests that approximately a quarter of

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[1] In this context, 'antibiotic' is used to mean 'antibacterial'.

prescriptions in hospital are inappropriate.[15] On a prescription per head of population basis, antibiotic use in the community is higher in Australia than many other countries, including the United Kingdom (UK), Canada and the United States (US).[11] Data from primary care in Australia shows that 31.2% of patients attending a General Practitioner in 2019 were prescribed at least one systemic antimicrobial.[15]

Although rates of resistance in Australia are lower for many pathogens compared to other countries, Australia has one of the highest rates of vancomycin resistance in *E. faecium* with between 49 and 57% of reported isolates not being susceptible to vancomycin.[16] The incidence of this resistant pathogen and other priority multi-drug resistant (MDR) organisms of high public health importance are monitored nationally in Australia by the CARAlert surveillance system.[17] For some bacterial species, there is emerging critical antimicrobial resistances to last-line antimicrobials, including reports of isolates of *Enterobacterales* resistant to colistin, and Enterococcus species resistant to linezolid.[18]

Antibiotics used in animal medicine, and their use as growth-promoters in animals produced for the meat industry, contribute to the increasing incidence of multidrug-resistant infections in humans.[9, 19-21] Antibiotic use in animals increases the risk of colonisation with multidrug-resistant bacteria that can be transmitted to humans through the meat when the animal is slaughtered, or to the environment via animal faeces. An example of the risks associated with inappropriate animal use of antimicrobials impacting human health is the use of colistin, one of the only remaining antibiotics for infections with highly resistant gram-negative *Enterobacterales* with New Delhi metallo-β-lactamase 1 (NDM-1) carbapenemases.[22] Despite being a reserve antibiotic for human medicine, an estimated 12,000 tons of colistin was used in food production worldwide in 2015, adding to the selection pressure towards colistin-resistant bacteria.[23] As of September 2016, isolates from human sources with transmissible plasma-mediated colistin resistance (designated MCR-1) had been reported from 29 countries.[23] The World Health Organization (WHO) strategy to address AMR globally is therefore constructed with a "One Health" approach, that is, with consideration of the worldwide interdependence of human, animal and environmental health.[9, 20, 24, 25]

Clinical and economic impact of antimicrobial resistance

AMR is associated with increased clinical and economic costs due to treatment failure.[9] Without antimicrobials, many medical interventions that are associated with an increased risk of infection, including most surgical procedures and chemotherapy treatment for cancer, would not be possible due to the consequent high risk of infection and death. Published estimations of deaths due to antibiotic-resistant infections vary widely, due in part to a lack of ICD-10 codes specifically for multi-drug resistant organisms which results in an under-reporting of MDR-infections as a cause of death.[26] The UK AMR report, commissioned by the UK government in 2016, estimated that with the increasing resistance to antibiotics, drug-resistant infections could kill more than 10 million people globally per year by 2050, including 22,000 per year in Oceania.[27] In March 2017, the World Bank estimated that without effective containment, AMR will likely reduce annual global GDP by between 1.1 – 3.8% by 2050, with the burden likely to be highest in low income countries.[28] Inferior hygiene and living conditions, in addition to weaker controls to prevent sales of antibiotics without prescriptions, inappropriate use of antibiotics and counterfeit or poor-quality drugs, all contribute to a higher burden in lower income countries.[29] Low income countries have weaker governance over antimicrobial use, impeding efforts to maximise access while preventing excess use.[30] While the UK AMR review predicted future global costs due to AMR to be high, it is acknowledged that there is considerable uncertainty regarding future mortality rates given the unpredictable emergence of new multi-resistant pathogens.[31]

The economic risks for pharmaceutical companies and the resultant decline in antibiotic drug development

In addition to the economic risks associated with microbial resistance, a number of other factors are a financial disincentive for manufacturers to invest in antimicrobial development. Antibiotics are usually short treatment courses and therefore do not garner the economic return of medicines designed to treat chronic diseases. In addition, because currently available antimicrobials are cheap generic products, in health systems that use value-based pricing illustrating the comparative cost-effectiveness of new antimicrobials can prove challenging.

The risk of clinical treatment failure is increasing due to both the increasing rate of resistance to currently available antimicrobials, in combination with a dramatic decline in new antimicrobials marketed.[32-35] Many large multinational pharmaceutical companies have withdrawn their interests in developing antibiotics in the past 20 to 30 years due to the economic risks associated with antimicrobial development, opting to invest in other technologies where the return on investment is greater and more predictable.[36, 37] As resistance continues to increase, there has been a steady decrease in novel antimicrobials being introduced into clinical practice (Figure 1.1). Since the discovery of the fluoroquinolones (the fluorinated analogues of nalidixic acid) in the 1980s, there have been no new systemic classes of antibiotics developed that have activity against Gram-negative bacteria.[38] In 2018, based on a set of criteria to determine the threat to morbidity and mortality worldwide, the WHO developed a list of priority pathogens to focus the development of effective drugs.[39] All of the priority pathogens deemed "critical" were Gram-negative bacteria, and of global concern is the increasing number of reported cases of pan-resistant isolates that are resistant to all available antibiotics.[40, 41]

Figure 1.1: The number of antibiotic classes discovered or patented by decade

*Cefiderocol was approved by the FDA in 2019 and EMA in 2020. The FDA-approved label for cefideocol classifies the drug as a cephalosporin, however some experts consider cefiderocol to be a first-in-class sideromycin.

* Note: This chart excludes bedaquiline, which is the first drug in a new class to treat tuberculosis
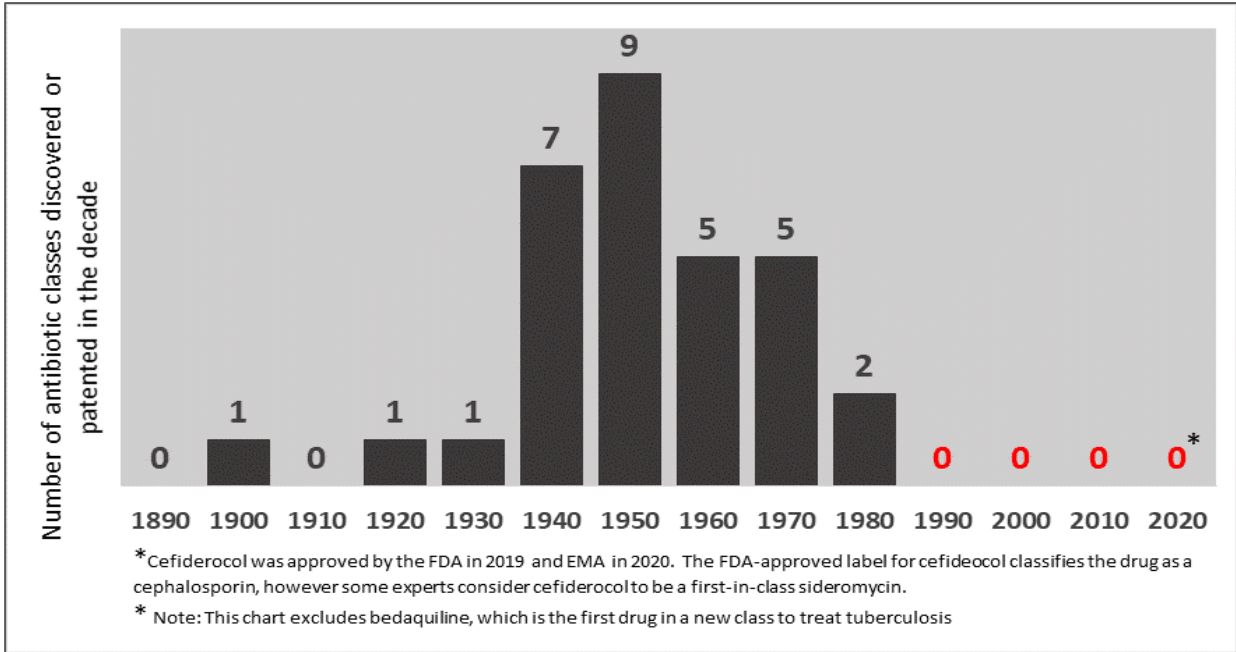
Source: https://carb-x.org/about/global-threat/ [42]

Maximising sales volumes and overuse in clinical practice jeopardises the sustainability of the effectiveness of antimicrobial products by increasing the risk of resistance. The current

method of antimicrobial reimbursement both in Australia and globally, whereby drug manufacturers maximise profit by increasing sales, is not in the interest of public health and does not support antimicrobial stewardship. Interventions and policies to minimise usage of new and current antibiotics result in insufficient return for pharmaceutical companies to justify the investment. Uncertainty regarding the development of resistance once a new antimicrobial is in clinical use introduces an additional level of financial risk to shareholders.

The link between antimicrobial resistance, antimicrobial stewardship, antimicrobial development and the antimicrobial supply chain is illustrated in Figure 1.2.

Figure 1.2   Impact of Antimicrobial Resistance and Antimicrobial Stewardship on economic return for manufacturers
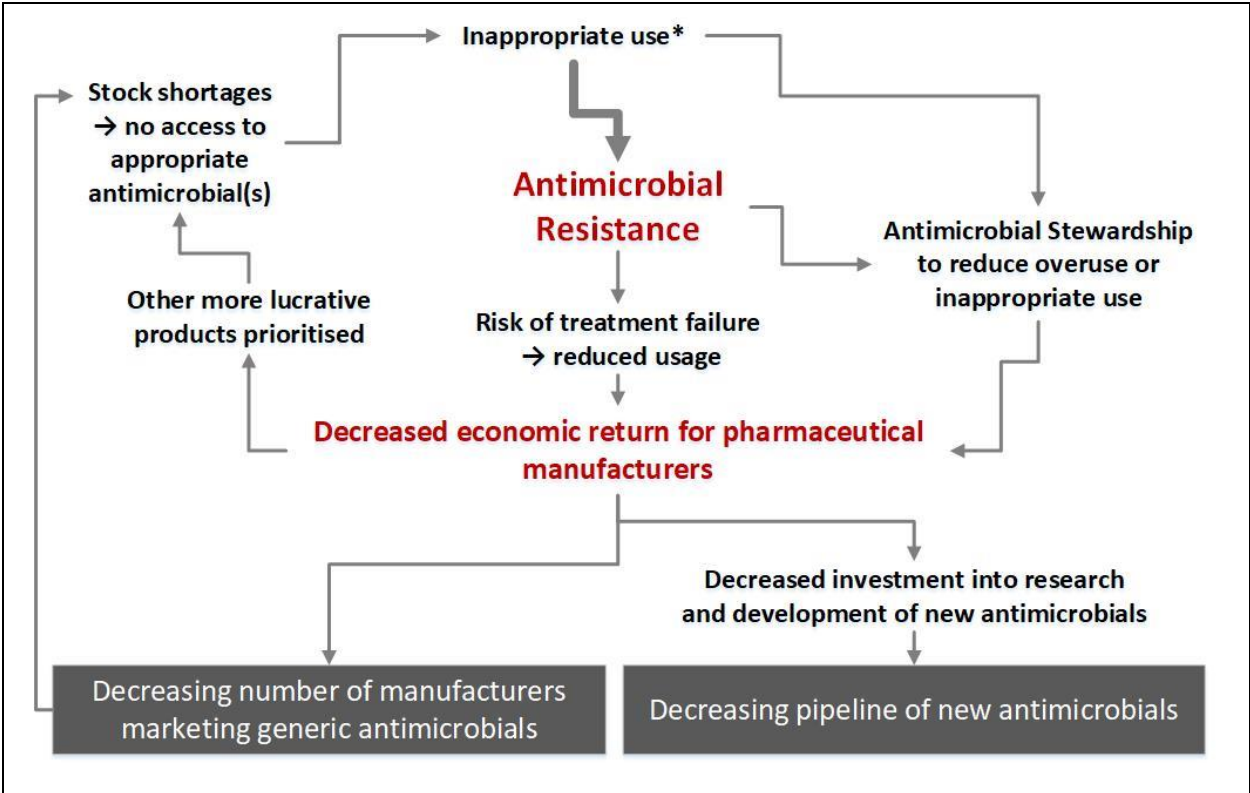
*Inappropriate use – multi-factorial

Alternative funding models have been considered by some governments internationally; however, the optimal approach is unclear and few countries have implemented any policy change. Due to the current drug reimbursement model not facilitating appropriate antimicrobial stewardship to minimise the risk of resistance, the concept of de-linking the financial return from the volume of sales has been proposed.[43-45] By separating the volume

of sales from the expected profit, the motivation to promote increased consumption by the manufacturer is removed. The UK is currently undergoing a collaborative pilot project between the National Health Service (NHS) and the National Institute for Health and Care Excellence (NICE) which aims to trial de-linked procurement for two antibiotics which have been developed to treat multi-drug resistant infections.[46]

When this PhD research was commenced in 2017, no steps had been taken by the Australian government to explore de-linked reimbursement models for antimicrobial drugs in Australia. In 2021, the Australian Government Department of Health contracted external consultants to evaluate optimal policy or funding incentives to stimulate the development of novel antibiotics in Australia.[47]

Theoretical framework

The theoretical concept of an alternative regulatory and funding model for antimicrobials aims to support two primary goals (Figure 1.3), interconnected under a One Health framework:

1. promote the appropriate use of currently available antimicrobials based on the principles of antimicrobial stewardship; and
2. promote and sustain a viable pharmaceutical manufacturing industry to ensure stability of antimicrobial supply, and strong investment into the antimicrobial research and development pipeline.

Figure 1.3: Balancing timely access while minimising excess use: Interdependence of conceptual frameworks supporting this thesis
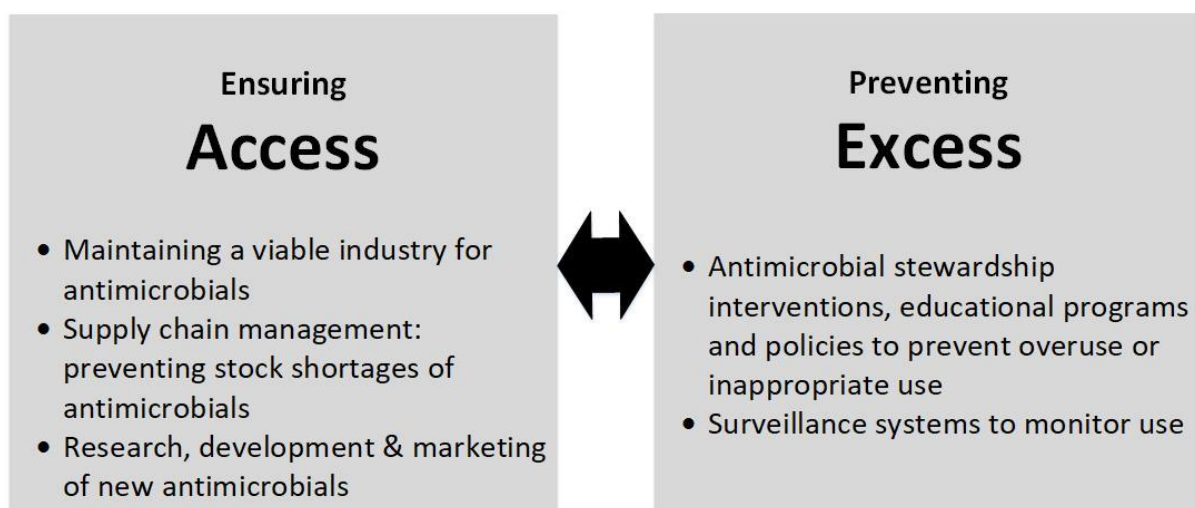
Network theory and 'One Health'

Instead of separating individual disciplines, research initiatives, jurisdictions and sectors, a 'One Health', systems-based framework acknowledges the critical linkages between dynamic systems.[48] A 'One Health' systems approach to addressing AMR aims to improve cross-sectoral collaboration, and advance beyond modelling of data and formulation of policy to include crucial linkages between issues that have traditionally been treated separately.

Network theory suggests that the structure of a system, in terms of the links between the various components, is important in defining how the system will react to various unpredicted pressures or forces.[48] Antimicrobials are used in the human, animal and environmental sectors, and the emergence of antimicrobial resistance can occur in any of these sectors and subsequently be transferred among the other sectors (Figure 1.4). Addressing funding models for access to antimicrobials in human healthcare therefore should not be considered discretely from access, supply and usage in other sectors, in both Australia and globally.

Figure 1.4: One Health and the epidemiology of Antimicrobial Resistance
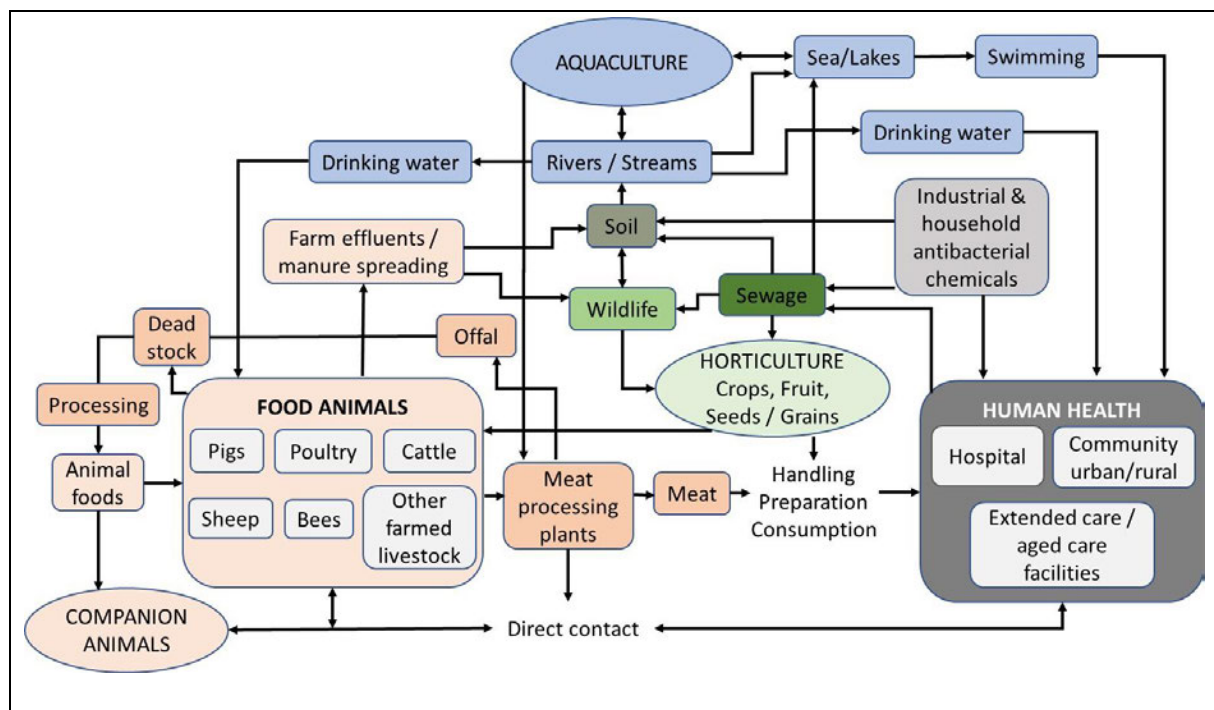
Source: Adapted from ACSQHC, 2013 [49]

The acquisition and dissemination of mobile antibiotic resistance genes between species and genera of bacteria appears to dominate over the process of mutation in response to

antibiotics in the bacterial environment.[50] Cooperation between bacterial species is an extension of Darwin's theory of evolution, and falls within the framework of evolutionary game theory.[51, 52] Bacterial species can adopt a cooperative relationship as donors or recipients of resistance genes for mutual benefit, with the complexity of the relationship increasing with the number of species and resistance mechanisms.[53] The assumption that bacterial species will become resistant to new antibiotics in the future is theoretically related not only to the exposure to that antibiotic, but also to the social interactions with other bacterial species.

Threat as a negotiation tool: Game theory and the 'Prisoner's dilemma'

The assumption in game theory is that individuals make rational and intelligent decisions in pursuit of maximising his/her own objectives and the objectives are measured in some measure of utility.[54] Game theory can also be applied to the investigation into potential solutions for the lack of new antibiotics entering the marketplace, where multiple 'players' have different aims or priorities. [54] The 'Prisoner's dilemma' is an example of game theory where the outcome for both players is optimal if they cooperate with each other, but if one chooses not to cooperate, one would benefit over the other.[55] For governments globally, there are clear advantages for cooperating with one another to find solutions to bringing new antimicrobials to market, however if a major player (for example, a high income country) decides to focus solely on their own interests, potential short term benefits may apply for that country but at the detriment of others. However, the global negotiations with manufacturers to attain vaccinations against the SARS-CoV2 virus (COVID-19) has illustrated inequity in access with distributions highly skewed in favour of high-income countries.[56]

The question of how much the Australian or any government should pay to incentivise pharmaceutical companies into antibiotic development is a balance between the perceived value of a new drug and the potential threat of not having that drug. Harris et al concluded that governments appear willing to pay a premium when the threat is great, for example, for a life threatening condition where there are no effective alternatives.[57]

This thesis challenges the status quo with regard to antimicrobial registration and funding in Australia, drawing and expanding on proposed policies considered internationally, to

consider the feasibility of alternative models for antimicrobial access within the theoretical construct of a 'One Health' systems-based approach.

Note: The term 'antimicrobial' is the broader term that encompasses antibiotics (antibacterials), antifungals, antivirals and other anti-infective agents. The term 'antimicrobial resistance' when referring to the threat to public health refers most frequently to bacterial resistance to antibiotics. Both terms are used interchangeably in this thesis, with antimicrobial being preferred unless the discussion is more specifically referring to only antibiotics.

Thesis outline

This doctoral thesis employs a mixed methods approach and is presented in the format of *Thesis by Publication* comprising ten chapters (Figure 1.5). The present chapter provides the introduction to the research topic, including the conceptual framework and aim and objectives of the research.

Chapter two provides a comprehensive literature review on the current regulatory and funding framework for access and reimbursement of antimicrobials in Australia. Challenges and barriers to access of antimicrobial drugs including shortages of current antimicrobials and a lack of new antimicrobials entering the market are detailed in the context of the Australian regulatory framework within a global market.

Chapter three describes the study design and the methods used for this research, including the rationale for the sequential mixed-methods approach. This chapter discusses the data collections methods, as well as an overview of the data analysis undertaken and the limitations of each of the methods used.

Chapters four and five aim to investigate the unmet need, by quantifying the utilisation of antimicrobials not registered in Australia and determining the clinical indications for which they are used.

Chapter six critically reviews the existing forecasting approaches used to scope the economic impact of AMR and this unmet need for new antimicrobials. It also discusses the utility of economic models of AMR to inform policy.

Chapters seven and eight include two publications arising from semi-structured interviews with stakeholders. Chapter seven explores the stakeholder perspective with regard to alternative methods of reimbursing pharmaceutical manufacturers whereby payment is disassociated from sales volume. Chapter eight examines stakeholder views on how the public health value of antimicrobials could be incorporated into the current HTA framework, particularly through accommodating future resistance into the economic evaluation of antimicrobials and the role of antimicrobial stewardship in retaining the 'value' or effectiveness of an antimicrobial.

Chapter nine presents the results of a discrete choice experiment aimed at determining the willingness of health professionals to pay for certain attributes of a new antimicrobial, including narrow spectrum of activity.

Finally, chapter ten presents the discussion and conclusion, reflecting on the key findings in relation to the aim and objectives of the research. The implications and contributions of the findings to inform policy are discussed, and areas for future research are proposed.

Figure 1.5: Thesis outline

SECTION ONE

Conceptual framework: Balancing access with excess

CHAPTER ONE
Introduction

CHAPTER TWO
Review of the literature

CHAPTER THREE
Study design and methodology

SECTION TWO

The current regulatory and funding framework for antimicrobials in Australia: Impact on access and antimicrobial development

CHAPTER FOUR
The unmet need: Quantifying the utilisation of unregistered antimicrobials in Australia

Publication:
Estimating the utilisation of unregistered antimicrobials in Australia. *Infection Disease and Health*, 2020; 25(2): 82-91

CHAPTER FIVE
Further exploration of the unmet need: Clinical conditions treated with unregistered antimicrobials

Publication:
Clinical indications treated with unregistered antimicrobials: The challenges of antimicrobial resistance and access to effective treatment for patients. *Aust Health Review*, 2020; 44(2): 263-9

SECTION THREE

Exploration of alternative regulatory and economic framework for antimicrobials in Australia with consideration of the impact on stewardship and manufacturer reimbursement

CHAPTER SIX
Methodological challenges with existing approaches to forecasting resistance

Publication:
Modeling the future clinical and economic burden of antimicrobial resistance: the feasibility and value of models to inform policy. *Applied Health Economics and Health Policy*, https://doi.org/10.1007/s40258-022-00728-x

CHAPTER SEVEN
Exploring alternative funding models

Publication:
Delinking the reimbursement of antimicrobials from sales: Feasibility from the Australian perspective – a qualitative study. *JAC-Antimicrob Res*, 2020; 2(2): 10.1093/jacamr/dlaa023

CHAPTER EIGHT
Understanding value

Publication:
Value assessment of antimicrobials and the implications for sustainable development, access and funding of effective treatments: Australian stakeholder perspective. *Int J Technol Assess Health Care*, 2021; 37(1): 1-7

CHAPTER NINE
Understanding choice

Manuscript (unpublished):
Is it worth the money? Healthcare practitioners' willingness to pay for narrow spectrum and other attributes of antimicrobials

CHAPTER TEN
Discussion and conclusion

CHAPTER TWO
Review of the literature

Antimicrobial resistance and the threat to public health

The overuse and inappropriate use of antibiotics in humans and animals, in addition to poor infection prevention and control, are considered the key drivers for the spread of antibiotic resistance.[9] Since the commercialisation of the first natural antibiotic, penicillin G, nearly 80 years ago, millions of tons of antibiotics have been produced for use in human and animal healthcare, as well as the food production industry where they are used for growth promotion of animals produced for the meat industry.[1] Bacteria can acquire resistance to multiple antibiotics, and can be defined as "multidrug-resistant" if they acquire resistance to three or more classes of antibiotic, where all antibiotics in those classes have been tested.[11] New mechanisms of resistance continue to emerge and spread globally, increasing the risk of antimicrobial treatment failure. With the incidence of multi-resistant infections increases globally, AMR is considered by the World Health Organization to be an increasingly serious threat to global public health, requiring urgent action across all government sectors and society.[9]

Overuse of antibiotics, especially those with broader spectrums of effect, has led to a rapid increase in the global incidence of multidrug-resistant bacteria over the last two decades.[8, 11]. The *First Australian Report on Antimicrobial use and resistance in Human Health*, known as AURA 2016, reported that antibiotic use in the community was higher in Australia than many other countries, including the United Kingdom (UK), Canada and the United States (US) on a prescription per population basis.[11] A cross-sectional survey of General Practice clinical activity in Australia between 2010 and 2015 estimated that the rate of antibiotic prescribing for acute respiratory infections in the community was up to nine times higher than that recommended in clinical guidelines.[58] The most recent AURA report estimated that 24.2% of prescriptions in Australian hospitals in 2019 were inappropriate, and that appropriateness of prescribing has not substantially changed in the last five years despite increasing global and national focus on antimicrobial stewardship.[15]

Antibiotics used in animal medicine, and their use as growth-promoters in animals produced for the meat industry, contribute to the increase in incidence of multidrug-resistant infections in humans.[9, 19-21] Antibiotic use in animals increases the risk of colonisation with

multidrug-resistant bacteria that can be transmitted to humans through the meat when the animal is slaughtered, or to the environment via animal faeces.

The increased focus of the WHO on the public health risks associated with AMR, and the consequent pressure for a global response, means that governments worldwide are developing national action plans and organised programs to reduce inappropriate or overuse of antibiotics, with the aim of prolonging the effectiveness of existing antibiotics.[11, 27, 59] In 2020, the Australian Government released the second national strategy outlining the priority areas for multi-sectoral action to address AMR.[60] Per head of population, Australia has one of the highest consumption rates of antibiotics in the world, with community use being higher than England, Canada, and many European countries.[11] Introduction of strategies across multiple disciplines of health to reduce over-use and optimise appropriate use of antibiotics is known as "Antimicrobial stewardship". Stewardship measures include ensuring prescribers have access to evidence-based clinical guidelines, educating clinicians and providing feedback regarding their prescribing, restricting the use of 'reserve' antibiotics, developing point-of care interventions to improve prescribing and ensuring appropriate laboratory reporting of susceptibility testing.[11] The need for stewardship is not limited to human health; global and national strategies to manage and minimise the risk of AMR are framed with a 'One Health' approach, engaging human, animal and environmental health, with a focus on cross-sector collaboration.[9, 20, 24, 25]

The clinical and economic burden of antimicrobial resistance

The final report of the AMR review commissioned by the UK government in 2016 predicted future global costs due to AMR to be high, with an estimated cumulative cost to global economic output of up to US$100 trillion by 2050.[27] Despite the acknowledged limitations and uncertainty regarding future mortality rates given the unpredictable emergence of AMR, the impact on clinical outcomes, higher healthcare costs and mortality are likely to be substantial.[31] The 2017 World Bank report into the economic threat of AMR also incorporated the impacts of AMR on the health of the workforce including the loss of productivity and deaths of workers, as well as costs associated with the AMR impacts on animal health.[28] The impact on livestock, including increased mortality, would result in lower livestock productivity and increasing costs associated with meat production.[28]

The authors of the World Bank report did acknowledge that their economic estimates likely underestimated the future burden of AMR as the modelling simulations for the report did not incorporate the impact on some medical procedures that would become too risky without effective antimicrobials.[28] Many surgical procedures, including births by caesarean section, would become life-threatening in the absence of effective antimicrobials to prevent post-surgical infection. The increased risk of adverse outcomes associated with surgical and other interventions with a high risk of infection would have adverse economic impact on patients, but also on the livelihood of healthcare providers that perform these interventions.[28]

In January 2022, a systematic analysis of data from 204 countries and 88 pathogen-drug combinations was published, which aimed to estimate the global burden of AMR in 2019.[61] Similar to the findings of the UK AMR review, this analysis identified substantial gaps in data in many low-income settings which likely underestimate global estimates. The results of the analysis estimated that in 2019 there were 1.27 million deaths attributable to bacterial AMR globally (95% CI: 0.91 – 1.71).[61] The authors acknowledged that the lack of data from low income countries was a limitation of their estimate, as the prevalence of AMR is unclear in many of these settings as well as the relative risk for each drug-pathogen combinations.[61]

Decline in new antibiotics marketed

The economic risks associated with antibiotic resistance has resulted in a dramatic decline in new antibiotics marketed.[32, 35, 62] Many large multinational pharmaceutical companies have withdrawn their interests in developing antibiotics in the past 20 years, opting to invest in other technologies where the return on investment is greater.[36] Pharmaceutical companies evaluate whether to proceed with a new drug development using an economic metric known as the "Net Present Value" (NPV), that is, the overall risk-benefit and estimated profitability of pursuing the development of a drug. Due predominantly to the low sales volumes expected when going to market (as new antibiotics are usually held in 'reserve' for small numbers of multi-drug resistant infections), the NPV for antibiotics has been estimated to be at least seventeen times lower than the NPV for neurological or musculoskeletal drugs.[63] Antibiotics are typically used for short duration, with a course of treatment often being less than a week for many indications. In contrast, medicines for chronic diseases such

as hypertension, are often used life-long, providing greater certainty for manufacturers in terms of return on investment.

The overuse of antibiotics, the key driver for AMR, is due to many factors, including but not limited to, diagnostic uncertainty and the fear of missing a life-threatening infection, marketing pressure from pharmaceutical companies and failure to review and cease treatment resulting in prolonged and unnecessary over-treatment.[64] Stewardship strategies to promote and monitor judicious use of antimicrobials to preserve their future effectiveness by exerting downwards pressure on usage has a sustained negative impact on antibiotic sales and on the economic return for pharmaceutical manufacturers (Figure 1.2).

In addition to the downward pressure on sales due to stewardship interventions, resistance to antimicrobials is a disincentive to manufacturers due to the negative impact on the expected return on the investment. Clinically significant resistance inevitably develops to all antibiotics, sometimes within a few years of introduction into clinical practice, or it may take two to three decades for resistance to develop[65, 66] (Figure 2.1). *Klebsiella pneumoniae* resistant to ceftazidime-avibactam, a new antibiotic licensed in the US in 2015, was reported in the same year it was marketed, in a patient with no prior treatment with the drug.[67]

In addition to the economic risks, clinical trials for antimicrobials have additional challenges. Severe bacterial infections require early empirical treatment, which cannot be delayed by the trial recruitment process. Due to the concomitant lack of rapid diagnostic tests to identify the pathogen, it is difficult to obtain sufficient patients to adequately power trials of antimicrobials.[14] The manufacturing process, from the discovery of a new compound with antibacterial activity to introduction into clinical practice, typically takes 15 years and it has been estimated that only between 1.5 – 3.5% of antimicrobial compounds successfully reach clinical practice.[34] Over 95% of antibiotics currently in development globally are being researched by small companies rather than the larger pharmaceutical companies. More than 70% of the companies researching the development of antibiotics have had no products marketed and are considered 'pre-revenue' or start-up businesses.[68]

Current pipeline of antimicrobials

Alexander Fleming discovered penicillin in 1928 however it wasn't until the 1940's when it was produced commercially for the treatment of infections in patients.[69] Many new classes of therapeutically effective antibiotics have been discovered since then, but in the last 30 years very few new antibiotics have been marketed, with no new classes being commercialised.[70] The development of resistance to an antibiotic often occurs soon after marketing and this poses a risk for companies seeking an economic return on their investment. For example, resistance to ciprofloxacin was observed in 1985, two years prior to the date ciprofloxacin was marketed for clinical use (Figure 2.1). The risk of resistance developing during the pre-market clinical trials is a substantial economic risk to companies, as the impact may affect the outcomes of the clinical trials as well as the post-marketing economic return.

Figure 2.1: Date antibiotic marketed compared to date resistance first reported
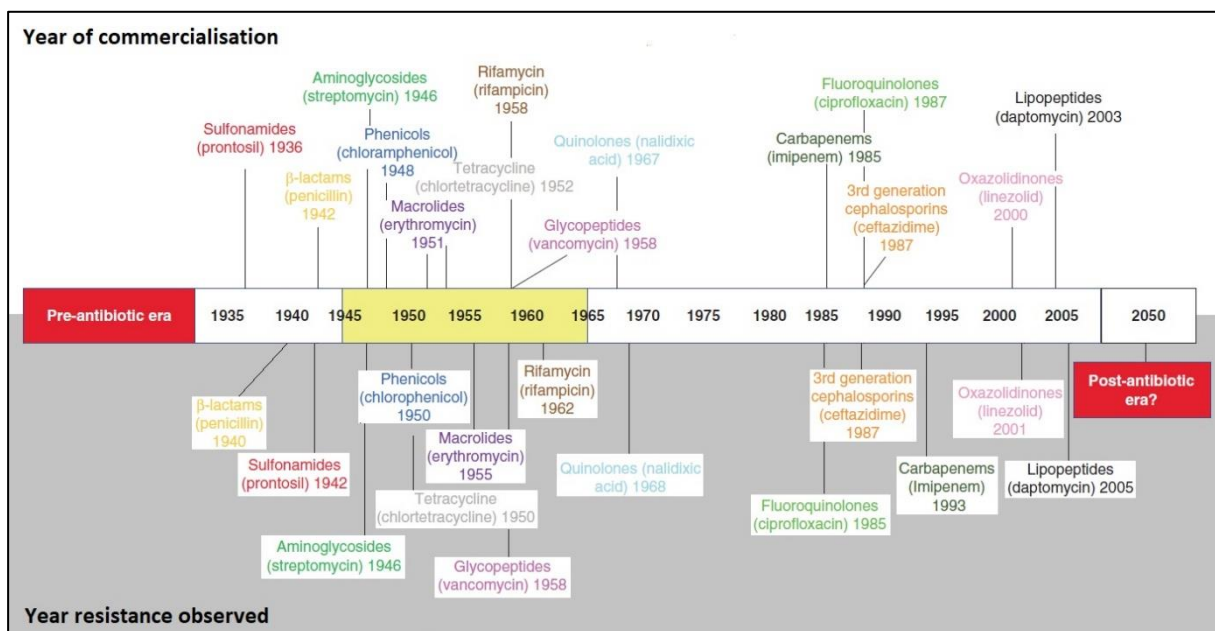
Source: Adapted from Stephens et al (2020) [70]

Since 2015 there has been increased global efforts to stimulate the antibiotic development pipeline. As of December 2020, there were 43 antibiotics in various stages of development globally, of which 13 were in Phase 3 trials.[68] Although a large proportion of chemicals with antibiotic activity do not reach human trials or are eliminated early due to toxicity, of the

antibiotics that reach Phase 3 trials, approximately 60% are likely to be approved for human use in the US or Europe based on historical approval data.[71] Approximately a quarter of the antibiotics in development globally are considered to belong to a novel drug class, where 'novel' is defined as acting on a previously unexploited bacterial target or binding site or new mode of action. Despite renewed investment in the development of new antibacterials, few novel agents are reaching clinical practice. A recent analysis of the clinical pipeline found that twelve new antibacterials have been marketed in the US and/or Europe between July 2017 and June 2021.[72] Ten of the twelve new antibacterials belonged to previously approved antibacterial classes and did not possess a new mechanism of action.[72] Of the twelve new antibacterials marketed since 2017, six target carbapenemase-producing Enterobacterales (CPE) and five target other WHO priority pathogens. [72]

Although advocacy by the WHO has led to increased public investment recently, the majority of antibacterial development remains driven by academic researchers and small to medium companies, with little global investment by larger pharmaceutical companies.[33]

"Push" and "Pull" incentivisation mechanisms

Since the publication of the WHO *Global Action Plan on Antimicrobial Resistance* in 2015, there has been increasing focus on sustainable mechanisms to incentivise the development of novel antimicrobials into the future, with particular focus on antibiotics to target multi-drug resistant bacteria. Broadly, these incentives can be categorised into pre-marketing ("push") mechanisms and incentives that are targeted at facilitating market access, and sustainable reimbursement for the manufacturer ("pull" mechanisms). Push mechanisms are aimed at reducing the costs associated with researching and developing new antimicrobials via the provision of research grants, offering tax incentives and establishing public-private partnerships to decrease the cost burden on one investor.[73] "Pull" mechanisms target overcoming the barriers to market access and ensuring there is sufficient future revenue for companies to continue marketing and ensure the supply chain for antimicrobials is reliable. In general, there is global agreement that a combination of 'push' and 'pull' incentives are required to ensure a long-term sustainable antimicrobial market. Much of the progress to date has focused on the push mechanisms, including a number of large public-private research and development partnerships being established, with total committed funding by

early 2020 exceeding US$750 million.[74] Less progress has been made with regard to "pull" mechanisms with little change implemented to the regulation and reimbursement of antimicrobials globally. [73, 75]

The major push and pull incentives that have been proposed in the published literature are summarised in Table 2.1:

Table 2.1: Push and pull incentives for antibiotic research and development

Push incentive strategies	
· Supporting open access to research	· Funding translational research
· Grants for scientific personnel	· Tax incentives
· Direct funding	· Refundable tax credits
· Conditional grants	· Product development partnership
Outcome-based pull incentive strategies	
· End prize	· Research tournament
· Milestone prize	· Advanced market commitment
· Pay-for-performance payments	· Strategic Antibiotic Reserve
· Patent buyout	· Service-availability premium
· Payer licence	
Regulatory and reimbursement pull incentive strategies	
· Accelerated assessment and approval	· Anti-trust waivers
· Market exclusivity extensions	· Sui generis rights
· Transferable intellectual property rights	· Value-based reimbursement
· Conservation-based market exclusivity	· Targeted approval specifications
· Liability protection	· Priority review vouchers

Source: Adapted from Renwick et al, 2016 [73]

In 2015 the Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR), a collaborative organisation established to advance the collaborative response between North American and European countries, agreed that a combination of both push and pull incentives was required, as well as methods exploring the de-linking of antimicrobial sales from the economic reward for manufacturers.[76]

The DRIVE-AB Report published in 2018 highlighted that the majority of financial incentives that have been implemented globally to incentivise antibiotic development are for "push" mechanisms focused on early stage research and the pre-clinical stages of the development process (Figure 2.2). [75] Little progress has been made in implementing pull incentives to

ensure that new drugs are not abandoned late in the development stage or in the post-marketing stage.[77]

Figure 2.2: Push-funding incentives for the phases of antibiotic development
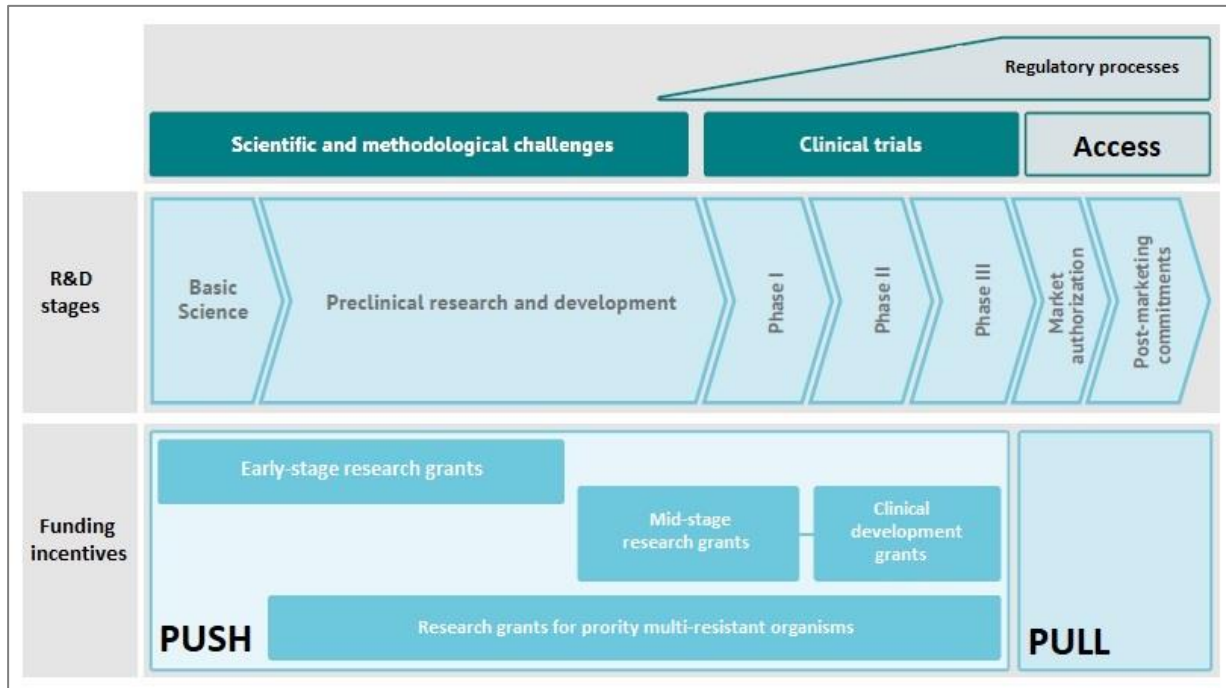
Source: Ardel C, et al. DRIVE-AB Report (2018)

Four potential financing models have been evaluated from the European perspective, including diagnosis-related group carve-out, stewardship taxes, transferable exclusivity voucher and a European-based 'pay or play' model:[78]

1. Diagnosis-related group (DRG) carve-out – Reimbursing hospitals for antibiotics separately to the reimbursement for procedures and treatments based on DRGs. In most European countries, hospitals are reimbursed based on the DRG categorisation for the treatment, however because MDR-infections are still relatively uncommon, the amount is based on the use of an inexpensive generic antibiotic. Separating and funding antibiotics independent to the DRG ('DRG carve-out') has been proposed as a financing mechanism to allow hospital antibiotics to be reimbursed at higher prices.[78]

2. Stewardship taxes – a national tax imposed to encourage antimicrobial stewardship. Additional financial incentives to encourage antimicrobial development requires a funding source. Taxation has been proposed to penalise excessive usage, for

example, a tax on antibiotics used in animals, charged similar to a prescription fee per animal. While this could raise substantial capital, an animal tax would raise costs for farmers which would ultimately increase the cost of meat for consumers.

3. Transferable exclusivity voucher – Granting a voucher to a manufacturer for successfully bringing a new antibiotic to market, allowing the manufacturer to extend the patent on any of their own currently marketed products.[79] This was an idea proposed in the REVAMP (Re-valuing Anti-microbial Products) Bill introduced into the US House of Representatives in June 2018 which proposed to offer a reward to any manufacturer that obtained FDA approval for a new antimicrobial in the form of a voucher to extend the market-exclusive period on another product.[79] The REVAMP Act was not passed into law, however an economic analysis to determine the impact had the law been in place between 2008 and 2018, estimated it would have cost US$4.5 billion over the ten years.[79] This idea has not been introduced in any country but has been deemed legally feasible in Europe.[78]

4. 'Pay or play' – a fee imposed on manufacturers dependent upon their contribution to antibiotic development. This proposal would essentially provide industry with the option to invest in bringing antibiotic development (through to marketing) or alternatively pay a charge or a fee not to. The rationale for this approach is that the healthcare system requires effective antibiotics, and other treatments and therapies developed by industry may be rendered useless without them.[78]

The World Economic Forum in 2018 agreed that any proposed pull mechanisms must be agreed globally and balance the risk between the private and public sector.[80] It is universally agreed that policy tools must not only focus on drug development, but also other modalities such as improved diagnostics and vaccines, in addition to 'One Health' policies to manage access and stewardship. Some European countries as well as the UK are beginning to explore methods of public reimbursement that are independent to the volume of antimicrobial use, engaging with companies with products in late-stage development that could be used in pilot programs of potential pull incentives.[81]

Critical areas of need – antibiotics for priority pathogens

In February 2017 the World Health Organization (WHO) published its inaugural global list of current "priority pathogens" to prioritise funding for antimicrobial development in line with the greatest public health need.[82] The list has twelve types of pathogens, categorised into three groups based on the urgency for new antimicrobials to target the organisms. Criteria for prioritisation included all-cause mortality, prevalence of resistance (including the 10-year trend of resistance), healthcare and community burden, transmissibility of infection, preventability in hospital and community settings, treatability and the current pipeline of new antibiotics.[82] Carbapenem-resistant Gram negative bacteria are listed as the most critical group requiring new antimicrobials, including *Acinetobacter baumannii, Pseudomonas aeruginosa* and extended-spectrum beta-lactamase (ESBL) -producing *Enterobacterales*.

In Australia, the rates of AMR in gram-negative organisms are lower than in other countries, however the rates of AMR in gram-positive organisms (*Staphylococcus aureus* and *Enterococcus faecium*) are high. Australia has one of the highest vancomycin resistance rates in *E. faecium* in the world, reported at between 45.7-49.9% of isolates, with some variation in resistance rates between settings.[11]

In March 2016, the National Alert System for Critical Antimicrobial Resistances (CARAlert) was established to collect surveillance data on organisms with critical resistance to last-line antibiotics, deemed to be of high priority in Australia (table 2, Appendix).[17] In 2020 there were 1,582 critically-resistant isolates reported from 76 laboratories across Australia. Although this number does not appear large, infections with CAR pathogens have limited treatment options resulting in significant morbidity for patients and increased risk of poor outcomes including death. The resistance mechanisms identified in these organisms are a serious threat to the effectiveness of last-line antimicrobials and the national surveillance system enables early detection and management of outbreaks.[18]

The purpose of the priority list developed by the WHO was identify key areas to target antibiotic research and development priorities. Since the publication of the list, there has been debate as to whether the most burdensome pathogen–drug combinations have been included.[61] A study investigating the pathogen–drug combinations that caused the most

deaths attributable to bacterial AMR in 2019 found only five of the seven on the WHO list, with the authors noting that MDR tuberculosis and fluoroquinolone-resistant *E coli* were not included. Methicillin-resistant *S aureus* is listed as 'high' priority by the WHO, but not 'critical' despite the authors finding it to be the likely cause of the most AMR-related deaths in 2019.[61]

The National Medicines Policy

The National Medicines Policy, 2000, is the overarching policy document providing the framework for the use of medicines in Australia, ensuring timely access to necessary medicines at an affordable cost to individuals and the community.[83] Furthermore, the national policy requires that the medicines meet appropriate safety, quality and efficacy standards, and that they are utilised according to accepted Quality Use of Medicines (QUM) principles, in addition to maintaining a viable medicines industry. New medicines must be evaluated for quality, safety and efficacy by the TGA in order to be licensed for use in Australia.[84]

The aims of the National Medicines Policy include the promotion of cost-effective care and value for taxpayer dollars, specifically that "*financing and supply arrangements for medicines optimise health outcomes and represent value for money*".[83] In addition the policy states that the responsibility for achieving value for money lies jointly with governments, health educators, health practitioners, the medicines industry, consumers and the media, and that "*financing arrangements for medicines avoid incentives for cost-shifting between levels of government or other funders*".[83]

The National Medicines Policy also acknowledges the importance of a continuing existence of a viable medicines industry in Australia:

> "*It is essential that industry policy and health policy be coordinated, providing a consistent and supportive environment for the industry, and appropriate returns for the research and development, manufacture, and supply of medicines*".[83]

The current regulatory process for antimicrobials in Australia

The Therapeutic Goods Act 1989 provides the legislative framework for the import, export, manufacture and supply of medicines, including antimicrobials, in Australia.[85] Like other medicines in Australia, antimicrobials are regulated by the Therapeutic Goods Administration (TGA) in the Australian Government Department of Health. Medicines licensed for use in Australia are listed on the Australian Register of Therapeutic Goods (ARTG), following assessment by the TGA for efficacy and safety. The TGA monitors and reviews the use of medicines according to their level of potential risk such as toxicity and adverse effects.

Application for listing a new medicine on the ARTG is associated with application and evaluation fees that must be paid to the TGA. For a new chemical entity sponsors must pay application and evaluation fees totalling over $231,000.[86]

The conduct of clinical trials to accumulate the safety and efficacy data sufficient to meet requirements for drug registration in Australia, may take many years. There is a balance between the minimum acceptable evidence (for efficacy and safety) and the speed of TGA approval for new medicines. Several countries globally have developed 'fast track' registration processes for new drugs where there is an unmet need, however there is a higher risk that drugs registered through these expedited pathways are more likely to be subsequently withdrawn or receive safety warnings due to safety concerns. [87, 88] Australia has recently implemented a provisional approval process for new medicines designed to treat serious or life-threatening conditions, which aims to allow faster access to these medicines while clinical trials to determine safety and efficacy are still on-going.[89]

There is provision in the *Therapeutic Goods Act 1989* to allow the importation of unapproved medicines (medicines not listed on the ARTG) under certain circumstances, including when there is a shortage of a licenced product.[90] Unregistered antimicrobials may also be accessed on an individual patient basis through the Special Access Scheme (SAS).[91] Prescribing of unregistered therapeutic products, which have not been evaluated for efficacy, safety or quality by the TGA, increases the liability and administrative burden on the prescriber.[92] The manufacturer or sponsor of the product is not obligated to supply an unregistered product, even if an application under the SAS has been approved.[92] The lack of obligation for a

manufacturer to supply an unregistered product increases the risk that a patient may not be able to access a treatment that may be the only therapeutic option for that individual and/or that particular infection. Ideally the TGA must protect the public from new drugs with limited safety data or products of poor quality, while minimising regulatory barriers to the access of both new and old antimicrobials needed for otherwise untreatable infections.[93]

In summary, the pathways for patient access to medicine, including antimicrobials, in Australia is complex, with the access to and funding being multi-dimensional, across healthcare settings and dependent on regulatory status (Figure 2.3)

Figure 2.3. Access to antimicrobials in Australia
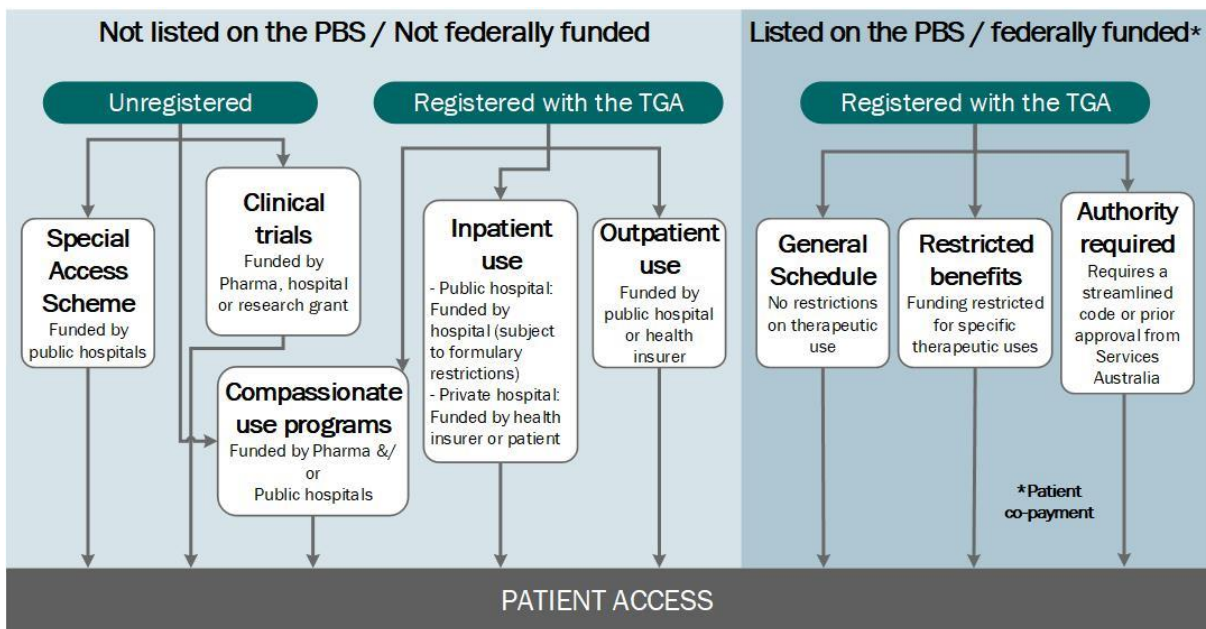
Medicines access programs (MAP) are initiatives implemented by pharmaceutical companies to supply new and publicly unfunded medicines to individual patients either free of charge, or via a cost-sharing arrangement with either the hospital or the patient themselves. MAPs are seen frequently across Australia, particularly for oncology drugs, where a pharmaceutical manufacturer will supply a new medicine that has not yet been approved by the TGA or recommended for public funding.[94]

In 2018, the Australian Government introduced a priority review pathway for the rapid approval of life-saving medicines. In addition, a provisional approval pathway was also introduced, which aimed to provide earlier access to new medicines based on preliminary (usually phase II) clinical data, where it is deemed by the TGA that early availability

outweighs the risks of incomplete efficacy and safety data.[95] This pathway was utilised in July 2020 to fast-track approval to remdesivir, the first antiviral in Australia to treat COVID-19.[96]

Challenges of achieving sufficient clinical trial evidence

One of the main challenges of antibiotic development is achieving sufficient toxicity to kill or inhibit bacterial cells, with minimal effect on mammalian or eukaryotic cells. Although many promising chemicals with antibacterial effects *in vitro* have been discovered, the unintentional toxic effects on human cells is one of the main reasons antibiotics fail to reach human trials and when they do, a high proportion do not progress through Phase 2 or 3 trials due to toxicity concerns.[73] A review of medicines withdrawn from the US market between 1980 and 2009 found that antibiotics were more likely to be withdrawn from the market than other drugs, with the most common reason for withdrawal being toxicity.[97]

The placebo-controlled randomised controlled trial (RCT) is considered the gold-standard evidence to support the registration and funding of a new medicine. The employment of adaptive study designs have recently been proposed to provide data that could be used to support the commercialisation of new antimicrobial therapies while reducing the time and cost of large RCTs. Adaptive designs have been used in clinical trials predominantly for oncology or cardiovascular drugs, however they have been used also for rarer infectious or parasitic diseases where a group sequential design was employed.[98]

When resistance to the drug that is currently the standard of care in clinical practice increases to a level where there is a high risk of treatment failure, the use of that drug as a comparator in clinical trials may become unethical. If the standard of care is the last effective product for that indication (due to resistance to all other drugs), as seen in multi-drug resistant infections where there may only be one or two possible treatment alternatives, conducting a superiority trial with a potential new drug is not possible. In these situations, non-inferiority trials must suffice.

Due to the still uncommon occurrence of resistant infections, most new antibiotics are tested through non-inferiority trials. Non-inferiority trials are considered much weaker than superiority trials with regard to the scientific rationale, the ethical justification and

historically have not been regarded as sufficient evidence to change standard of care.[99] In settings where there is an unmet clinical need, such as the treatment of drug-resistant infections, new antimicrobials have recently been approved based on non-inferiority trials where there was no direct evidence of their efficacy against multi-drug resistant bacteria. [99] Post-launch data collection is important to ensure future patient safety and to collect further real-world efficacy data with endpoints that are considered clinically appropriate in relation to the epidemiology of the disease.[100]

Antibiotic development is challenging: the aim of an antibiotic is to reach a particular target in the bacteria at sufficient concentration to inhibit bacterial growth, but while minimising toxicity in the host. Resistance therefore occurs when bacteria modify their target or develop methods to reduce the concentration of antibiotic accessing the target, for example, by producing inactivating enzymes or efflux pumps.[101] A number of older antibiotics have retained excellent *in vitro* activity against highly resistant infections however clinical trial data to support their use is rare. Clinicians are increasingly using these older antibiotics, repurposed for life-threatening multi-drug resistant infections that have limited treatment options due to resistance. Because older antibiotics are very cheap, there is little incentive for companies to invest in clinical trials to provide evidence of efficacy beyond currently approved conditions.[102]

Australia has not yet considered the regulation of alternative potential antimicrobial products such as bacteriophage therapy. Bacteriophages are viruses that kill bacteria, and are currently being widely researched as potential therapeutic tools against multi-resistant bacteria [103]. The Food and Drug Administration (FDA) which is responsible for the regulation of therapeutic goods in the United States have not yet licensed any bacteriophage therapy for human use, however the adaptation of drug approval pathways to include a pathway for bacteriophage-based therapies has been investigated.[104] The FDA have however approved bacteriophage products to decontaminate food and food-processing facilities from a number of pathogens.

Real world evidence

Real world evidence (RWE) is defined as "health-related information reported and collected in real-world medical settings, outside of traditional randomised controlled trials".[105] Real

world data extracted from electronic records from clinical practice are increasingly used to inform healthcare decision making at the point of care, but also influencing major health policy decisions.[106] RWE can be a useful source of evidence in uncommon clinical conditions where it is difficult to recruit sufficient numbers for clinical trials, and has been considered as an alternative method of collecting evidence for the treatment of life-threatening infections where it is not possible to delay therapy for enrolment processes including consent for clinical trials. Despite the advantages of collecting electronic medical record data to inform decision making, RWE is subject to bias as it is based on the secondary analysis of existing data that is not randomised.[106] Therefore transparent reporting of study methodologies would be required to assess the quality and validity of RWE to inform antimicrobial registration or funding decisions. In 2016, the US passed the *21st Century Cures Act*, which aimed to expedite access to new medicines and directed the FDA to develop guidelines defining the appropriate use of RWE into regulatory decision making. Japan has established a Medical Information Database Network to collect a repository of clinical data to assist in regulatory decisions for new therapeutics. The European Medicines Agency has now established an 'Adaptive Pathways' approval path which incorporates the use of RWE to accelerate the regulatory approval of products for rare conditions where there is an unmet need and where clinical trial data may be difficult to generate.[107] Although an increasing number of regulators are providing guidance on eligibility criteria for accelerated approval, there are concerns regarding balancing the risk, and potential lack of clarity regarding processes post-authorisation should a safety issue emerge following accelerated approval.[108]

In 2021 the Australian Therapeutic Goods Administration commissioned a review regarding RWE and patient reported outcomes in the regulatory context.[109] As a result of the review the TGA is planning to provide more transparent guidance on the use of RWE for medicine registration in Australia with the aim of enhancing the use of RWE into the future.

In addition to real world evidence, there is a regulatory push in the US in particular, to allow pharmacokinetic/pharmacodynamic (PK/PD) data to be used to demonstrate efficacy of antibiotics, particularly when it is difficult to conduct large clinical trials.[110] If an antimicrobial has been shown in trials for other indications to be safe, and effective at killing the pathogen of interest, the PK/PD trials have been shown to be strong predictors of efficacy for other infections (in other parts of the body) caused by the same pathogen.[110]

Definition of 'orphan drug' and applicability to antimicrobials

The definition of an orphan drug is one that is either: intended to treat, prevent or diagnose a rare disease; or one that is not commercially viable to supply to treat, prevent or diagnose another disease or condition. [111] For medicines where expected patient numbers are low, there is an orphan drug pathway for registration in Australia, where the application and evaluation fees usually charged to the manufacturer by the TGA are waived.[112]

The exact definition of what is considered 'not commercially viable' is not explicit in the Australian legislation governing orphan drug status.[90] The definition of a 'rare disease' was recently updated in the *Therapeutic Goods Regulations 1990* and is specified as "a condition affecting fewer than 5 in 10,000 individuals in Australia" at the time the company applies for orphan drug status.[111] In the US, a 'rare disease' is one affecting fewer than 200,000 people at any given time. For antibiotics, it is challenging to meet the definition of 'orphan', because the development of resistance to currently available medicines is unpredictable and not static, and the incidence of diseases caused by multi-drug resistant bacteria can rapidly change if there is an outbreak of infections. When a new antibiotic is developed there may still be other medicines available to treat the particular infection that the antibiotic is designed to treat. As antibiotic resistance to the standard of care increases, the new antibiotic may become the only (potentially life-saving) antibiotic to treat future infections. As the resistance increases further, while it still meets the definition of 'life-threatening', it may no longer be a rare indication.

Orphan drug status implies a small market, and therefore companies must charge high prices to make the drug commercially viable. For rare conditions it is potentially harder for researchers to recruit sufficient participants for clinical trials to establish safety and efficacy. Orphan drug status acknowledges these challenges and designation of orphan status frequently occurs without Phase 3 trial evidence. Historically antibiotics have not been considered for orphan status by regulatory authorities in the US or Europe. The exception is antibiotics for cystic fibrosis have received orphan status under these two regulatory agencies, as well as by the TGA in Australia.

In light of the reduced number of antibiotics reaching the market, there has been a call internationally to review orphan drug policies.[100] A review of legislation, regulations and

policies in 35 countries that pertained to access of orphan drugs found that there are substantial differences in legislation and in reimbursement policies regarding orphan drugs globally.[113] The European criteria for orphan drug status specifies that there must be "no satisfactory treatment for the condition in question in the EU" and that marketing of the product "would not generate sufficient return to cover the investment made".[114]

The Life Saving Drugs Program (LSDP) is an alternative public funding program in Australia whereby the federal government directly funds new medicines diseases or clinical indications that are life-threatening. Medicines included in the LSDP are usually those that may not have demonstrated cost-effectiveness due to limited data resultant from very small numbers of patients having the condition. There are prescriptive criteria for eligibility on the LSDP including the absence of alternative treatments.[115]

In August 2015 the FDA granted orphan status for the first time to a therapeutic agent that was in Phase 2 clinical trials at the time, being developed as a novel class of biological drugs designed to restore the function of a dysbiotic colonic microbiome, and prevent recurrent *Clostridioides difficile* (previously named *Clostridium difficile*) infection (CDI).[116] *Clostridioides difficile* is considered by the WHO to be a critical antibiotic-resistant pathogen with limited therapeutic options.[82] Exposure to antibiotics is the predominant risk factor for CDI – antibiotic use can disrupt the normal gut flora enabling opportunistic infection by *Clostridioides difficile.* In the US, it is a leading cause of hospital-acquired infections and approximately 13,000 Americans die from CDI annually.[117] This delegation was considered significant in the US as orphan drug status is rarely given to agents used for infectious disease indications.[113]

Public funding of antimicrobials in Australia

The funding of medicines in Australia is multi-tiered, and dependent upon where the patient is located at the time the medicine is required.[115] In the public sector within Australia there is a dual funding arrangement for medicines, with the federal government publicly funding medicines in the community (non-hospital setting) via the Pharmaceutical Benefits Scheme (PBS), and state governments funding medicines administered to inpatients in public hospital and hospital-in-the-home (HITH).[118]

The Pharmaceutical Benefits Scheme

The PBS (also known as the Schedule for Pharmaceutical Benefits) is governed by legislation in the *National Health Act 1953* as well as the *National Health (Pharmaceutical Benefits) Regulations 1960*.[119] The schedule contains a list of medicines able to be prescribed by medical practitioners and other qualified prescribers that are subject to public subsidisation by the Australian Government. Medications may be listed on the PBS with no restrictions (general benefit) or for specified clinical indications only (restricted benefit). Expenditure on the PBS comprises a substantial part of the total cost of Australian healthcare; in 2020-2021 the supply of medicines via the PBS cost the Australian government 13.6 billion Australian dollars.[120] Of the top 50 PBS-listed drugs (by active ingredient) sorted by highest Government cost in 2020-2021, there were no antibacterials or antifungals included.[120] Antiviral drugs to treat hepatitis C are included in the list, with the combination product of sofosbuvir and velpatasvir listed as the highest expenditure antiviral costing just over $171 million Australian dollars in the 2020-2021 financial year.[120]

Currently in Australia, the assessment of new antibiotics for public funding on the PBS is approached in a similar manner to other medicines with the onus on the manufacturer to make a submission to the Pharmaceutical Benefits Advisory Committee (PBAC) that demonstrates comparative clinical safety, effectiveness and cost-effectiveness relative to current standard of care. The only additional requirement for antibiotics is that submissions must demonstrate "prudent-use principles" to minimise the development of resistance, and "provide relevant data about the development of resistance". It is not explicit how manufacturers or evaluators should consider the value of minimising resistance in their assessment or recommendations concerning the public funding of antimicrobials. [121]

Decisions regarding which medicines, including antimicrobials, are publicly funded in Australia are based on recommendations made by the Pharmaceutical Benefits Advisory Committee (PBAC). The PBAC decision making process is based on the use of an implicit incremental cost-effectiveness ratio (ICER) threshold, reflecting the opportunity cost of choosing to fund a new technology.[122] This method is based on the premise that most new medicines are more effective and more expensive than the current standard of care.

There have been no new antibiotics listed on the PBS in the last 10 years.[123] A small number of new antibiotics have been registered in Australia in the last decade, but the manufacturers have not submitted applications for listing on the PBS as there is little incentive if the medicine is used to treat conditions that are predominantly treated in the hospital inpatient setting; this is the case for many intravenous antibiotics for example, that are primarily, or solely used in the inpatient setting. Approximately 40% of antimicrobial products (unique drug and route of administration) included in the National Antimicrobial Utilisation Surveillance Program (NAUSP) are not listed on the PBS and therefore are not eligible for federal funding.[124]

Hospital-funded antimicrobials

Public hospitals in Australia are administered and funded by the State and Territory governments, and medicines administered to inpatients are provided at no cost to the patients. For private hospitals, medicines are usually funded partly by the state and federal governments, with some private health insurance policies covering the cost of some medicines.[115]

Medicines used in public hospitals are managed by hospital Drug and Therapeutics Committees (DTCs) or equivalent committee, who decide which medicines will be listed on the hospital formulary or list of drugs available for use in inpatients. For new medicines that are not listed on the PBS but are instead used in the hospital setting, there is currently not a clear and consistent approach across all hospitals and/or states as to whether those medicines will be made available to patients and whether they will be funded by the hospital.[125] For expensive new medicines, there are documented inconsistencies in equity of access between hospitals in Australia.[125] Evidence regarding patient outcomes, in addition to the comparative cost, is important in determining whether a new medicine introduced into the hospital setting is providing 'value'. When new antimicrobials enter the market and are introduced at the hospital level, there is often only clinical trial data for one particular infection type or indication, with very little understanding of the effectiveness of infections caused by the same pathogens but in different anatomical locations.

Hospitals often have pooled procurement mechanisms, by which lower prices for medicines are secured through a tender purchasing system. Tendering is commonly used to minimize

and fix the price of generic drugs, including antimicrobials, particularly where hospitals are operating with fixed budgets. For off-patent or generic antimicrobials where there is more than one pharmaceutical manufacturer, tenders are awarded based on a competitive bidding process where hospitals request offers from suppliers and select the offer with the lowest purchase price. [126]

The admission status of patients impacts the source of funding. Intravenous antimicrobials that are administered in the patient's home as 'hospital-in the home' (HITH) are funded by the public hospital pharmacy providing the service. HITH is more commonly used in the public sector as a method of reducing hospital costs, however in the private sector, if the antimicrobial is listed on the PBS it may be administered as outpatient parenteral antimicrobial therapy (OPAT). When the antimicrobial is listed on the PBS, the cost of the drug itself is subsidised by the Australian government for outpatient use, with the costs of administration being covered by the hospital, or in the case of private hospitals, by the patient or patient's private health insurer. Because not all antimicrobials are listed on the PBS, there may be variation in prescribing based on whether the patient is admitted, resulting in differing access to medicines for patients with identical clinical indications.[115] Cost-shifting between federal and state funding has been cited as a key factor in limiting equity of access, and ensuring the most appropriate medicine is administered to individual patients.[115]

Patient contribution

When treated as an inpatient in the public hospital setting, there is no patient contribution to the cost of medicines, including antimicrobials administered while in hospital. Co-payments may or may not be charged on discharge, depending upon whether the take home medicines are funded on the PBS or not. In the community setting, for antimicrobials listed on the PBS, patients can be charged up to $42.50. Certain patient groups including pensioners and beneficiaries have a concessional co-payment fee of $6.80. Many generic antimicrobials on the PBS are very cheap and fall below the patient co-payment threshold, however pharmacists are then able to charge discretionary fees up to the level of the maximum co-payment. [127] Patient contributions account for approximately 10% of the total cost of all medicines listed on the PBS, and in the 2020-2021 financial year amounted to 1.5 billion Australian dollars.[120]

For antimicrobials not listed on the PBS, in the community setting these are provided as private prescriptions and the patient must pay the cost of the medicine. In some situations however, if the antimicrobial is prescribed to a public hospital outpatient, the public hospital may cover the cost with no patient co-payment. In general, the cost of private prescriptions varies between pharmacies with the price to the patient determined by the pharmacies themselves.

Health Technology Assessment

Health Technology Assessment (HTA) is "a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle." [128] The purpose of HTA is "to inform decision-making in order to promote an equitable, efficient, and high-quality health system".[128] Economic evaluation, including cost-effectiveness analysis, is required as part of the HTA process undertaken by the Australian government when deciding whether or not to fund a new medicine.[121] Similar requirements for demonstrating the safety, efficacy and cost-effectiveness of a new medicine are required in the UK, Europe and Canada. In Australia, the *Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (v 5.0)* provide detailed instructions on how pharmaceutical companies must present submissions when seeking public funding for a new product. Submissions for antimicrobial agents must follow the same structure as for other medicines, however the guidelines allow an option to present the following additional relevant information:

> Ensure that the submission for a new antimicrobial agent considers the government-endorsed prudent-use principles proposed by the 1999 report of the Joint Expert Advisory Committee on Antibiotic Resistance and the 'General principles of antimicrobial use' contained in *Therapeutic guidelines: antibiotic* when considering target populations. Provide relevant data about the development of resistance, as appropriate (cross-reference Section 2 if the development or potential development of resistance has been demonstrated to affect health outcomes). Address any issues, and indicate whether any aspect of any restriction requested in response to Subsection 1.4 is designed to minimise the development of resistance.[121]

Until recently guidelines for technology appraisal in Europe have had no specific guidance for the assessment of novel antibiotics despite the negative externality, antimicrobial resistance, which exposes a risk to public health.[129] Depending upon which aspects of antimicrobial stewardship are incorporated into the appraisal, the conclusions drawn could be variable. Antimicrobial stewardship not only encompasses interventions to minimise quantity of use, but also optimising appropriateness of use. Whenever an antimicrobial is used in an individual, whether the outcome of the use is clinically successful or not, there is an increased likelihood that the antimicrobial will be less effective for either that individual or for other populations in the future. The French and German governments have recently agreed with the pharmaceutical industry that additional public health benefits of antibiotics should be addressed in the Health Technology Assessment (HTA) process, including elements of additional value such as 'insurance value' and 'enablement value'.[130, 131] 'Enablement value' has been coined as an attribute of antibiotics that enable other medical procedures with higher infection risk to take place, such as surgery, dialysis and chemotherapy. Manufacturers advocate that the economic value of reducing transmission risk due to successful treatment of an infection should also be incorporated into funding decisions. Having alternative antibiotics with different and novel mechanisms of action ('diversity value') allows the withdrawal of an antibiotic from use for a period of time, in order to reduce resistance and restore susceptibility.[130]

Costs and health outcomes are estimated on a 'per patient' basis to determine the cost-effectiveness compared to current standard of care. The quality-adjusted life-year (QALY), a health-related measure of quality of life, is the most commonly used metric used to determine the cost-effectiveness of a new medicine. [132] Cost-utility analyses are preferred by the PBAC where "there is a claim of incremental life-years gained in the economic evaluation", to assess the impact of quality adjusting that survival gain. If a cost-effectiveness analysis is submitted by the manufacturer, there is a requirement that they justify why the quantified health outcomes are not translated into QALYs and presented as a cost-utility analysis.[121] Health outcomes for future patients may be adversely affected due to resistance, caused by previous overuse of the new medicine at both an individual level and a population level, and it is unclear in current guidelines how these population level outcomes should be included in the cost-effectiveness analysis of an antibiotic.[121] For example, if a

new antibiotic is shown to provide superior outcomes in an individual for a particular indication, maximising the use of that antibiotic does not provide superior outcomes at a population level as overuse increases the risk of resistance developing.

In considering the cost-effectiveness of antimicrobials, other factors that affect future resistance rates and costs need to be accounted for. Patterns of organisms prevalent in a given setting, case-mix or patient demographic profile, infection control measures and care practice in the ambulatory setting may all affect resistance rates. Similarly for new antibiotics, in addition to measurable outcomes such as clinical cure from acute infection, the long-term cost-effectiveness of a new antibiotic is dependent upon the resultant effect on resistance rates in the future.

Modelling the future benefits or other outcomes of antibiotic use for the purposes of estimating cost-effectiveness over a particular time horizon is challenging due to uncertainty regarding the duration of effectiveness of an antimicrobial before the development or increase in resistance. The prevention of transmission of multi-drug resistant infections to other individuals is dependent upon the ongoing availability of effective treatment as well as the implementation of infection control policies. Although a sensitivity analysis can model alternate scenarios, there is substantial uncertainty regarding the development of resistance over time, a variable that is highly dependent on intrinsic factors of the drug itself as well as external variables such as national and international prescribing policies. Predicting the future benefits of a new antimicrobial at a population level is unlikely to be proportional to the beneficial outcomes in an individual into the future. For example, efficacy at achieving a clinical cure in an individual may be superior with broader spectrum agents, especially for empirical treatment where the causative organisms have not been identified, as there is greater certainty that the drug will cover all possible pathogens. However, because of their wider spectrum of activity against a greater number of organisms, usage of broad-spectrum drugs is more likely to drive resistance and therefore a larger negative impact on the population as a whole.

In addition to challenges designing trials to collect good quality evidence for HTA, another issue is that most comparator drugs are very cheap. Because there have been a lack of new antibiotics entering the market in the last two decades, the patent has expired on most

currently marketed antibiotics and they are relatively cheap compared to other medicines. Where the best available evidence achievable is non-inferiority to an already cheap comparator, the price a company can ask for their medicine (and still be considered cost-effective within currently used methodology) is very low and not economically viable for manufacturers.

The exclusion of costs associated with resistance from comparative economic evaluations has been attributed to extensive practical issues in calculating the costs.[133] A systematic review of studies that measured the cost-effectiveness of interventions to reduce the development of resistance highlighted that much of the evidence is from micro-level studies rather than "the big picture" macro-level approaches.[134] The authors suggested that this is because micro-level interventions are more easily evaluated than macro-level, however macro-level approaches are needed given the externality-producing effects of AMR both within and between countries.[134]

Pricing of new medicines

Determination of the price that the government agrees to pay for public access to medicines is based on negotiations between the manufacturer and the 'Pricing Section' in the Australian Government Department of Health, following a positive recommendation by the PBAC to list the medicine on the PBS.[135] A number of different factors are considered by pricing decision-makers including the clinical and cost-effectiveness, the comparative price of medicines used for intended clinical indication, and estimated volume of use into the future.[135]

Pharmaceutical manufacturers that have pulled out of the antibiotic market have cited the high costs of development and the low prices achievable as the main reason for their withdrawal. Prices in Australia, and in many other countries with developed HTA processes, are largely determined by cost-effectiveness, and the choice of comparator is one of the main determinants of cost-effectiveness. [136] Historically, antibiotics have always been relatively cheap compared to other medicines, therefore it is challenging for companies to achieve a price for a new antibiotic that is comparable to prices achieved for other new medicines, because the comparator antibiotics are often only a few dollars for a treatment course.

The WHO recognise that "ensuring a fair, viable and affordable price" is challenging but that it is important to ensure that reimbursement to manufacturers is sufficient to support quality products and help guarantee continuity of supply worldwide.[137]

There are multiple factors contributing to the economic cost associated with AMR including higher treatment costs due to an increased risk of failing initial treatment, increased length of hospital stay, higher risk of mortality.[138] Coast et al, 1996, concluded that the exclusion of costs associated with antibiotic resistance from economic evaluations contributes to the notion that antibiotics are cheap, and the assumption that they are cheap may be associated with the tendency for clinicians to overprescribe.[133]

Advocates for the pharmaceutical industry have argued that antibiotics have additional 'unaccounted value' simply by existing, and allowing the safe delivery of healthcare interventions where there is an increased risk of infection, an attribute that has been cited as "enablement value".[131] Other elements of value that companies argue have been unaccounted for in pricing include "diversity value", whereby there are a range of antibiotics available which has been shown for some bacteria to reduce the selection pressure on other drugs. And "option value" is cited as an insurance-like value that is provided to society by having an effective antibiotic in existence in case of need. There is currently no consensus on how these 'added values' can be incorporated into the HTA of a new antibiotic. [131]

Generic antimicrobial market and the impact of shortages on stewardship

Generic medicines are products that are equivalent to originator brands that are no longer protected by patent. Because there have been very few new innovator antibiotics entering the market in recent years, most antibiotics used in clinical practice in Australia are generic products. It is acknowledged that long-term sustainability of the generic medicines industry is important to ensure affordable health care, and for antimicrobials the on-going availability of generic medicines is crucial to global public health.[139] While there is an increasing global focus on the need for investment into new antibiotics, there has been less focus on addressing the underlying economic causes of the increasing problem of unavailability of older, currently licensed antibiotics. Older antibiotics, which are often still effective and considered the first-line option for some infections, don't offer attractive profit margins for manufacturers and are frequently in short supply in Australia and other countries

worldwide. Antibiotic shortages are an increasingly common problem worldwide and the WHO believes it will continue to be a problem without a globally coordinated approach.[140] Factors attributed to antibiotic shortages include general manufacturing delays, unexpected demand changes, or inability to access raw materials at a price that is affordable given the low prices attained for the end product.[141, 142]

For low cost generic medicines, profitability is volume-based, and a feasible production line is only possible for manufacturers with sales of large volumes. Sales need to exceed regulatory costs including the cost for market entry as well as on-going annual fees that are charged by regulatory authorities.[139] For some antibiotics, the historically low prices attained for antibiotics has been a disincentive for the sponsors considering the generic market. Lack of licensed generics is an additional concern when originator products encounter manufacturing and supply problems.

The practice of healthcare systems or hospitals tendering for single-source contracts can adversely affect supplies although it is difficult to determine the extent of the impact.[137] Striving for low prices for medicines in Australian hospitals is driven by capped health budgets however purchasing unregistered antimicrobials to replace unprocurable licensed products is associated with unpredictable increased costs.[143]

The downward pressure on antimicrobial prices and sales has resulted in manufacturers withdrawing generic products from the marketplace leaving fewer suppliers to meet the demand, leading to an increased risk of shortages. A 2018 retrospective study reviewed drugs shortages over a period six years to investigate whether there was an association between price and the risk of a shortage, and found that as the price of generic drugs decreases the risk of shortages increases.[144] In addition to generic product withdrawal, the increasing number of global mergers of generic manufacturers has resulted in a decline in the number of providers and increased risks globally short supply of certain antimicrobials.[145]

The reduced number of manufacturers continuing to make injectable generic antibiotics in Australia, and globally, has left the market vulnerable if one manufacturer has supply chain problems.[142] In the 12 year period between January 2001 and December 2013, 148 antibiotics were in short supply in the United States for an extended period, with many

antibiotics having multiple periods of short supply.[141] Australian hospital pharmacists report increasing difficulty procuring intravenous antimicrobials to treat life-threatening infections.[143] No published studies have been conducted specifically to measure the effect of antibiotic shortages on patient clinical outcomes, however as infections with multi-resistant bacteria increases, shortages of the reserve antibiotics effective in treating those infections would likely have fatal consequences.

A recent point of prevalence survey published by the Society of Hospital Pharmacists of Australia (SHPA) illustrated the extent of the ongoing problem of medicines shortages in Australia.[146] Antimicrobials were singled out in the report as the class of medicine most frequently reported as unprocurable, and also the most likely to be stockpiled by individual hospitals.[146] Stockpiling by larger metropolitan hospitals reportedly increased the risk that smaller facilities such as rural sites were less able to obtain essential antimicrobials when needed.

Prior to 2019, the reporting of shortages to the Therapeutic Goods Administration (TGA) was not mandatory in Australia.[147] A global notification system and response mechanism for shortages of essential medicines has been proposed by the WHO.[148] Mandating reporting of shortages to regulatory bodies is feasible when the shortage is due to a manufacturing issue, however if there is a change in demand (often due to unavailability of another product), shortages are less foreseeable by manufacturers.[140] Since January 2019 the TGA maintains a database of information on medicine shortages, however as information is provided voluntarily by suppliers, pharmacies are often unaware of a shortage until it is too late to arrange alternative supplies of an unregistered brand.[149, 150]

Antimicrobial supply problems are also potentially jeopardising government investment of resources into AMR. If recommended first-line treatments are unprocurable, alternative antibiotics must be used, often with much broader spectrums of activity, which increase the risk of resistance developing.[151]

Prior to 2020 it was not mandatory for pharmaceutical companies to report a medicine shortage to the TGA. Since then it has been mandated and the TGA has established an online database to enable information on current and pending shortages to be publicly available. The legal definition of a medicine shortage in Australia is:

"There is a shortage of a medicine in Australia at a particular time if at any time in the six months after that particular time, the supply of that medicine in Australia will not, or will not be likely to, meet the demand for the medicine for all of the patients in Australia who take, or who may need to take, the medicine".[152]

When first-line treatments are unprocurable, patients may be administered alternative, potentially inappropriate, antibiotics, often with much broader spectrums of activity, which increase the risk of resistance developing. There are also reported cases of patient deaths and other adverse outcomes as a result of suboptimal treatment due to the inability to access effective treatment in a timely manner.[153] Antibiotics with a broader spectrum are more likely to have a greater impact on a patient's commensal bacteria (microbiome) with an increased likelihood of diarrhoea or *Clostridioides difficile* infection. [154]

The less visible consequence of shortages is the increased use of broader spectrum drugs with a higher propensity towards the development of resistance (Figure 1.2). Broad-spectrum antibiotics exert activity over a wider range of bacteria and therefore exert a wider selective pressure towards the development of resistant bacterial strains. The impact of the shortage therefore extends beyond the individual and ultimately has a negative impact on public health.[155] 18 countries reported problems accessing benzathine penicillin G over a period of three years.[140] Rheumatic heart disease, caused by Group A streptococci, has an estimated prevalence of 38 million people worldwide and benzathine penicillin G is critical to control it and prevent further infections.[156] Benzathine penicillin G is also the recommended first-line treatment of syphilis, a sexually transmitted disease caused by the bacteria *Treponema pallidum*. The global shortage of benzathine penicillin G potentially contributed to prescribers using alternative broad-spectrum macrolides such as azithromycin, which are usually reserved for penicillin-allergic patients. The prevalence of macrolide-resistant streptococci is increasing, reducing options available if first line penicillin-based therapy is unavailable, and the pathogen is resistant to the second-line macrolide.[157]

While difficulties accessing raw ingredients can be a cause for shortages, in general shortages typically occur due to market conditions or policies that deflate the price attainable below an economically feasible level.[139]

Price reduction policies are an attempt by governments to reduce the overall cost of healthcare however strategies such as tendering, deflate prices to a level where smaller suppliers cannot compete for marketshare they are forced to drop the product altogether or merge with a larger manufacturer. As generic manufacturers leave the market, the risk of shortages increases because if one supplier has a manufacturing problem, there are a reduced number of suppliers able to upscale production to compensate for the one with the manufacturing issue. The WHO considers that at least three suppliers are required per generic product to minimise the potential for medicine shortages.[140]

International policies and public investment to promote antibiotic development

Since the publication of the WHO Global Action Plan on AMR in 2015, public debate has increased with regard to policy discourse and public investment into novel antimicrobials.[36, 158-165] As of 2015, 46 countries had developed a national AMR strategy.[166] While there have been many methods of boosting research into new antibiotics proposed, only the United States (US) have passed federal legislation to expedite licensing of new antimicrobials. The GAIN Act (Generating Antibiotics Incentives Now Act) was passed in July 2012, providing an extension of patents by 5 years for "new antibacterial or antifungal drugs for human use that are intended to treat serious or life-threatening infections" and a 'fast-track' review process by the FDA for licensing.[167] Six systemic antibiotics have been approved by the FDA since the GAIN act was passed in 2012, although none have novel mechanisms of action.

The recommendations of both the Trans-Atlantic Task Force on Antimicrobial Resistance (TAFTAR), published in 2016, and the Drive-AB report in 2018, were in agreement that a combination of "push" (pre-marketing) and "pull" economic incentives are necessary to drive antibiotic development.[63, 75] Research grants and pre-marketing financial incentives have been applied generously by multiple global governments to researchers into antibiotic discovery, however less progress has been made on the global implementation of "pull" incentives to facilitate market entry.

In 2019, as part of the US government's strategy to address AMR, the Centers for Medicare and Medicaid Services (CMS) introduced a new policy called the "Fiscal Year (FY) 2020 Inpatient Prospective Payment System (IPPS) rule".[168] The policy changed the federal

reimbursement of hospitals based on "Diagnosis-Related Groups" (DRGs) to include a new severity level to include a drug-resistant infection. This enabled increased funding to allow hospitals increased resources dedicated to stewardship and the increased costs associated with new antibiotics.

There is concern that a fully delinked model may not be sustainable due to the cost, and that a lower market-priced market entry reward combined with some sales-based income may be more sustainable, and may allow future rewards to be linked to successful stewardship and supply chain security.[77, 169] Increased prices have been proposed as a method of reducing usage, and economically rewarding manufacturers however this approach would likely reduce antimicrobial access to patients in low to middle-income countries.[77, 170]

Regulatory obstacles have been identified as a disincentive to manufacturers entering new markets.[159, 169, 171, 172] In June 2017, regulators in Europe, Japan and the US agreed to streamline certain aspects of their trial data requirements for regulatory approval of new antibiotics.[173] Greater uncertainty regarding the risk-benefit balance may be accepted in regulatory decision-making, if the new drug can be used to treat patients with limited treatment options and there is a high risk of morbidity or mortality.[174]

In mid-2018 Novartis withdrew its investment in antimicrobial research to 'prioritise resources to other areas', with the plan to sell the licences of products in development. 140 employees with expertise in the development of antimicrobials lost their jobs. There has been concern globally that the withdrawal of larger pharmaceutical companies from the antibiotic market is depleting the general expertise in this area of drug development.[175]

In June 2018 a bill was introduced into the US House of representatives, known as the 'REVAMP Act', or 'Re-valuing anti-microbial products Act of 2018', which aimed to reward pharmaceutical companies who develop and market an antimicrobial product that has been identified as addressing a priority need, by granting them an additional 12-month market-exclusivity on another product. The bill proposes that a 12-month extension on a patent can be used by the company themselves, or potentially sold or transferred to another company, and potentially could be worth billions of dollars if the market exclusivity is extended for a 'blockbuster' drug.[176] As of April 2022, the bill has not been enacted.

Another alternative financing option that has been proposed to promote the marketing of new antibiotics is a fee imposed on all medicine manufacturers who do not have an antibiotic marketed. This is intended to incentivise larger manufacturers to be interested in bringing antibiotics to market.[27] Concern has been raised about this approach negatively impacting other therapeutic areas where there is also minimal investment, or alternatively that companies may manipulate the system by investing minimally in antibiotics, just sufficient to avoid the fee.[78]

Merck Healthcare Pty Ltd, one of the few multi-national pharmaceutical companies still investing in antimicrobial development has recently proposed to the Australian Government the establishment of a pilot fund for novel antimicrobials.[177] The company has suggested a three-year pilot of up to five novel antimicrobials, funded at a rate of AUS $10 million per drug per year, using a de-linked model whereby the company is reimbursed independent of quantity used.[177]

The lump sum approach to public funding of a class of medicines occurred for the first time in Australia in 2016 when the Australian government negotiated an agreement to spend approximately AU$1 billion over five years in exchange for an unlimited quantity of direct-acting antivirals for the treatment of hepatitis C virus.[178] Companies involved in the agreement are effectively remunerated for their innovation and receive guaranteed revenue over the time period. Australians in return have guaranteed publicly-funded access to these effective medicines, irrespective of disease severity, whereas other counties have had to restrict access based on disease severity in order to keep expenditure manageable at a national level. Whether this de-linked approach could be adopted for antibiotics has been debated in the literature, suggesting that three conditions are required: the ability to reasonably predict volumes of usage over the contract period, manufacturing cost must be a relatively small proportion of the price and suppliers need to be willing and able to adjust to changes in demand.[179]

Some authors suggest that the only sustainable method of maintaining a development pipeline for antibiotics is a not-for-profit approach.[180] The arguments for the not-for-profit approach include the removal of the need to increase sales for profit for shareholders,

however sizable initial funding is required to establish these organisations and ongoing funding is required to secure and retain expert personnel.

A 2020 review of policy tools implemented to minimise antimicrobial resistance reported the majority of policy interventions are aimed at restricting prescribing to improve the appropriateness of usage and limit overuse.[181] More recently, five countries have implemented policy initiatives aimed at increasing the reimbursement of new antimicrobials bought to market while not incentivising overuse (Table 2.2).[81]

Table 2.2: New implemented reimbursement mechanisms relevant to AMR

Country	Year initiated	Mechanism
France	2015	Medicines with 'moderate' or higher added therapeutic value guaranteed a price not lower than the lowest price across 4 reference countries. Extended to include antibacterials with 'minor' therapeutic benefit.
		Sales of certain antibacterials exempted from turnover liable to clawback (if annual sales exceed a certain level)
		Companies may request permission for price increase on antibacterials from the pricing authority if continued commercialisation would not be viable (details confidential)
Germany	2017	*Ad hoc* exception of antimicrobials from internal price reference groups. Decided by consideration of resistance patterns
	2020	Automatic exception of 'Reserve' antimicrobials from internal price reference groups, accelerated review process ('Reserve' not defined)
Sweden	2020	Public Health Agency of Sweden – sets minimum guaranteed annual revenue for selected novel antibacterials in exchange for guaranteed supply volume.
UK	2020	Innovative model for evaluation and purchase of two antimicrobials – annual fee, delinked from volume supplied. Targeting WHO-priority pathogens.
US	2012	GAIN Act – legislated 5-year extension of patent, faster regulatory review for drugs designated as 'qualified infectious disease products' (QIDP) pathogens
	2019	Revision of Inpatient Prospective Payment System (IPPS) rule to increase hospital reimbursement costs for novel antibacterials
	2019	CivicaRx – non-profit generic drug company to manufacture generic drugs subject to shortages (private initiative)

Source: Adapted from Gotham et al, 2021 [81]

The UK are the only country as of early 2022 to pilot a de-linked subscription model for the purchase of novel antimicrobials. The pilot is in the early stages and has completed a procurement process to select two antibacterial products, ceftazidime with avibactam and cefiderocol. An independent expert committee has been convened to make a judgement on the 'value' of these two drugs to the NHS in the UK.[46] No countries have attempted to implement a subscription model for currently available, generic antimicrobials.

Australia's current position in the global antibiotic market

Although there is substantial uncertainty regarding total human antibiotic consumption in Australia, it has been estimated that Australasia consumes only approximately 0.6% of total global human consumption. However, per capita Australasia has one of the highest consumption rates in the world.[182] Australia relies heavily on imported antimicrobials due to a relatively small generic pharmaceutical industry locally. The relatively small market size and high regulatory costs have been cited as a barrier for multi-national generic companies structured for high-volume markets.[183]

For new antimicrobials, Australia has a strongly positioned research sector involved in antimicrobial discovery that is largely supported and funded by the Australian Government. In addition there is a strong not-for-profit, academic sector in Australia screening compounds for antimicrobial activity against multi-drug resistant infections.[184] While these "push" incentives are valuable in the global search for new products, the relatively small post-market sales, in addition to the high regulatory costs, makes Australia a less attractive market once clinical trials are completed.

A key objective of Australia's *National Antimicrobial Resistance Strategy – 2020 and beyond* is to identify innovative and sustainable ways to fund, or stimulate the discovery and development of new treatment options for multi-drug resistant infections, while minimising the impact those new therapies may have on antimicrobial resistance. Another key priority in the national strategy is to "influence the global antimicrobial resistance agenda by active engagement and collaboration with other countries".[60] Despite Australia being a relatively small player in the development of antimicrobials globally, a collaborative response by all countries is required to manage the future threat antimicrobial resistance poses to public health.

Research aims and objectives

The overall aim of this thesis is to explore the feasibility of adopting an alternative regulatory and funding model for antimicrobials in Australia in order to ensure a sustainable supply of effective medicines, maintain industry commitment to the research and development of new antimicrobials, while also ensuring overuse and inappropriate use is minimised. The aim of the thesis will be met by the following objectives:

1. To identify and quantify the usage of unregistered antimicrobials in Australian clinical practice, and to determine the range of clinical indications for which no registered antimicrobials are available or appropriate to use.

2. To determine stakeholder opinion, particularly the perspective of pharmaceutical manufacturers and policy makers, to determine what regulatory changes could assist in ensuring sustainable access for patients to new innovative antimicrobials, economic viability and security of supply, and maintain the balance between access and appropriate use. In particular, stakeholder perspectives were sought on the feasibility of de-linked funding models that have been proposed or piloted internationally, in addition to alternative pathways for assessing and valuing new antimicrobials for reimbursement in the Australian healthcare setting.

3. To determine which attributes, both economic and drug-specific, of a new antimicrobial have the greatest value for health care professionals and to estimate their willingness to pay for those attributes.

CHAPTER THREE
Study design and methodology

Preface

This chapter provides an overview of the research design and the rationale for the methods used to address each of the research questions in this thesis. The justification for each of the methods used is provided, together with an explanation of the data collection and analytical methods employed.

To limit repetition, the details provided in this chapter are generally not present in the publications or submitted manuscripts which are presented subsequently.

Theoretical framework and mixed methodology

There are multiple variations of mixed-methods designs in the published literature, with mixed-methodology being increasingly common in health policy research. The collection, analysis and interpretation of quantitative and qualitative data to investigate the same underlying research objectives may be conducted concurrently or sequentially. [185] Sequential designs are effective where the quantitative results may provide a "general picture of the problem", with the subsequent qualitative data providing further insight, often resulting in emergent questions for further exploration. [186] This thesis utilised a sequential mixed-methods approach, combining both quantitative and qualitative methods, as illustrated in Figure 3.1.

Figure 3.1: Sequential Mixed-Methods included in thesis
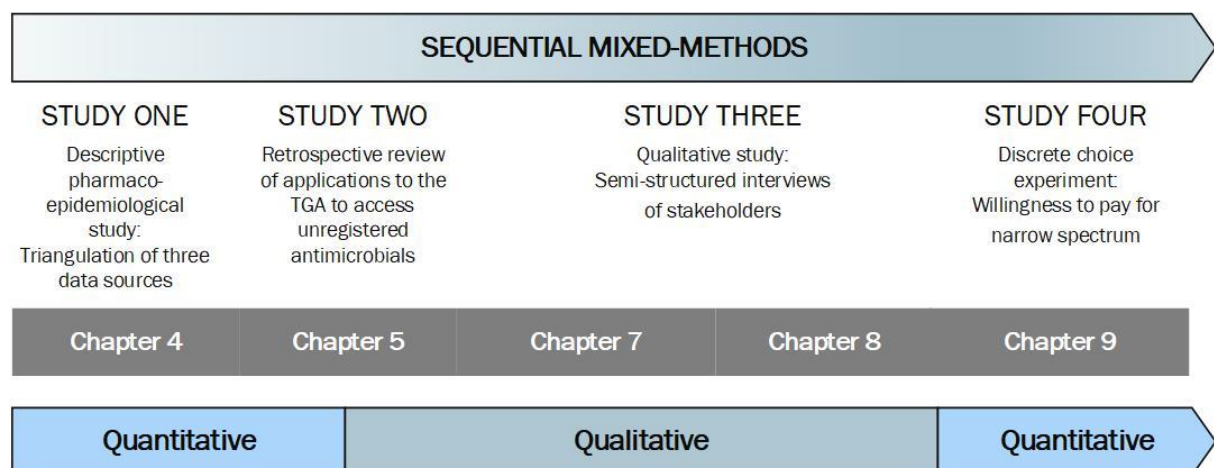
The research methods in this thesis include:

- Pharmacoepidemiological methods, including a drug utilisation study and a non-clinical audit
- Qualitative methods | semi-structured interviews
- Discrete Choice Experiment

An overview of these methodologies is provided below, along with a justification for their use in the context of the research questions.

Pharmacoepidemiological methods

Drug utilisation research falls within the field of pharmacoepidemiology and can be defined as the 'collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes'. [187] Drug utilisation research has been described as the bridge between pharmacoepidemiology and health services research (Figure 3.2). [188] Health services research is the "multidisciplinary field of scientific investigation that studies how social factors, financing systems, organisational structures and processes, health technologies, and personal behaviour affect access to health care, the quality and cost of health care, and ultimately our health and well-being". [189]

Figure 3.2   Drug Utilisation Research as a bridge between epidemiology and health services research
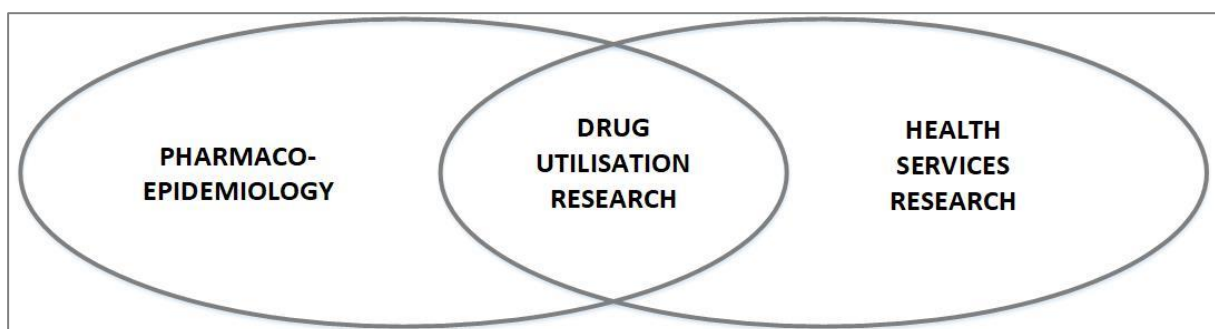
Adapted from Wettermark et al, 2016.[188]

Drug utilisation methodologies are employed to estimate trends in the utilisation of medicines or classes of medicines, including the extent of appropriate use, overuse or underuse. Trends in use and costs over time, and/or in certain hospitals, states, regions or countries can help determine whether educational or policy interventions are required, and help generate hypotheses for further research. [190]

The initial objective of this research was to determine the unmet need for new or registered antimicrobials in Australia. This was achieved in two steps: the first study aimed to quantify the utilisation of unregistered antimicrobials in Australian clinical practice. The second study aimed to identify the clinical indications most commonly treated with unregistered antimicrobials.

Drug utilisation study – data sources and analysis

The initial aim of this research was to quantify the utilisation of unregistered antimicrobials in Australia to estimate the unmet need for new or alternative products. As no single dataset is available to directly quantify the procurement and utilisation of unregistered antimicrobials across Australia in both the hospital and the community settings, three data sources were utilised, each with varying scope and differing limitations:

- Special Access Scheme (SAS) – a *Freedom of Information* request was submitted to the Commonwealth Department of Health requesting data on SAS applications for individual patient use submitted to the TGA for unregistered antimicrobials identified in Australian clinical guidelines.

- SA Pharmacy data – data on all antimicrobials dispensed or distributed by the pharmacy service provided within South Australian public hospitals (including hospitals > 50 beds), for use by inpatients or outpatients.

- National Antimicrobial Utilisation Surveillance Program – Australia-wide hospital inpatient data, collected from public and private hospitals voluntarily participating in the national surveillance program.

Each of the datasets used different metrics to quantify the use of unregistered antimicrobials:

Table 3.1: Utilisation metric for each dataset

	Metric for utilisation
Special Access Scheme	Count data (no. of applications)
South Australian Public Hospital Pharmacy Data	Volume (grams)
National Antimicrobial Utilisation Surveillance Program	Rate (Defined Daily Dose / 1000 Occupied Bed Days)

Because of the differing metrics between the three data sources, the datasets could not easily be combined for analysis. Triangulation, or the use of two or more independent measures to answer a research question, allows the strengths of one data source to compensate the limitations of another.[191, 192] By triangulating the data sources we aimed to determine the extent of unregistered antimicrobial utilisation and if there was consistency in usage trends across the health sector. All unregistered antimicrobials identified by all three data-sources were cross-tabulated to identify which antimicrobials were included in one or more of the data sets (Table 4.1). Utilisation rates were calculated for each of the datasets separately and compared:

- The total number of SAS applications were calculated for antimicrobials for each 12-month period to determine any trends over a 5-year period.

- For the analysis of the antimicrobial data from SA Pharmacy, the monthly usage of all antimicrobials used was converted from grams to the standardised drug consumption metric Defined Daily Doses (DDDs). DDDs are defined by the World Health Organization (WHO) as "the assumed average maintenance dose per day for a drug used for its main indication in adults".[193] The proportion of total systemic antimicrobial usage (DDDs used) in the South Australian public hospital sector used that were unregistered products (or manufactured from unregistered products) was calculated on a monthly basis over a two-year period. The analysis excluded paediatric use as standard daily doses have not been defined for paediatric patients.[193]

- Data from the National Antimicrobial Utilisation Surveillance Program (NAUSP) was collected from over 200 Australian hospitals.[194] Dispensing and distribution data

from the hospital pharmacies were converted from the total number of grams used in DDDs for each antimicrobial. A standardised usage density rate was calculated for each antimicrobial used in the inpatient setting, with occupied bed days (OBDs) being the denominator used. Annual usage (DDD/1,000 OBD) for each antimicrobial was calculated over a 5-year period.

Audit of Special Access Scheme applications from South Australian tertiary hospitals – data retrieval

The Special Access Scheme (SAS) in Australia is an access pathway for health practitioners to procure unregistered medicines for individual patient use.[91] Medicines that are not included on the Australian Register of Therapeutic Goods (ARTG) are considered to be 'unapproved' by the TGA.[195]

To investigate the clinical indications for which unregistered medicines are used, data on the utilisation of unregistered antimicrobials were extracted from the original Special Access Scheme (SAS) application forms retained by two tertiary hospital pharmacies in South Australia for the two-year period July 2015 to June 2017. Access is now achievable via online applications, however at the time this study was conducted, only manual applications were possible. To access medicines via the Special Access Scheme (SAS) health practitioners were required to complete a form which was forwarded to the TGA for processing. To conduct the audit of applications submitted from the two hospitals, data were manually extracted from the SAS application forms submitted during the study period. Data fields extracted included the date of application, the antimicrobial requested, dosage form or route of administration, the intended dose, the quantity of supply requested or duration of treatment, clinical indication, and (for Category B applications) the justification for use of the unregistered product. No patient or prescriber identifying information was extracted and patient medical record numbers were replaced with a unique study number for each patient. The average weighted price for the unregistered antimicrobials was provided by SA Pharmacy. Although the procurement costs vary substantially for these medicines, depending upon which country and supplier they are sourced from and the transport costs, the weighted average cost represents the mean price paid by the South Australian public sector for these medicines.

Qualitative methods

The semi-structured interview is a qualitative methodological tool that enables the collection of rich data specifically addressing the research topic, while also allowing participants to offer new meanings or directions to the study focus.[196-198] Semi-structured interviews are increasingly utilised in health policy research to elicit the perspectives of multiple stakeholders in order to inform policy decision-making.[199] This methodological approach was utilised to draw in-depth accounts from the primary stakeholders in antimicrobial supply and access; that is, the pharmaceutical manufacturers and policy-makers involved in the regulation or funding of medicines. The overall objective of this qualitative research was to determine stakeholder opinion on potential regulatory changes that could assist in ensuring sustainable access for patients to new innovative antimicrobials, including the economic viability and security of supply, while maintaining the balance between access and appropriate use. A particular focus was to seek the stakeholder perspective on the feasibility of de-linked funding models that have been proposed or piloted internationally, in addition to alternative pathways for assessing and valuing new antimicrobials for reimbursement in the Australian healthcare setting.

Stakeholder interviews – participant recruitment and interview process

The study population for the stakeholder interviews consisted of two groups, policy-makers and the pharmaceutical industry. Both purposive and snowball sampling was utilised to recruit participants. Purposive sampling was used initially whereby individuals were identified and selected based on their roles and expertise relating to antimicrobial development, access, and funding. This sampling approach is the most efficient method for research questions where individuals with specific expertise are sought, and the strategy stems logically from the research questions being addressed.[200] Pharmaceutical companies still involved in antimicrobial supply in Australia were approached with an invitation to nominate individuals who might be interested in participating. Policymakers involved in registration and funding decisions at a federal level were invited to participate, as well as individuals at the state-government level involved in state-wide formulary decision-making. Snowball sampling was also used for the stakeholder interviews, whereby individuals already recruited identified other possible participants in a process analogous to a snowball rolling down a hill. The advantages of snowball sampling include: reduced time and cost of

recruiting a representative participant group of sufficient size and diversity, particularly in hard-to-reach or highly specialised expert populations.[201] The main disadvantage of the snowball sampling technique is that there poses a risk that participants only refer to individuals with similar opinions to themselves.[201]

Recruitment of participants for interviews was continued in this study until no new codes or themes relevant to the research questions transpired. Acknowledging that it is always possible for something 'new' to emerge, saturation was considered to be reached when it appeared no new data pertaining to the study objectives would be forthcoming. This is in accordance with literature on sample sizes for qualitative research, which notes that the point of saturation should be the guiding principle, but noting the limitation of saturation being it cannot be predicted whether subsequent participants may introduce new material.[202] Qualitative samples must be large enough to assure all, or most, of the ideas and perceptions are uncovered, but not too large that the data becomes repetitive or unmanageable because of sheer volume, given the labour-intensive analytic process.

The guide for the semi-structured interviews (Appendix 4) was developed with questions framed around the research objective, and based upon a search of published and grey literature with questions relating to the following domains: alternative business models, Australia's current regulatory process, evaluation of antimicrobials for reimbursement, antimicrobial stewardship and sustainable supply. The structure of the questions was open-ended to allow participants to determine the nature of their responses and enable additional explanation or provision of examples.[196] The semi-structured nature of the interview questions allowed the conversation to evolve based on the participant's responses.[196]

Interviews were conducted either face-to-face or via video or phone conferencing, and lasted between 22 and 60 minutes (median duration 42 minutes). The outcomes of qualitative research may be impacted by the prejudices and attitudes of the interviewer.[196,197] While any bias due to the subjectivity of the interviewer cannot be entirely eliminated, care was taken to minimise potential bias in the framing of the questions, the tone of voice and body language, and the level of interest; any casual comments made were non-judgemental. Data collection and analysis was conducted concurrently.

Framework method of qualitative data analysis

The framework method of qualitative content analysis is a process of identifying both commonalities and differences in qualitative data, and determining relationships between different parts of the data in order to draw descriptive conclusions assembled around themes.[203] The framework method is a structured approach to organising and categorising qualitative data, and is most commonly used for the thematic analysis of semi-structured interview transcripts.[204] The development of themes followed a combined approach to the analysis of the interviews, both inductively from the interviews (opinions and experiences of participants) and deductively (using the research questions to group the data) from the literature, to look for similarities and differences.[203]

The analytic process included the following steps:

- Transcription: Each of the interviews was digitally recorded, and then transcribed verbatim prior to coding. All transcripts were checked for errors by listening back to the audio-recording and reading the transcripts simultaneously. Notes taken during the interviews were added to the transcripts as supplementary data, and non-verbal contextual detail was added in parentheses to assist with interpretation, for example, laughter or extended pauses.
- Familiarisation with the interviews
- Coding: All transcripts were imported into NVivo® by a single researcher. Code definitions were regularly discussed and agreed among three researchers (student and two supervisors).
- Developing a working analytic framework
- Applying the analytical framework
- Interpreting the data: Coded data was initially displayed in NVivo® in the form of a code-cluster map allowing visualisation of the relationships and connections among constructs, and identification of the dominant themes in the data.

Discrete choice experiments (DCEs) are increasingly utilised in health economics to elicit patient preferences and to evaluate the relative importance of attributes or features of healthcare interventions or services to inform policy or funding decision-making,[205-208] DCE methodology is a stated-preference survey method and falls under the umbrella of "conjoint analysis" methods. Conjoint analysis broadly describes a range of state-preference methods where respondents choose, rank or rate a set of experimentally controlled items based on varying features.[209] The methodology is founded on the characteristics theory of demand, developed in 1966, which states that individuals attain utility not from the goods themselves, but from the "characteristics of the goods from which utility is derived".[210] In a DCE, individuals are requested to indicate their stated preference choices when offered two options with different sets of attributes in hypothetical scenarios designed to investigate a particular research question. Within the sets of attributes, each attribute takes one of several levels over which the attribute varies.[211] The DCE methodology makes the assumption that participants will respond in a 'utility-maximising' manner based on the particular attributes in each scenario.[205] The underlying economic theory on which this assumption is based, the random utility theory (RUT), assumes the underlying utility being estimated is a function of the different attributes and their levels, in addition to a random component or preference variation.[205]

Although the majority of published DCEs in healthcare research focus on the valuation of the patient experience (analysing trade-offs between health outcomes and patient experience), DCEs have also been used to investigate individual preferences from the decision-maker perspective regarding the allocation of public funding and how different stakeholders may value outcomes.[208, 212]

Bridges et al (2011) published broad consensus guidance on good research practices for conjoint analysis, including DCEs and other multi-attribute stated preference methods.[207] The guidance provided a checklist which outlines a systematic process of good research practices for conjoint analysis (Figure 3.3).

Figure 3.3 Checklist for conjoint analysis in health care
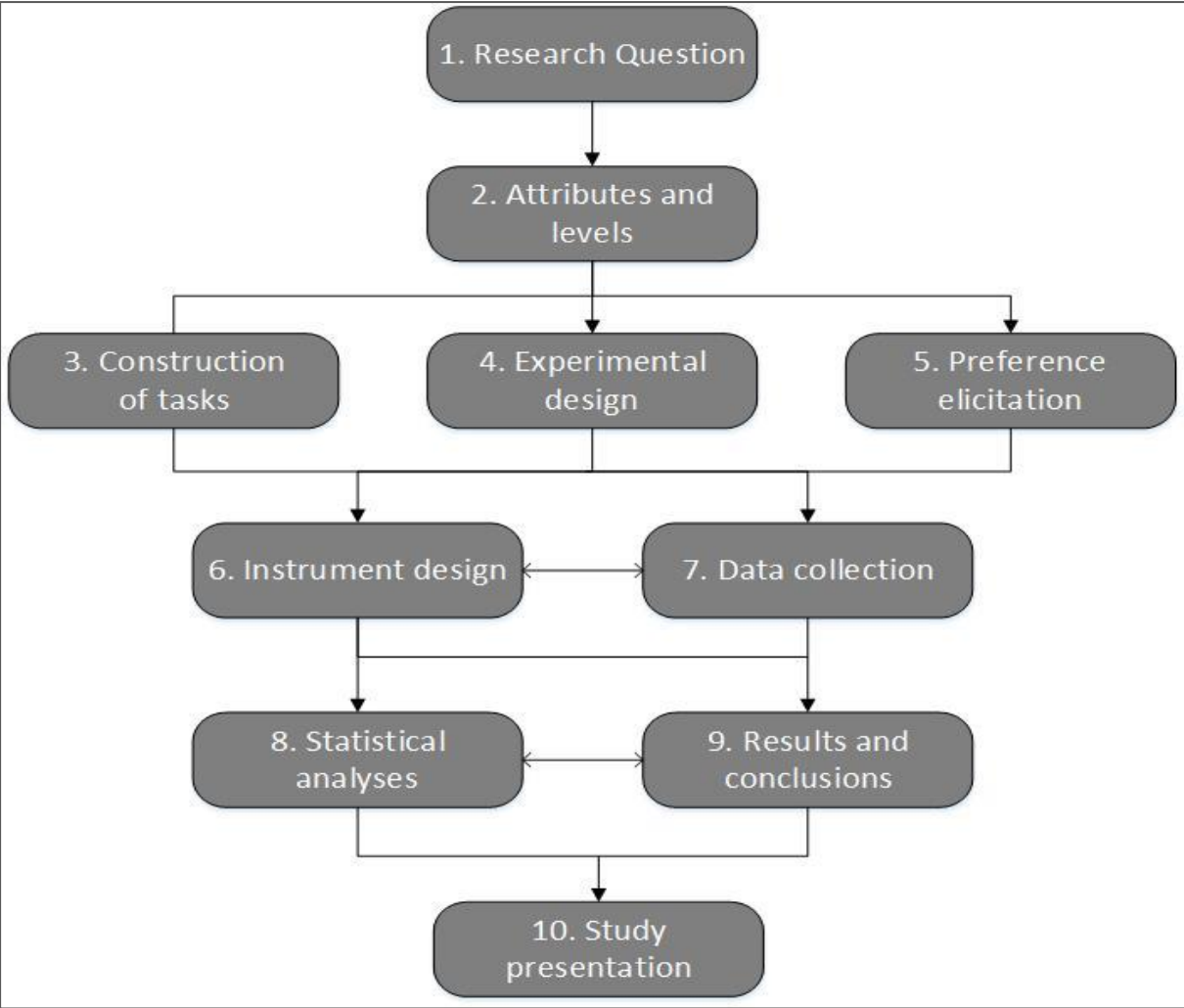
Source: Bridges et al, 2011.[207]

Selection of discrete choice tasks and statistical efficiency

Traditional methods of calculating the minimum sample size for DCEs are based on sampling theory, so as to provide confidence intervals around the choice probabilities based on a level of acceptable error.[213] The number of choice sets offered each participant, the number of attributes in each choice set and the number of attribute levels all affect the estimation precision of the parameters and therefore directly influence the minimum number of participants required.[214] In 2013, the ISPOR Good Research Practices for Conjoint Analysis Task Force published guidance on the construction of DCEs which focused on the overall statistical efficiency of the experimental design.[206] Efficient experimental designs maximize the precision of estimated choice-model parameters without imposing an impracticably large number of choice questions on participants.[206] For example, if a discrete choice study

investigates the preferences of four attributes and each attribute has three levels, there would be 3^4 [=81] possible profiles, and 3240 possible combinations of choice questions with two alternate options [3^4 x (3^4-1)/2].

The design of a DCE is considered efficient if the design yields data that enables the parameters to be estimated while minimising the standard error.[215] The most commonly used metric to measure for inefficiency is the *D-error* which is a function of the experimental design, the probability distributions and the number of parameters to be estimated.[216] For this research study, 24 binary choice sets were generated using Ngene® software, in accordance with a D-efficient design (the lowest possible *D-error*).[215] Ngene® was also utilised to divide the resulting 24 choice sets into three blocks of eight discrete choice sets. Optimal DCE designs must limit the burden on participants by not including too many tasks, which ensuring there are sufficient tasks to be statistically efficient.[216] The number of choice tasks included in the survey for each participant was 17, two DCEs containing eight choice tasks plus a fixed task.

Test for non-attendance

A number of tests have been published in the literature that test the validity and reliability of DCEs.[217] Responses of inattentive or unengaged respondents in DCEs can lead to biased or imprecise estimates.[218] Choice validity examines whether participants engage with the choice task as expected based on assumptions about their usual behaviour. Tests for task non-attendance investigate whether participants are actively engaged in the task, and may identify if a task is too cognitively burdensome, or if not sufficiently realistic resulting in inattention to the questions. [217] Dominant choice tests are the most commonly applied test in DCEs to assess the rationality in the choice behaviour of survey participants.[219] All participants are assigned the same choice task, where one of the two alternatives is clearly superior. Participants who fail to select the dominant choice are considered to have failed the test and are excluded from the final analysis.[219] There is an alternative argument that the dominant-choice test for non-attendance should not necessarily exclude participants who fail the test, as a proportion may be expected to fail the test due to random error.[220] The inclusion of a dominant choice task however allows the analysis to be conducted with or without the inclusion of responses from those participants who may not have been fully attentive to all the choice tasks.[219]

DCE analysis: Random Utility Framework and conditional logit modelling

The framework of random utility theory assumes that an individual, when faced with a choice between two or more alternatives, will select the option that maximises their utility.[221] The utility associated with the alternative selected is assumed to be a function of observed characteristics influencing choice as well as a random component (hence the term 'random utility').[209] McFadden (1974) demonstrated that conditional logit was consistent with random utility theory and can be applied to preference data involving hypothetical or stated choices.[209]

The random utility framework assumes that a participant i maximises their utility when choosing between j alternatives.[221]

For this research, a conditional logit model was applied to the preference data to investigate preferences for a new antimicrobial:

$$logit(V_{ij}) = \beta_1 spectrum_{ij} + \beta_2 price_{ij} + \beta_3 novel_{ij} + \beta_4 route_{ij} + \beta_5 PBS_{ij} + \beta_6 Patcopay_{ij} + \varepsilon_{ij}$$

where $i = 1,…, I$ participants

$j = 1,…, J$ choices

V_{ij} = the utility that participant i obtains from choosing alternative j

X_j = attributes of choice j

β = preferences for observed choice attributes

ε_{ij} = random ('unexplained') component of the utility associated with any choice j for participant i

The error term, ε_{ij}, captures the unobserved characteristics or influences on the participant's choice. In some situations, a participant's choice may truly be random, or they may not be fully aware of the benefits or otherwise of each attribute.[221]

The conditional logit model has two main limitations:[209]

· The model assumes that the choice tasks measure utility equally well across all participants and all choice tasks; and

- The model does not account for unobserved systematic variation in preferences between survey participants (preference heterogeneity).

Sensitivity analysis – mixed logit model

Mixed Logit models may overcome the limitations of conditional logit models by avoiding potential estimation bias from unobserved preference heterogeneity between respondents by estimating a distribution of preferences for each preference parameter.[222] Mixed Logit models however may not always provide comprehensive information on preference heterogeneity, and running separate conditional logit models for different subgroups (for example, comparing pharmacists and infectious disease specialists) can also identify differences in preferences by establishing whether attributes appear to be valued differently by different groups of participants.[223] It is then possible to observe whether the range of statistically significant variables differs between the groups, and the differences in the point estimates for attribute coefficients.

Marginal rates of substitution

Trade-offs between attributes in a DCE are calculated by the negative of the ratio of any two coefficients. When the cost is included as the denominator in trade-off calculations, marginal willingness-to-pay can be estimated.[224]

Inclusion of multiple-choice questions as an additional preference elicitation method

Different elicitation methods have been shown to sometimes result in preference reversal for both health and financial outcomes. Different elicitation methods have been shown to sometimes result in preference reversal for both health and financial outcomes.[225, 226] DCEs are a multi-attribute stated preference method to estimate value for the utility of the attributes, and the marginal rates of substitution, that is, the attribute values relative to one another. Participants are required to consider multiple competing attributes simultaneously in a DCE. In contrast multiple-choice questions are less complex, focussing on just a singular question. Two static, multiple-choice questions, were included in the survey to substantiate the findings of the DCE.

Ethics

This research involved collaboration with researchers from the University of Adelaide, the Central Adelaide Local Health Network and Monash University.

Ethics approval for the analysis of Special Access Scheme applications from the Southern Adelaide Local Health Network and the Central Adelaide Local Health Network was obtained from the Human Research Ethics Committees (HREC) of the following institutions:

- The Central Adelaide Local Health Network (Ethics Approval R20171210 HREC/17/RAH/570) (Appendix 1)
- The University of Adelaide (Ethics Approval No 32651)

No patient or prescriber names or other identifying characteristics were collected in the data collection process.

For the semi-structured interviews and the online survey (for dissemination of the Discrete Choice Experiments), ethics approval was obtained from the University of Adelaide HREC (Ethics Approval No H-2018-136) (Appendix 1). Interview participants were provided with a Participant Information Sheet (Appendix 2) and Signed Informed Consent (Appendix 3) was obtained from all participating interviewees. Signed consent forms will be retained securely in accordance with the University of Adelaide data management policy.

Participants of the online survey were also provided with a Participant Information sheet (Appendix 6), which was circulated with the email invitation to participate. Consent to participate was obtained electronically on the first page of the online survey.

Chapter synopsis

This chapter has provided details of the sequential mixed-methodology utilised in this thesis. Multiple data collection strategies were used to address the research questions, providing different perspectives and strengthening the conclusions made. The sequential approach allowed findings to inform and expand subsequent studies. In particular, the qualitative data

collected via the semi-structured interviews provided in depth insight into the perspective of both policy-makers and the pharmaceutical industry, which was incorporated into the discrete choice experiment / online questionnaire distributed to healthcare practitioners.

The following chapters include the results obtained from each of the studies, provided in the format in which they were published.

CHAPTER FOUR

The unmet need: Quantifying the utilisation of unregistered antimicrobials in Australia

Preface

This chapter contains the text, tables, figures and appendices from the initial publication contributing to this thesis. Published in *Infection, Disease and Health*, this pharmaco-epidemiological study utilised three data sources to estimate the utilisation of antimicrobial drugs not registered for use within Australia. This paper provides policymakers with a greater understanding of the proportion of clinical practice where unregistered antimicrobial drugs fulfil the unmet need.

Publication

Hillock NT, Karnon J, Turnidge J, Merlin T (2019). Estimating the utilisation of unregistered antimicrobials in Australia. *Infection, Disease & Health*. 25(2): 82-91. doi:10.1016/j.idh.2019.12.001

Available at: https://pubmed.ncbi.nlm.nih.gov/31911133/

Statement of Authorship

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Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Hillock NT, Karnon J, Turnidge J, Merlin TL (2020). Estimating the utilisation of unregistered antimicrobials in Australia. *Infection, Disease & Health.* 25(2): 82-91

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Contribution to the Paper	Designed the study, collected the data and performed the analysis, interpreted the data and drafted the manuscript
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 14/5/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature	Date 25/5/2022

Abstract

Objective: To identify and estimate the usage of unregistered antimicrobial drugs in Australian clinical practice.

Design, setting: A descriptive pharmaco-epidemiological study, utilising three data sources: analysis of Special Access Scheme (SAS) applications over a five year period for unregistered antimicrobials included in clinical guidelines, analysis of antimicrobials dispensed from South Australian public hospital pharmacy departments over a two year period and analysis of National Antimicrobial Utilisation Surveillance Program data for reported inpatient usage of unregistered antimicrobials in Australian hospitals over 5 years.

Results: 59 unregistered antimicrobials were identified using the mixed methods. 18,362 Special Access Scheme applications were submitted between May 2012 and April 2017 to access the 20 unregistered antimicrobials identified in the *Therapeutic Guidelines*® (*eTG complete*); 51.4% were determined by the prescriber to be for life-threatening indications. Annual applications more than doubled over the five years. 34 unregistered antimicrobials were dispensed from South Australian public hospitals between July 2015 and June 2017. On average, 1.1% of total antimicrobial usage (Defined Daily Doses) per month was accessed via the SAS, of which 87.7% were for outpatients or discharged patients. 34 unregistered antimicrobials for systemic use identified in the NAUSP database were used in Australian hospitals between 2013 and 2018.

Conclusions: The use of unregistered antimicrobials in Australian clinical practice is not uncommon. With increasing antimicrobial resistance, there will be a continued reliance on older less-used antimicrobial agents and an increasing need for novel drugs. Regulatory pathways need to facilitate security of supply and assurance of medicine quality and safety.

Highlights

- Applications to the Therapeutic Goods Administration to access unregistered antimicrobial drugs are increasing

- The usage of unregistered antimicrobial drugs is not uncommon in clinical practice in Australia

- A high proportion of unregistered antimicrobials dispensed from public hospitals are used in the outpatient setting

- Unregistered drugs are not eligible for federal funding on the Pharmaceutical Benefits Scheme

- The current regulatory framework in Australia may be a disincentive to research and development of new antimicrobials

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Introduction

There is a revival of antibiotic research and development worldwide in response to the *Global Action Plan on Antimicrobial Resistance* published by the World Health Organization (WHO), which highlighted the need for sustainable investment in new antimicrobials as part of the global strategy to combat resistance.[9] Despite substantial global investment in the development of new antimicrobials, regulatory obstacles have been identified as a disincentive to manufacturers, including the notable lack of regulatory alignment between countries.[169, 173] With increasing antimicrobial resistance, the therapeutic importance of older "forgotten" antimicrobial products is also recognised, many of which have never been or are no longer registered in Australia.[102, 142, 227, 228] The application and evaluation fees for registration of prescription medicines are a disincentive for manufacturers, particularly for those with low volume of use.[229] For older low-priced generic antimicrobials with relatively low utilisation, the annual fees required to maintain registration may make it economically unviable for companies to maintain registration.

In Australia, there is provision in the *Therapeutic Goods Act 1989* for unregistered medicines to be imported and prescribed on an individual patient basis through a Special Access Scheme (SAS) of the Therapeutic Goods Administration (TGA).[91] Prescribing of unregistered

therapeutic products, which have not been evaluated for efficacy, safety or quality by the TGA, increases the liability and administrative burden on the prescriber. Unregistered products are not publicly funded on the Pharmaceutical Benefits Schedule (PBS) in Australia, nor are they usually funded by private insurers, increasing the risk that a patient may not be able to access the treatment outside the public hospital setting. For some products, there may be no Australian sponsor or company willing to act as the agent, increasing the risk that access to the drug may be delayed or not possible.

This study aimed to identify and estimate the current utilisation of unregistered antimicrobials in Australia, including those recommended in commonly-used clinical practice guidelines.

Methods

As no dataset is available to directly quantify the utilisation of unregistered antimicrobials Australia-wide in both the hospital and the community settings, a triangulation of three datasets was used to estimate the current usage of these drugs in Australian clinical practice. A sequential analysis was undertaken including identification of unregistered antimicrobials in clinical guidelines, analysis of SAS applications over 5 years, analysis of antimicrobials dispensed from South Australian public hospitals over a two-year period, and finally analysis of hospital inpatient utilisation across Australia over the last five years.

- The online *Therapeutic Guidelines* [©] (*eTG Complete*) was systematically reviewed to identify all clinical indications that included antimicrobials not registered on the Australian Register of Therapeutic Goods (ARTG) for use within Australia as at 6th August 2017.[230] Guidelines directly referred to from within the *eTG Complete* were also reviewed.

- For each unregistered antimicrobial identified in the *eTG Complete*, data on the number of applications submitted to the TGA for unregistered antimicrobials for individual patient use for the period May 2012 to April 2017 were retrieved from the custodians of the Special Access Scheme (SAS) at the Commonwealth Department of Health via a *Freedom of Information* request.

- De-identified antimicrobial utilisation data was retrieved from all South Australian (SA) metropolitan public hospitals and regional SA hospitals with greater than 50 beds. Inpatient, outpatient and discharge data was included to identify unregistered systemic antimicrobials dispensed or distributed from the hospital pharmacies. To calculate the relative proportion of all antimicrobials used that were unregistered, stock units were converted to the number of Defined Daily Doses (DDDs) as defined by the World Health Organization (WHO).[2] The proportion of total DDDs used that were unregistered products (or manufactured from unregistered products) was calculated on a monthly basis over a two-year period. Paediatric use was excluded from the DDD analysis as standard daily doses have not been defined for paediatric patients.

- To identify unregistered antimicrobials used in Australian hospitals, antimicrobials included in the database of the National Antimicrobial Utilisation Surveillance Program (NAUSP) were cross-checked against the Australian Register of Therapeutic Goods (ARTG) to determine registration status within Australia.[195] Annual utilisation rates (DDDs per 1000 occupied bed days) for the unregistered antimicrobials were extracted for the five year period 2013-2018. NAUSP does not include unregistered topical agents, anti-malarial, anti-tubercular or anti-helminthic drugs.[124] Paediatric, rehabilitation and psychiatric data are excluded from NAUSP, as well as day procedure wards and outpatient usage.[124]

The scope and limitations of each data source is shown in table 4.1. By triangulating the data sources we aimed to determine the extent of unregistered antimicrobial utilisation and if there was consistency in usage trends across the health sector.

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[2] https://www.whocc.no/atc_ddd_index/

Table 4.1: Scope and limitations of each dataset

	Special Access Scheme	South Australian Public Hospital Pharmacy Data	National Antimicrobial Utilisation Surveillance Program
Healthcare sector	Australia-wide (All sectors: i.e. public & private hospitals and community)	South Australian public hospitals	Australia-wide, public & private hospital inpatients, partial coverage (participation is voluntary)
Time period	May 2012 - April 2017	July 2015 - June 2017	Jan 2013 - Dec 2018
Metric	Count data (no. of applications)	Volume (total DDDs)	Rate (DDDs/1000 overnight bed days)
Other limitations	Data retrieved only for unregistered drugs identified in the eTG. Name of drug and number of applications only - no data on volume of use	Paediatric & neonatal excluded from analysis of systemic use (included for topicals only)	Paediatric, psychiatric and rehabilitation beds excluded. Anti-tubercular, anti-parasitic and anti-malarials excluded. For some antimicrobials DDDs do not align with usual Australian dosing regimens

Results

A total of 59 unregistered antimicrobials were identified either as recommendations in the *eTG Complete* or included in South Australian public hospital pharmacy dispensing data, or in the NAUSP database (Table 4.2).

Table 4.2: Unregistered antimicrobials used in Australia

Unregistered antimicrobial	Route of administration	Included in Therapeutic Guidelines: Complete® (as at August 2017)[e]	Dispensed from South Australian public hospital July 2015-June 2017	In NAUSP database with reported usage (2013 - 2018)
Amikacin	Nebulised (liposomal)	No	No	Yes
Amphotericin (conventional)	IV	Yes	Yes	Yes
Amphotericin cholesterol sulphate (lipid complex)	IV	No	No	Yes
Artesunate	IV	Yes	Yes	No
Bedaquilline	Oral	No	Yes	No
Bithionol	Oral	Yes	No	No
Boceprevir	Oral	No	No	Yes
Ceftazidime – avibactam[a]	IV	No	No	Yes
Ceftolozane – tazobactam[b]	IV	No	No	Yes
Chloramphenicol	Oral	No	Yes	Yes
Chloroquine phosphate	Oral	No	Yes	No
Cidofovir	IV	No	Yes	Yes
Clindamycin solution^	Oral	No[g]	Yes	No[h]
Clofazamine	Oral	Yes	Yes	No
Cycloserine	Oral	No	Yes	No
Dasabuvir	Tablets	No	Yes	No
Demeclocyline	Oral	No	Yes	No
Diethylcarbamazine	Oral	Yes	No	No
Doripenem	IV	No	No	Yes
Doxycycline hyclate	IV	Yes	Yes	Yes
Faropenem	Oral	No	No	Yes
Flucytosine	Oral	Yes	Yes	Yes
Fosfomycin[c]	Oral	Yes	Yes	Yes
Fosfomycin	IV	No	Yes	Yes
Fumagillin	Oral	Yes	No	No
Fusidic acid suspension[g]	Oral	No[g]	Yes	No[h]
Ketoconazole	Oral	No[i]	Yes	Yes
Isavuconazole[d]	Oral	No	No	Yes
Isavuconazole[d]	IV	No	No	Yes
Itraconazole	IV	No	No	Yes
Levofloxacin[f]	Oral	Yes	Yes	Yes
Levofloxacin	IV	No	No	Yes
Miltefosine	Oral	No	Yes	No
Minocycline	IV	No	No	Yes
Moxifloxacin	Eyedrops	No	Yes	No
Natamycin	Eyedrops	No	Yes	No
Niclosamide	Oral	Yes	No	No
Nitazoxanide	Oral	Yes	Yes	No

Oritavancin	IV	No	No	Yes
Paromomycin	Oral	Yes	Yes	No
Paromomycin	Ointment	No	Yes	No
Peramivir	IV	Yes	No	No
Pivmecillinam	Oral	Yes	No	Yes
Polymyxin B	IV	No	No	Yes
Pristinamycin	Oral	No	Yes	Yes
Prothionamide (Protionamide)	Oral	No	Yes	No
Pyrazinamide	Oral	Yes	Yes	No
Quinupristin with Dalfopristin	IV	No	No	Yes
Ribavirin	IV	No	Yes	Yes
Simeprevir	Oral	No	No	Yes
Spiramycin	Oral	No	Yes	Yes
Streptomycin	IM	Yes	No	Yes
Sulfadiazine	Oral	Yes	Yes	No
Telaprevir	Oral	No	No	Yes
Tetracycline[f]	Oral	Yes	Yes	Yes
Triclabendazole	Oral	Yes	Yes	No
Trimethoprim	IV	No	Yes	No
Zanamivir	IV	Yes	No	Yes
Zidovudine	IV	No	Yes	Yes

Note: Colloidal bismuth subcitrate is active against *Helicobacter pylori*, however it has been excluded as it is not categorised as an anti-infective by the WHO

a.   Ceftazidime/avibactam was listed on the Australian Register of Therapeutic Goods in Feb 2019
b.   Ceftolozane/tazobactam was listed on the Australian Register of Therapeutic Goods in Feb 2019
c.   Fosfomycin (oral) was listed on the Australian Register of Therapeutic Goods in Sept 2017
d.   Isavuconazole (IV and oral) was listed on the Australian Register of Therapeutic Goods in May 2019
e.   Review of *eTG Complete* was undertaken prior to the release of *eTG: Antibiotic (v16)* in April 2019
f.   Included in eTG: Gastrointestinal
g.   Oral dosage form referred to in eTG but not specifically the unregistered proprietary product (capsules registered from which an extemporaneous product can be prepared)
h.   NAUSP data cannot distinguish between proprietary products and extemporaneously-prepared products
i.   Oral ketoconazole in the eTG: Bone and Metabolism guidelines for a non-infectious indication.

The review of the *eTG Complete* online identified a total of 20 unregistered antimicrobials recommended for the treatment of 26 indications (S1, Supplementary data). The 20 unregistered antimicrobials were recommended in either the *Antibiotic* (version 15, 2014) or the *Gastrointestinal* (version 6, 2016) guidelines of the *eTG*, or in guidelines provided by direct link from the *eTG*.[3] Five of the 21 antimicrobials identified in the *eTG Complete* were

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[3] Oral ketoconazole was included in the Bone & Metabolism guidelines for treatment of a non-infectious indication. This was excluded from the analysis of SAS applications.

not found in the SA public hospital dataset, nor was there any usage reported to NAUSP between 2013 and 2018 (Table 4.2).

There were 18,362 SAS applications to access the 20 unregistered antimicrobials recommended in the *eTG Complete* over the five-year period to April 2017 (Table 4.3). No applications were made for three of the 20 unregistered antimicrobials. The median number of total applications for the remaining 17 drugs was 215 over the five years (IQR: 910). Available data were limited to the date of application, the drug requested and under which SAS category the clinician applied for access. The four antimicrobials with the most applications to access via the SAS were pyrazinamide, tetracycline, fosfomycin and levofloxacin respectively.

Table 4.3: Number of applications via SAS (May 2012 - April 2017) for unregistered anti-infective drugs recommended in the eTG complete.

Unregistered antimicrobial	Number of Category A applications (%)	Number of Category B applications	Total
Amphotericin B desoxycholate	4 (100)	0	4
Artesunate	163 (99.4)	1	164
Bithionol	0	0	0
Clofazimine	442 (47.3)	492	934
Diethylcarbamazine	3 (60)	2	5
Doxycycline (IV)	340 (51.1)	325	665
Flucytosine (oral)	431 (90.0)	48	479
Fosfomycin*	2887 (89.4)	341	3228
Fumagillin	0	0	0
Levofloxacin	139 (14.2)	2840	2979
Niclosamide	5 (19.2)	21	26
Nitazoxanide	370 (45.7)	440	810
Paromomycin	24 (100)	0	24
Peramivir	0	0	0
Pyrazinamide	4151 (80.1)	1030	5181
Streptomycin	16 (94.1)	1	17
Sulfadiazine	156 (72.6)	59	215
Tetracycline	259 (7.2)	3318	3577
Triclabendazole	28 (71.8)	11	39
Zanamivir (IV)	15 (100)	0	15

* Fosfomycin (oral) was listed on the Australian Register of Therapeutic Goods on the 4th Sept 2017

Note: Colloidal bismuth subcitrate is active against *Helicobacter pylori*, however it was excluded as it is not categorised as an anti-infective by the WHO (There were 6020 applications to access colloidal bismuth subcitrate)

Prior to July 2017, applications to access unregistered antimicrobials were categorised as either Category A, for "persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment", or Category B, for all other

patients who do not fall into category A. 51.4% (9433) of the applications were determined by the prescriber to be for life-threatening indications. Annual applications to access all unregistered antimicrobials recommended in the *eTG complete* increased by 144.5% over the five-year period to April 2017 (Figure 4.1). Annual pyrazinamide applications more than doubled (an increase of 104%), fosfomycin applications increased by 705% and clofazimine by 237% over the five-year period.

Figure 4.1: Number of individual applications to access unregistered antimicrobials via the Special Access Scheme May 2012 – April 2017
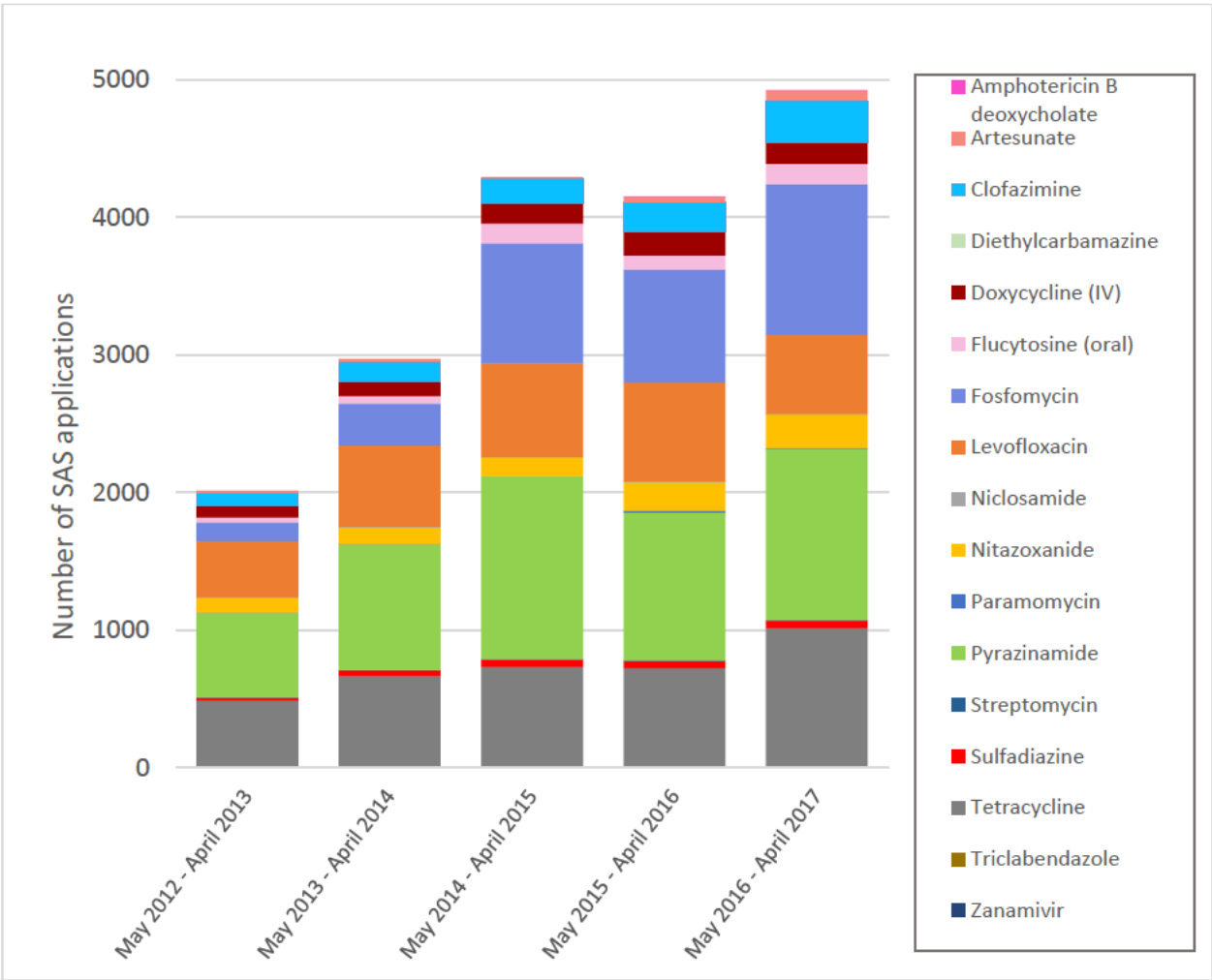
34 unregistered antimicrobials (unique antimicrobial and dosage form) were dispensed from South Australian public hospitals for inpatients, outpatients or on discharge, in the two-year period July 2015 to June 2017 (Table 4.2). On average, 1.1% of the total antimicrobial usage per month was accessed via the Special Access Scheme (Figure 4.1). Recent antimicrobial shortages were reflected in the marked increase in unregistered antimicrobials accessed via

section 19A[4] of the *Therapeutic Goods Act 1989* which allows for importation of unregistered substitute stock (Figure 4.2). Of the total usage of unregistered products accessed via SAS, 87.7% was for treatment of outpatients or on discharge. Total pristinamycin usage increased 7.7%, from 5219 DDDs between July 2015 – June 2016, to 5620 DDDs between July 2016 – June 2017, with 95.0% being used for outpatients. 162 stock units of unregistered topical antimicrobials were accessed via the SAS in the two-year period.

Figure 4.2: Unregistered antimicrobials dispensed from South Australian hospital pharmacies, July 2015 – June 2017 (Excluding paediatric data)
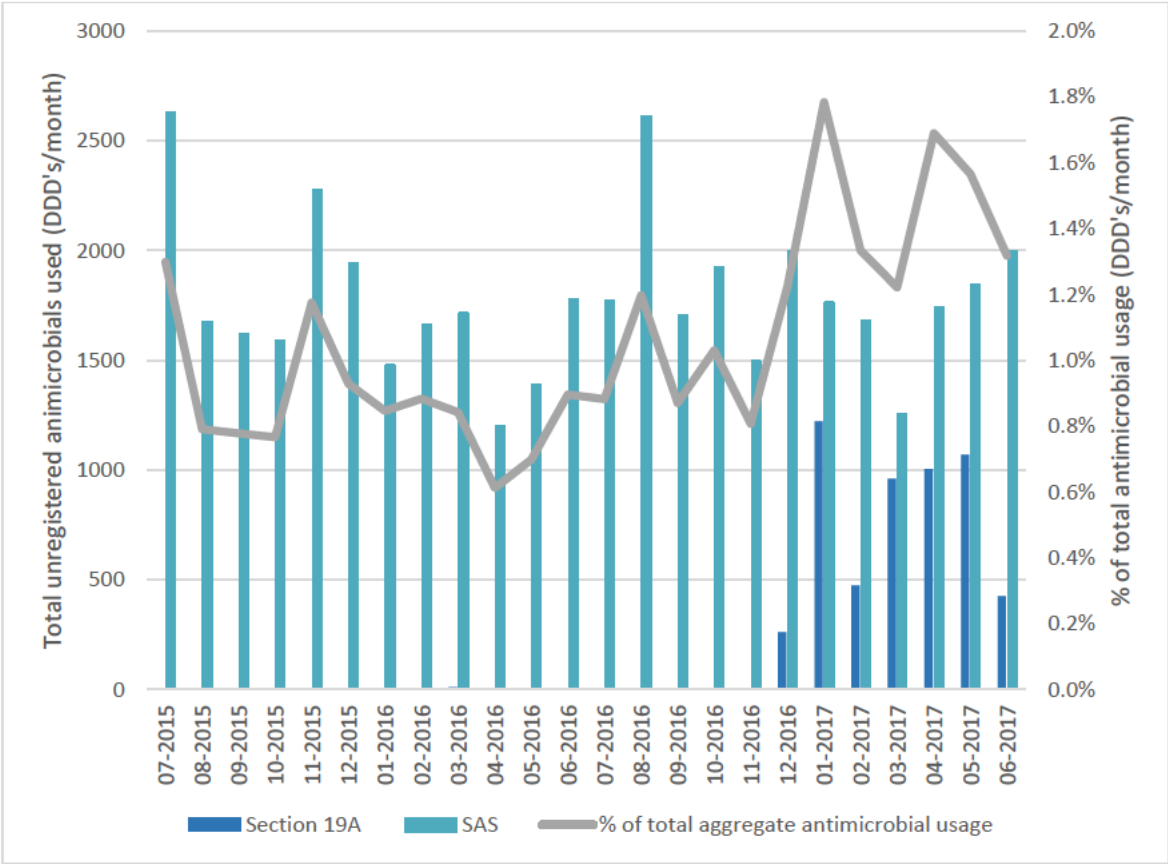
(Note: Section 19A = Provision in the Therapeutic Goods Act 1989 allowing supply of unregistered medicine to replace a registered medicine that is unavailable or in shortage)

There were 34 unlicensed proprietary antimicrobial products for systemic use (unique antimicrobial and dosage form) identified in the NAUSP database that were used in

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[4] Section 19A of the Therapeutic Goods Act 1989 allows a company to import an unregistered medicine to replace a medicine in shortage. More information: https://www.tga.gov.au/publication/section-19a-guidance-industry. This differs from importing through SAS, which on a per patient basis.

Australian hospitals between 2013 and 2018 (Table 4.2). Although the aggregate total-hospital usage rate for unregistered antimicrobials in hospitals contributing to NAUSP is relatively low, the rate is trending upwards in the last few years (Figure 4.3). In 2018, the total annual aggregate usage rate for all unregistered antimicrobials in the NAUSP was 1.25 DDDs per 1000 OBDs, up from 1.00 in 2017.

Figure 4.3: Annual aggregate total-hospital usage rate for unregistered antimicrobials 2013 - 2018

Annual total-hospital use of unregistered antimicrobials in NAUSP database 2013 -2018

[Note: NAUSP data excludes antitubercular, antimalarial & antihelminthic drugs]
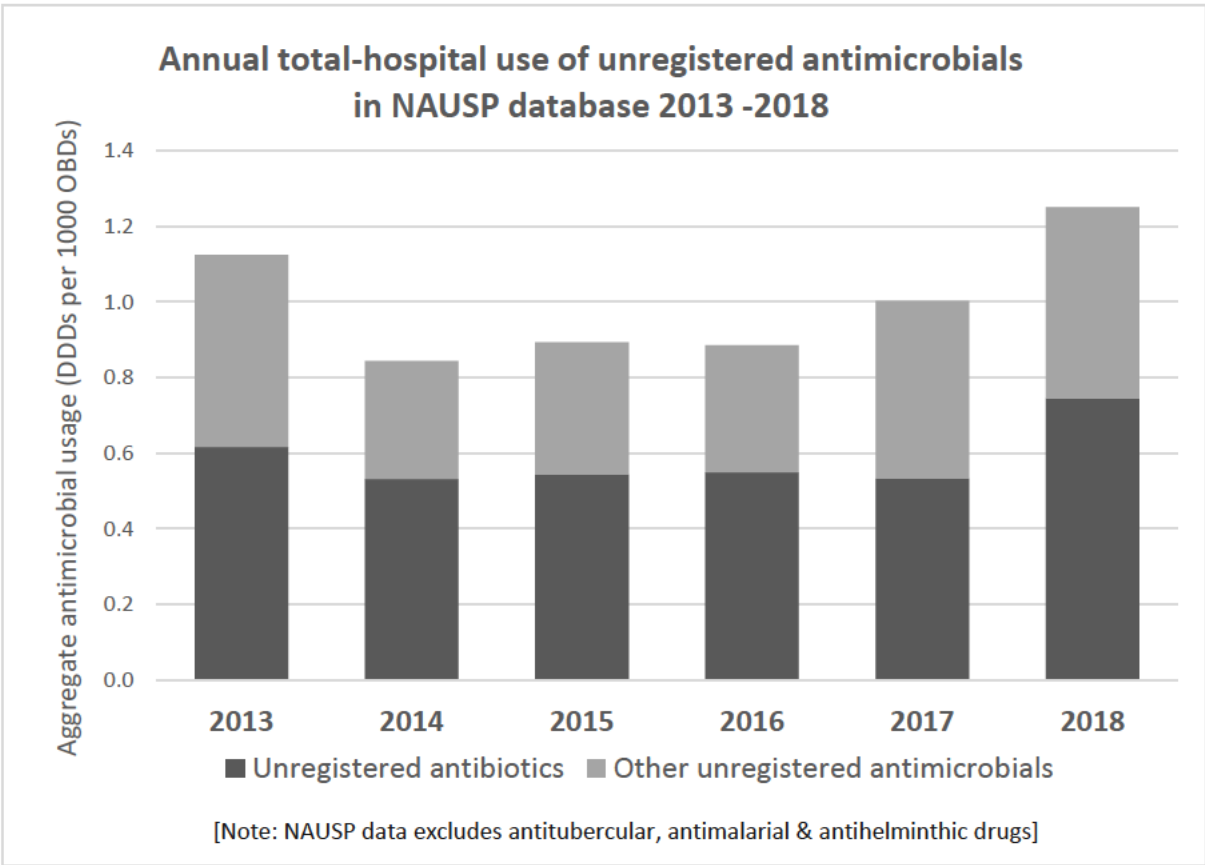
Source: National Antimicrobial Utilisation Surveillance Program (NAUSP)

Discussion

No single database contains comprehensive data on the utilisation of unregistered antimicrobials in Australia. Each of the three data sources used to estimate the utilisation had limitations (Table 4.1), and linking the three datasets was challenging due to the different methods of measurement: the SAS data is count data, the SA Pharmacy data was total volume (total DDDs) and the NAUSP data was measured as a rate (DDDs / 1000 OBDs).

Tabulation of all 59 identified unregistered antimicrobials (unique drug and route of administration) illustrated the variation in data captured across each source (Table 4.2) Drug registrations have occurred during the time-period of this study (Table 4.2, footnotes); oral fosfomycin was registered in September 2017, and was notably the antimicrobial with the greatest increase in annual SAS applications in the five years to May 2017, increasing by 705%.

Guideline recommendations evolve as new evidence becomes available and with consideration to antimicrobial resistance epidemiology. 20 unregistered antimicrobials were included in the *eTG Complete* as at August 2017; a revised version of the *eTG: Antibiotic* (version 16) was released in April 2019 and a subsequent analysis identified 22 unregistered antimicrobials in the *eTG Complete* as at July 2019 (S2, supplementary data), many of which were recommended as first or second line treatment. The annual number of SAS applications to access the antimicrobials in the *eTG Complete* increased by 144.5% over the five-year period. However, analysis of comprehensive state-wide utilisation data from South Australian public hospitals over a two-year period did not indicate a significant increase in the proportion of total antimicrobial usage that was accessed through the SAS. This suggests that the increasing number of SAS applications has been from states other than South Australia, the reason for this is unclear. It was not possible to obtain information on the state or territory from which applications were made as prior to July 2018 the SAS data collection was not automated. Although the rate of unregistered antimicrobial use in the NAUSP database has trended upwards in recent years, it is not clear whether this is due to an increase in absolute numbers or a reflection of increased doses. Data on clinical indications or doses for the SAS applications were also unavailable via the freedom of information request.

Although not an objective of this study, analysis of the SA Pharmacy data highlighted the increased use of unregistered generic antimicrobials in 2016, imported to replace registered products in short supply. An alternative pathway to access medicines not registered in Australia is under section 19A of the Therapeutic Goods Act 1989, which allows a company to import an unregistered medicine to replace a medicine in shortage. The medicines imported via section 19A must be therapeutically equivalent to an already registered

product. This differs from importing unregistered medicines via the Special Access Scheme, which is on an individual patient basis.

With increasing global focus on research and development of urgently needed new antimicrobials, it is essential that regulatory pathways and access to public funding adapt to accommodate the unique attributes of this group of medicines to ensure timely access in clinical practice while limiting excess or inappropriate use. Notably 87.7% of the total volume of unregistered antimicrobials (total DDDs) dispensed from SA public hospitals over two years was for outpatients. Some unregistered oral antimicrobials such as pristinamycin are increasingly used to treat chronic infections such as prosthetic joint infections as a step down to oral treatment for discharge, when the infection is caused by organism(s) that is resistant to other oral options.[231] Although the cost is usually covered by the public hospitals, because unregistered medicines are not funded on the Pharmaceutical Benefits Scheme, this potentially causes inequity of access in private hospitals and the community sector.

The TGA evaluates medicines prior to registration to ensure not only that they are clinically safe, but that they comply with Good Manufacturing Practice. Once registered, medicines are monitored with a number of product vigilance tools to identify any potential or emerging safety risks and there are requirements for medicine sponsors to provide periodic benefit-risk evaluation reports and comply with Australian requirements for labelling and quality control.[84] This does not happen for unregistered medicines.

The reasons for a medicine not being registered in Australia may include either a lack of evidence regarding the clinical efficacy or safety of the medicine in a particular condition (including medicines undergoing clinical trials), the lengthy regulatory evaluation process is already underway for the product, or the manufacturer has either withdrawn or not sought registration in Australia for economic reasons.[232] For example, tetracycline was previously registered in Australia, but the relatively low usage, the low price and the regulatory fees to maintain registration in Australia, make it economically unviable to a manufacturer. Unregistered antimicrobials are often used to treat rare indications where the expected incidence is low. The 'orphan drug' regulatory pathway designed to treat small patient populations, waives the application, evaluation and ongoing regulatory fees.[233] Regulators

have strict eligibility criteria for orphan status however, and new antimicrobials would not meet the requirement of filling an unmet need until resistance to all current antibiotics occurs, a status that cannot be easily predicted. Regulatory pathways for old and new antimicrobial products need to facilitate access and provide security of supply as well as provide prescribers and patients with assurance of medicine quality and safety. Regulatory barriers have been cited as a disincentive for manufacturers to invest in antimicrobial development, particularly for drugs targeting resistant pathogens and narrow-spectrum indications which are the areas of greatest unmet medical need.[43, 171]

Changes were made to the Special Access Scheme in July 2017, with the establishment of a new access pathway (Category C) for medicines deemed to 'have an established history of use' [234]. Pyrazinamide for the treatment of tuberculosis was an example of an unregistered antimicrobial that not only has an 'established history of use', but is a recommended first-line treatment. Although endorsement of the indications in the new category suggests TGA support for the use of these medicines for specified indications, without full regulatory approval the quality and availability of these products is not assured. In addition, unregistered products cannot be included in the TGA monitoring of short supply therefore there is no method of knowing the availability in advance.

The need to improve access to older, clinically-useful antibiotics in Australia has been highlighted previously.[93] In light of the significant unmet need for old and new drugs with activity against highly drug-resistant bacterial pathogens, regulatory bodies internationally are reviewing their policies regarding their evaluation of antibacterial agents for regulatory purposes.[173, 235, 236]

The collection of clinical outcomes of patients treated with unlicensed antimicrobials is not a requirement of use through the Special Access Scheme, however this is a potential missed opportunity to contribute to the evidence base, especially for rarer indications or for medicines which have been marketed internationally through an expedited pathway. Not only could safety be monitored, but independent data gathering and analysis by regulators could be used to expand indications, or provide clarity where there is uncertainty due to the small numbers in pre-marketing trials. Managed entry agreements, with or without prospective outcome monitoring, are used in other areas of medicine (e.g. oncology) as a

method of balancing the risk of providing earlier reimbursed entry into the market against any uncertainty regarding efficacy, effectiveness or safety. Real world data collection could reduce this uncertainty.

This study indicates that the use of unregistered antimicrobials is not uncommon in Australia. Very few new antibiotics have been registered by the TGA and none funded by the Pharmaceutical Benefits Scheme in the last 10 years. Significant global monetary investment is now reviving research into the discovery of new antimicrobial compounds [42], but there is a need for governments to consider feasible more adaptive regulatory pathways for new, and especially old or infrequently used, antimicrobials. While there is uncertainty regarding the future regulation and funding of antibiotics, industry will likely remain wary of investing in the development of new drugs. The slow development of new antimicrobials, especially orally bioavailable ones, means that there will continue to be strong reliance on older, currently unregistered antimicrobials for which funded timely and equitable access to quality products is not assured.

Ethics: This research was considered to be negligible risk research and exempt from HREC review as it satisfied both the conditions of: 'It is negligible risk research: there is no foreseeable risk of harm or discomfort and any foreseeable risk is no more than inconvenience' and 'It involves the use of existing collections of data or records that contain only non-identifiable data about human beings'.

Conflicts of Interest: The authors have no conflicts of interest to declare associated with this paper.

<div align="center">*****End of published paper*****</div>

Chapter synopsis

The findings of this chapter have demonstrated that there is increasing use of unregistered antimicrobials in clinical practice in Australia. Unregistered products are accessed to treat patients when available registered products are inappropriate or ineffective for the clinical

condition. These results illustrate that there is a growing unmet need for effective and appropriate registered antimicrobials, particularly in the public hospital setting.

The following chapter further explores this unmet need, to determine the clinical scenarios where unregistered antimicrobials are predominantly used.

CHAPTER FIVE
Further exploration of the unmet need: Clinical conditions
treated with unregistered antimicrobials

Preface

This chapter contains the text, tables, figures and appendices from the second publication contributing to this thesis. Published in *Australian Health Review,* the aim of this study was to expand on the previous study and gain a greater understanding of the range of clinical indications for which unregistered antimicrobials are prescribed. The study setting was two large tertiary hospitals in Adelaide, and data was retrospectively reviewed for a two-year period. In addition to identifying the clinical indications, a secondary objective was to determine the main reasons for the usage of the unregistered antimicrobials, in particular, the proportion of applications where there was no registered drug or alternative treatment available to use.

Publication

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Contribution to the Paper	Conceived and instigated the study, wrote the study protocol, collected and analysed the data, interpreted the results and drafted the manuscript.
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 14/5/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i.   the candidate's stated contribution to the publication is accurate (as detailed above);

ii.   permission is granted for the candidate in include the publication in the thesis; and

iii.   the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Abstract

Objective: Increasing antimicrobial resistance and a concurrent paucity of new antimicrobials marketed increases the risk that patients will develop infections resistant to currently available drugs. This study aimed to determine the range of clinical indications for which unregistered antimicrobials are prescribed at two tertiary hospitals in South Australia, to identify any trends over a two-year period. The impact of recent regulatory changes to the Special Access Scheme (SAS) was assessed.

Methods: Data were extracted from application forms submitted to the Therapeutic Goods Administration to access unregistered antimicrobials via the SAS pathway at two Australian tertiary hospitals for the period July 2015 to June 2017. Average weighted antimicrobial prices were retrieved from the hospital *Ipharmacy®* dispensing system. To estimate the impact of a new access pathway (Category C), the SAS classification for each application was retrospectively assessed over time with each regulatory change.

Results: Between July 2015 and June 2017, a total of 477 SAS applications for 29 different antimicrobials were submitted for 353 patients at the two hospitals. The most common indications were tuberculosis (43.6%) and refractory *Helicobacter pylori* (10%). Regulatory changes reduced the proportion of applications requiring pre-approval for access.

Conclusions: While the introduction of a new pathway has decreased the administrative burden when accessing unregistered antimicrobials, this study highlights the range of clinical conditions for which there are no registered drugs available in Australia.

What is known about the topic? With increasing antimicrobial resistance and a paucity of novel antimicrobials entering the market, access to older previously less-used antimicrobials is increasingly important in clinical practice. Accessing unregistered antimicrobials is common practice in Australian hospitals however the range of clinical indications for which they are used is unclear.

What does this paper add? Increasing antimicrobial resistance and a concurrent paucity of new antimicrobials being marketed globally is increasing the risk that patients may develop infections which cannot be treated with registered products. This study describes the range of clinical conditions for which registered antimicrobials are not available or appropriate, illustrating the challenges associated with sustainable access to effective treatments.

What are the implications for practitioners? Access to effective antimicrobials in a timely manner is essential for optimal patient outcomes. Reliance on unregistered products is associated with increased risks regarding timely access to safe, quality-assured, effective medicines.

Introduction

Effective antibiotics are an essential part of modern healthcare, enabling medical interventions such as surgery and chemotherapy. While most infections remain treatable with currently available antimicrobials, increasing rates of resistance to these antimicrobials, in addition to a paucity of new antimicrobial drugs entering the market, has resulted in the utilisation of older antimicrobials being considered an increasingly important alternative in clinical practice. [102, 142, 227] Very few new drugs have been recently marketed to treat multi-drug resistant infections and therefore older drugs which have not been routinely used for years, are viable alternatives where there are no other treatment options. In Australia, many older antimicrobials are not registered with the Therapeutic Goods Administration (TGA) and access is limited to individual applications through a 'Special Access Scheme' (SAS) to import and prescribe unregistered drugs.[91] The process of procuring an unregistered medicine for an

individual patient has a significant administrative burden for both the prescriber and hospital pharmacy staff and may jeopardise timely administration to the patient. In addition, medicines which are not registered with the TGA are not eligible for federal funding via the Pharmaceutical Benefits Scheme (PBS).[237] All prescribers, including GPs, may apply to access an unregistered medicine via the SAS, however outside the public hospital setting access may not be realised as the patient may be required to pay the full cost of the medicine. When unregistered medicines are accessed through a public hospital, the cost is usually covered by the dispensing hospital if the access is approved by the hospital drug committee.

Prior to July 2017, there were two pathways to access unregistered drugs via the SAS: Category A for life-threatening conditions and Category B for conditions not falling into category A. Access via the Category B pathway require prior approval from the TGA who assess whether there is "sufficient justification to approve supply" of the drug.[238] The clinical justification provided by the prescriber should include a reason as to why a registered product could not be used.[237]

In July 2017, regulatory changes to the SAS were implemented to improve access and reduce the administrative burden on prescribers, based on recommendations of an expert review of medicines regulation in Australia.[232] An additional notification pathway (Category C) was introduced for drugs that 'are deemed to have an established history of use'.[91] Unregistered medicines in Category C can be supplied and administered for specified indications without prior approval from the TGA, however the TGA must be notified within 28 days of supply. Inclusion of products in Category C is at the discretion of the regulator however the level of evidence required to determine 'established history of use' is not transparent or defined. Since July 2017, there have been two legislated amendments to products included in Category C.[234, 239] As of March 2018, there are 11 antimicrobials that can be accessed via the Category C pathway.[234]

Aim

The objectives of this study were to determine:

1. the range of clinical indications for which unregistered antimicrobials are prescribed, and to identify any particular trends or changes in utilisation of individual

unregistered antimicrobial drugs at two large tertiary hospitals in South Australia over a two-year period, from July 2015 to June 2017;

2. the justification for the usage of the unregistered antimicrobials accessed through the Category B pathway, in particular, the proportion of clinical infections where there was no registered drug available or appropriate to use;

3. the expenditure on the requested unregistered antimicrobials in the two hospitals over the two-year period;

4. the impact of the introduction of Special Access Scheme Category C, for drugs "deemed to have an established history of use", on the proportion of unregistered drugs requiring pre-approval prior to use.

Method

Data on the utilisation of unregistered antimicrobials were extracted from the original Special Access Scheme (SAS) application forms retained by two tertiary hospital pharmacies in South Australia for the period July 2015 to June 2017. Data were manually extracted on: the date of application, drug, dosage form or route of administration, dose, quantity requested or duration of treatment, clinical indication, and (for Category B applications) the justification for use of the unregistered product. Medical record numbers were replaced with a unique study number for each patient to ensure the data were not identifiable.

Antimicrobial prices in the present study are the average weighted price paid by the two hospitals to procure the drugs either from an Australian importer, or from an overseas supplier. Total expenditure for each unregistered antimicrobial was calculated using the average weighted prices for each antimicrobial at the time of dispensing and the total utilisation of each antimicrobial over the two-year period at each hospital (Table 5.1).

To estimate the impact of the SAS regulatory changes on the proportion of applications requiring TGA pre-approval prior to use, each of the 477 applications were cross-checked against the *Therapeutic Goods (Authorised Supply of Specified Medicines) Rules* to determine whether the antimicrobial/clinical indication combination would be classified as Category C as at July 2017, September 2017 and March 2018.[234, 239, 240]

The study was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC/17/RAH/570).

Results

In the two-year period from July 2015 to June 2017, a total of 477 SAS applications were submitted to the TGA for 353 patients seen at the two hospitals to obtain access to unregistered antimicrobial drugs. The number of applications per patient ranged from one to eight (median one application per patient). Approval was sought to access a total of 29 different antimicrobial drugs. Most applications were for an anti-tuberculosis drug (43.6%; Figure 5.1)

Figure 5.1: Type of unregistered antimicrobial accessed
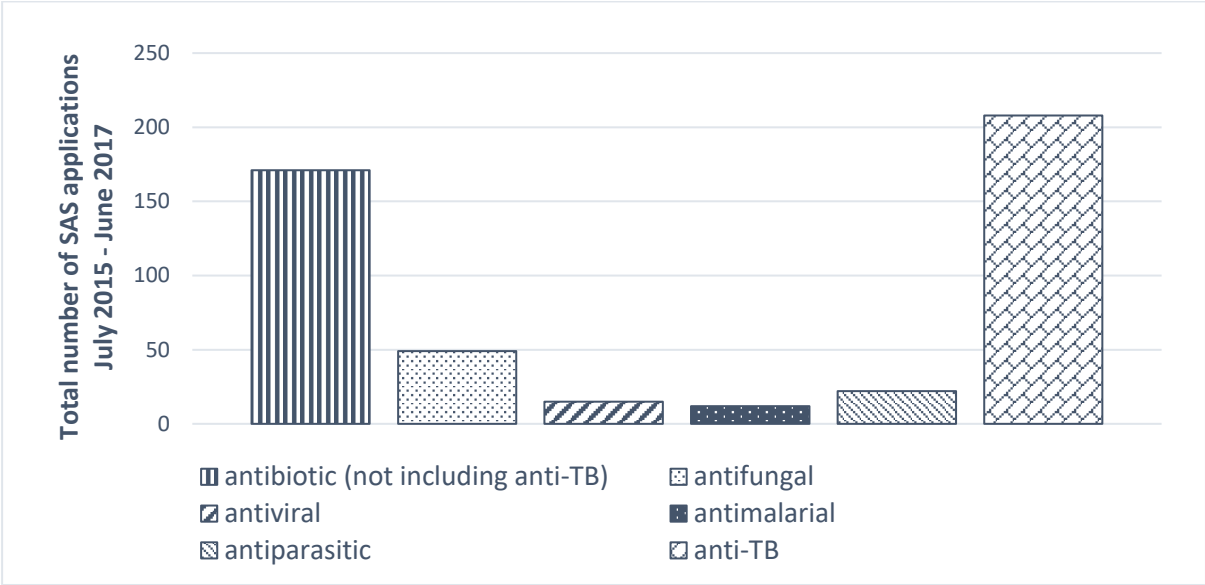
The most common clinical indications for these unregistered antimicrobials are provided in Table 5.2. A comprehensive list of all clinical indications for which unregistered antimicrobials at the two tertiary hospitals is provided as Supplementary Material to this paper (Appendix 7, Tables A7-1 and A7-2). More than three quarters (77.1%) of all applications to use unregistered antimicrobials drugs were 'Category A' applications, for life-threatening indications. Twenty-six patients were treated with more than one unregistered antimicrobial (Table 5.3).

Table 5.1: Total expenditure on each unregistered antimicrobial, July 2015 – July 2017

Antimicrobial	Dosage form / route of administration	Expenditure (A$)		
		Inpatient	Outpatient	Grand total
Amphotericin B 50mg	Injection / For manufacture of intraocular/intranasal product	$958.52	$876.87	$1835.38
Artesunate 60mg	Injection	$220.00	$0.00	$220.00
Aztreonam 1g	Injection	$8,376.00	$0.00	$8,376.00
Bedaquiline 100mg	Oral	$28,844.65	$9,533.40	$38,378.05
Bismuth Subcitrate 120mg	Oral	$0.00	$702.26	$702.26
Chloramphenicol 500mg	Oral	$0.00	$447.00	$447.00
Cidofovir 375mg/5mL	Injection / For manufacture of intraocular product	$4,988.32	$26,915.69	$31,904.01
Clofazimine 100mg	Oral	$1,440.35	$2,848.73	$4,289.08
Clofazimine 50mg	Oral	$53.04	$271.00	$324.04
Cycloserine 250mg	Oral	$2,727.59	$12,078.51	$14,806.10
Flucytosine 500mg	Oral	$4,183.95	$2,639.80	$6,823.75
Fosfomycin 3g	Oral	$644.32	$5,015.54	$5,659.85
Isavuconazole 100mg	Oral	$5,948.55	$0.00	$5,948.55
Ketoconazole 200mg	Oral	$76.52	$5,425.73	$5,502.25
Levofloxacin 500mg	Oral	$0.00	$69.73	$69.73
Miltefosine 50mg	Oral	$0.00	$6,975.00	$6,975.00
Moxifloxacin	Eye drops	$59.50	$0.00	$59.50
Natamycin 5%	Eye drops	$949.90	$1,234.87	$2,184.77
Nitazoxanide 500mg	Oral	$272.48	$560.84	$833.32
Paromomycin 250mg	Oral	$0.00	$1,362.25	$1,362.25
Primaquine 7.5mg	Oral	$698.43	$2,341.97	$3,040.40
Pristinamycin 500mg	Oral	$4,700.88	$96,850.69	$101,551.57
Prothionamide 250mg	Oral	$4,259.81	$4,585.50	$8,845.32
Pyrazinamide 500mg	Oral	$1,770.50	$15,101.14	$16,871.64
Ribavirin 1.2g/12mL	Injection	$13,898.79	$0.00	$13,898.79
Sulfadiazine 500mg	Oral	$776.51	$11,482.88	$12,259.38
Tetracycline 250mg	Oral	$0.00	$1,307.78	$1,307.78
Tetracycline 500mg	Oral	$0.00	$40.13	$40.13
Triclabendazole 250mg	Oral	$0.00	$1,010.25	$1,010.25
Grand total		**$85,848.59**	**$209,677.55**	**$295,526.15**

Table 5.2: Most common clinical indications for unregistered antimicrobials

Mycobacterium tuberculosis

Refractory *Helicobacter pylori* infection

Chronic bone / prosthesis or graft infection

Multi-drug resistant urinary tract infection

Fungal eye infection / keratitis

Cryptosporidium infection

Cryptococcal infection

Malaria

Table 5.3: Patients for whom more than one unregistered antimicrobial was accessed

Combination of unregistered antimicrobials accessed	Indication	No. patients
Cycloserine, Prothionamide, Pyrazinamide	Multi-drug resistant tuberculosis	3
Clofazimine, Prothionamide Pyrazinamide	Miliary tuberculosis (CNS involvement)	1
Bedaquilline, Clofazimine, Prothionamide, Pyrazinamide	Multi-drug resistant miliary tuberculosis	1
Bismuth subcitrate, Tetracycline	Refractory *H pylori* infection	18
Artesunate, Primaquine	Malaria	2
Chloramphenicol, Fosfomycin	Infected (EVAR) graft – ESBL* *E.coli*	1

CNS = Central Nervous System; ESBL = Extended-spectrum beta-lactamase; EVAR = endovascular aneurysm repair

The clinical justification for use of unregistered antimicrobials via the Category B pathway was in many cases multi-factorial. Resistance to registered antimicrobials or failure to respond to a registered product were the predominant reasons for the use of an unregistered product. Reported allergy or intolerance to registered options was also provided as justification, although to a lesser extent. Details of the clinical justification provided for the use of the 109 Category B applications are provided in Table 5.4.

Table 5.4: Clinical justification provided for the use of Category B applications

Summary of reason provided for use of unregistered drug*	Number of applications
Pathogen resistant to registered antimicrobials(s) / Failed registered option(s)	76 (71.7%)
Pathogen resistant to all other oral antimicrobials (only other options are IV)	9 (8.5%)
Patient allergic to / intolerant of registered drugs(s) or co-morbidities preclude use of registered options	11 (10.4%)
Unregistered drug recommended first-line in clinical scenario	4 (3.8%)
Non-microbial indication	7 (6.6%)
Not provided	2 (1.9%)
Total:	109

*Main reason provided (however justification often multifactorial)

Justification for the use of unregistered drugs is not required to be provided when accessed through the Category A pathway as the indications are deemed by the applicant or prescriber to be life-threatening to the patient without treatment. Of the 24 antimicrobials accessed through this pathway, three were for ocular use: two proprietary products (moxifloxacin eye drops & natamycin eye drops) and parenteral amphotericin for the extemporaneous preparation of ocular preparations. A large proportion of applications for unregistered antimicrobials were for chronic infections or for long-term use, with 68% of Category A applications requesting a duration of treatment greater than or equal to one month.

The total expenditure for each unregistered antimicrobial at both tertiary hospitals over the two-year period was calculated using the average weighted prices (at the time of dispensing) for each antimicrobial and the total utilisation of each antimicrobial, and is given in Table 5.1. The total annual expenditure on unregistered antimicrobials between July 2016 and June 2017 was A$169, 029, an increase of 34.6% on the previous financial year (A$126,497).

The median expenditure per unregistered antimicrobial was $4,289 over the two-year period at the two hospitals. 71% of the total expenditure on unregistered antimicrobials over the two-year period was for the treatment of outpatients or patients discharged from hospital. The mean and median cost per antimicrobial per patient were $752 and $92 respectively (range $1.56 - $38,378).

To estimate the impact of the Special Access Scheme regulatory changes on the proportion of applications that require pre-approval prior to use, each of the antimicrobial/clinical indication combinations were cross-checked to determine whether they would have been classified as Category C when the pathway was introduced, and after the two subsequent changes to the antimicrobials included in Category C. Of the Category B applications, 84.9% (90 of the total 106) would now be eligible for access via the Category C pathway, without prior approval from the TGA (Table 5.5). In addition, of the 368 Category A applications for life-threatening indications, 65.5% would be classified as Category C as at March 2018, with three quarters of those being for the treatment of tuberculosis.

Table 5.5: Estimating the effect of implementation of the Category C pathway

SAS category	No. applications	Classification as at March 2018		
		No change	Registered*	Category C
A	368	84 (22.8%)	43 (11.7%)	241 (65.5%)
B	109	13 (11.9%)	3 (2.8%)	93 (85.3%)

*Oral fosfomycin was registered in Australia in September 2017

Category A = antimicrobials used for life-threatening conditions; Category B = antimicrobials used for conditions not falling into Category A; Category C = drugs that 'are deemed to have an established history of use'; SAS = Special Access Scheme

Since the introduction of the Category C pathway in July 2017, there have been two revisions to the drugs included in the category, with an increasing number of new antimicrobials included at each revision.[234, 239] A list of currently included antimicrobials and the indications for which they are "deemed to have an established history of use" are listed in table 8 (supplementary data). For the SAS applications in this review, the estimated impact of the legislated changes to Category C (July 2017, Sept 2017 and March 2018) are illustrated in Figure 5.2.

The regulatory changes to the drugs included in Category C has resulted in a reduction in the number of SAS applications that require pre-approval from the TGA prior to use. Overall 70% of all the applications to use unregistered antimicrobials during the study period (July 2015 to June 2017) would be classified as category C as at 01 June 2018. Pyrazinamide for tuberculosis, pristinamycin prescribed by an infectious disease specialist, and tetracycline and bismuth

subcitrate for *Helicobacter pylori* infection were the main drug/indication combinations that were accessed under Category A or B, but would currently be considered Category C. The substantial change in the proportion of applications that would be considered Category C with the regulatory changes between July 2017 and March 2018 was largely due to the classification of pyrazinamide. Pyrazinamide was included in Category C when the pathway was introduced in July 2017, but was restricted to treatment of *drug-resistant* tuberculosis. This was amended to include *any* tuberculosis cases in the legislated changes as of September 2017 which is illustrated in Figure 5.2.

Figure 5.2: Effects of regulatory changes to antimicrobials included in Category C.
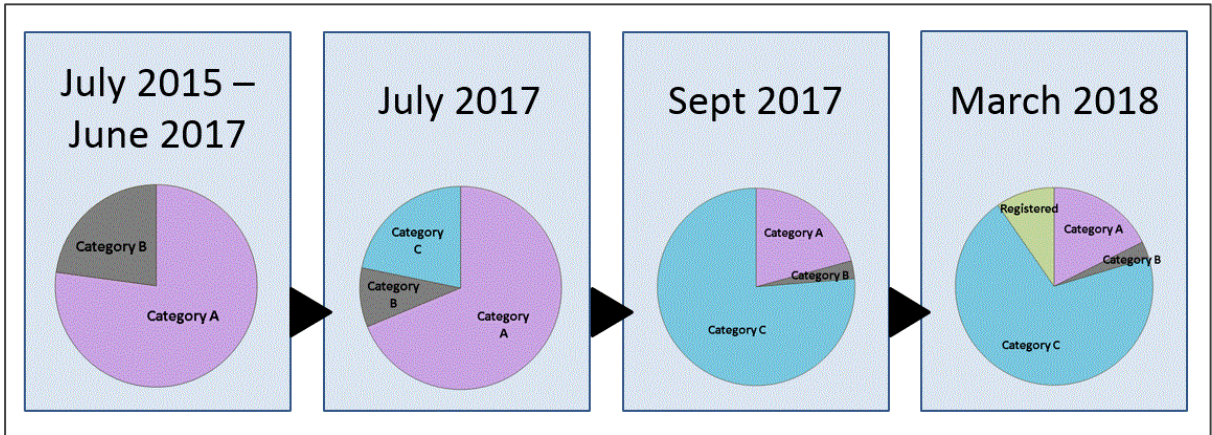
Category A = antimicrobials used for life-threatening conditions; Category B = antimicrobials used for conditions not falling into Category A; Category C = drugs that 'are deemed to have an established history of use'.

Discussion

Antimicrobial resistance is a growing issue with infections caused by multi-drug resistant organisms becoming increasingly prevalent and more difficult to treat. In some cases there are no available registered treatment options and this can lead to an increased reliance on prescribing unregistered or experimental antimicrobials. This review of unregistered antimicrobials accessed by two Principle Referral (AIHW Peer Group) Australian public hospitals illustrates the range of clinical indications for which access to unregistered antimicrobials is clinically necessary. Although absolute numbers are small, with only 353 patients requiring an unregistered antimicrobial over the two-year period, more than three quarters of the applications for unregistered antimicrobials at the two hospitals over the two

year period were deemed by the prescriber to be life-threatening. The two hospitals together (Hospital 1: 680 beds, Hospital 2: 593 beds) represent approximately 6.4% of the estimated 19,770 hospital beds in principal referral hospitals in Australia in 2015-2016.[241, 242]

The Special Access Scheme allows individual patients access to antimicrobials which are not approved by the TGA for use in Australia, but which are available overseas. This raises the question as to why these products are registered elsewhere but not in Australia. For some drugs, it may be that the incidence of a particular clinical indication is higher in other countries. For example, there were 1,339 new cases of tuberculosis reported in Australia in 2014 (an estimated incidence of 5.7 cases per 100,000).[243] In contrast, one of our closest neighbours, Indonesia, has one of the highest incidences of tuberculosis infections in the world with 391 cases per 100,000 in 2017.[244] Many drugs for tuberculosis are not marketed in Australia, including pyrazinamide, prothionamide, clofazimine, cycloserine and bedaquiline. Although the incidence of tuberculosis is lower in Australia, it is still essential that access to effective treatment is possible. Although it is unclear whether the two hospitals included in this study are representative of other Australian tertiary hospitals, South Australia currently has lower reported rates of multi-drug resistant isolates (including TB) than the eastern states of Australia.[16]

This review of SAS applications from two large public hospitals highlights the need to access unregistered antimicrobials to treat multi-drug resistant infections, such as the use of pristinamycin to treat chronic bone or prosthetic infection caused by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci* or azithromycin-resistant *Mycoplasma genitalium.* Salvage therapy for *Helicobacter pylori* infection was also a common indication for which unregistered drugs were accessed. First-line triple therapy (containing clarithromycin) for the treatment of *H pylori* infection is registered in Australia, however rates of pre-treatment resistance to clarithromycin in Australia is estimated to be 5-7% and increasing.[245] For these patients who fail first-line treatment, prescribers are left with having to access unregistered drugs for salvage therapy. Unregistered drugs are not funded on the Pharmaceutical Benefits Scheme (PBS), and although public hospitals may cover the costs there is no obligation for them to do so, particularly for out-patients. Notably, 71% of the expenditure on unregistered antimicrobials over the two-year period was for outpatient use.

For unregistered antimicrobials accessed through the Category B pathway, in many cases the justification for the use of an unregistered antimicrobial was multi-factorial, for example a combination of resistance to some registered treatment options and allergy or intolerance to of others. 'Treatment failure' to a registered drug may or may not be due to resistance (e.g. *H.pylori* resistance to clarithromycin), but may also be due to adverse reactions, poor compliance or pharmacokinetic reasons, for example the inability to achieve appropriate concentrations of drug at the site of infection.

The increasing need to access unregistered products to treat multi-drug resistant infections is challenging for regulators. Our results illustrate that the introduction of an additional access pathway (Category C) through the Special Access Scheme in July 2017 has potentially reduced the administrative load for prescribers and bureaucrats with many applications that would have previously required preapproval for use (Category B) now being reclassified in the Category C notification pathway. It is unclear however what inclusion criteria or level of evidence was required by regulators in order for a drug to be "deemed to have an established history of use". The drugs included in the new access pathway as per the legislated regulations were updated twice in the first nine months since the pathway was introduced, with the inclusion of more antimicrobials in September 2017 and then again in March 2018.

Although pre-approval by the TGA is not being required to access drugs via the Category C pathway, as with the original two SAS pathways the availability of the drugs is not guaranteed given that there is no obligation for manufacturers to supply unregistered products. The TGA have taken steps to improve communication with manufacturers regarding anticipated drug shortages of registered products, however unregistered products are outside of the scope of any reporting requirements.[246] The underlying issues that lead to shortages of registered generic products are equally a risk to the access of the many unregistered antimicrobials in current clinical practice.

For manufacturers, the process of applying to register a drug with the TGA can be lengthy and expensive. The marketing of drugs for small target patient populations, with potentially small and unpredictable sales (such as drug-resistant infections), is not an attractive investment for pharmaceutical manufacturers. As illustrated in Table 5.4, most of the unregistered antimicrobials accessed via the Special Access Scheme are older generic products that are

cheaply procured from overseas. The median expenditure per product was $3,569 for the two hospitals over two years. The combination of low sales volume and low cost per drug does not justify the costs to industry associated with the registration process. This means that the quality control measures applied by the TGA as part of the registration process will not be realised.

However, would access be improved if these small volume antibiotics were expensive? The fragility of the antibiotic market and the reliance on small numbers of manufacturers can be illustrated by the recent 400% price increase in the price of nitrofurantoin suspension to over US$2000 per bottle.[247] The economic incentives for the manufacturer may be increased if there is greater financial return per drug, but high cost / low volume products can be problematic for pharmacies from the perspective of stock management. Pharmacies in smaller hospitals with lower stock turnover, as well as private hospital pharmacies, are less likely to commit to having high cost drugs on the shelf, at risk of expiring due to low and unpredictable use.

A similar issue occurs with orphan drugs, where the volume of use is low but the procurement cost is high, however with orphan drugs for non-infectious indications the need to initiate treatment immediately is usually not critical and pharmacies can order stock when required. The unpredictability of the future incidence of multi-drug resistant infections is more challenging for manufacturers and suppliers. Not only are small patient numbers challenging from a regulatory perspective, the heterogeneity of patient populations and pathogenic aetiology is a problem for manufacturers who require evidence of efficacy to support applications to register a new (or old) drug. There is a need for adaptive regulatory pathways in Australia (and globally) to collect evidence of efficacy for antimicrobials to treat life-threatening, drug-resistant infections where patient numbers are small.

Many of the applications to access unregistered antimicrobials over the two-year period of this study would now fall into the Category C pathway. An acknowledged limitation of this study is the estimated impact of the new category is inferred rather than observed, however with a large proportion of Category B antimicrobials being reclassified as eligible for the new pathway, the responsibility to provide the documentation to access these unregistered drugs has shifted from the prescriber to another health practitioner, usually the supplying

pharmacy. In some cases the administrative burden can be great, involving seeking approval from a hospital Infectious Diseases specialist, completion and submission of the TGA application form, and potentially applying for funding from the hospital drug committee on behalf of the individual patient. For drugs and indications previously classified as Category B, for example tetracycline for resistant *Helicobacter pylori* infection, there is no longer the need for approval from the TGA prior to use, nor the need to provide a "clinical justification". Beyond this however, the new category offers no further guarantee of access, nor any incentive for manufacturers to apply for registration. As there is no compulsion to supply, unregistered drugs are exempt from reporting requirements to the TGA regarding pending or current shortages.

While the reliance on unregistered antimicrobials carries risks regarding access, the administrative burden associated with the SAS may potentially prevent over-usage of older, inexpensive antimicrobials. Any future policy changes aimed at assisting the regulation of antimicrobial drugs in Australia must not enable the overprescribing of older drugs that are currently only used for multi-drug resistant infections. This risk has been illustrated with the recent registration of oral fosfomycin with the TGA, potentially enabling direct marketing to general practitioners. In March 2018 the Australian Society for Infectious Diseases (ASID), the Australian Society for Antimicrobials (ASA) and the Australian Society for Microbiology (ASM) communicated their concern to the government, the sponsor and key medical colleges, about potential overuse threatening the longevity of fosfomycin as a therapeutic agent.[248]

This review illustrates that there is a reliance on unregistered antimicrobials in Australian clinical practice where there is an unmet need, in many cases due to antimicrobial resistance to currently registered drugs. Therapeutic drugs in Australia are classified into Schedules according to the level of regulatory control over the availability of the drug in order to protect public health and safety.[249] Perhaps antimicrobials should be scheduled separately from other drugs so that legislation and regulation can be tailored to ensure access to these life-saving treatments, but also governance over appropriate prescribing which is critical in this era of multi-drug resistance.

Competing interests

None of the authors have any competing interests to declare.

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Chapter synopsis

This chapter has explored the clinical scenarios for which clinicians are seeking unregistered antimicrobials to address the lack of treatment options in Australia. This chapter, together with chapter four, provide empirical evidence to demonstrate that in clinical practice clinicians are seeking unregistered antimicrobials to address the lack of registered treatment options in Australia, particularly for multi-drug resistant infections. These findings have implications for patient care, particularly as the timely supply of unregistered products is not guaranteed, nor are they subject to the same quality testing that registered products must undertake. The reliance on unregistered antimicrobials in clinical practice, and the lack of newer registered antimicrobials entering the market, is a potential risk to ensuring timely access to effective treatment for patients. Together, the findings of both this chapter and the previous one, have illustrated that there is an unmet need for effective, registered antimicrobials in Australia to treat a number of clinical conditions, including multi-drug resistant infections.

CHAPTER SIX
Methodological challenges with existing approaches to forecasting resistance

Preface

This chapter expands from the local (Australian) estimations of unmet need due to AMR provided in the previous two chapters, to capture broader international perspectives on the problem. An overview of the challenges of accurately predicting the clinical and economic burden of antimicrobial resistance into the future are explored within this chapter. The objective of this peer reviewed discussion paper, published in *Applied Health Economics and Health Policy*, was to review and establish the feasibility and utility of modelling antimicrobial resistance, given the current available data. The sources of uncertainty are highlighted, which could potentially mislead policy decision-making, and the paper highlights the need for model transparency and standardised reporting standards to ensure accurate interpretation by policymakers.

The relevance of this review paper is that it provides context to the challenges of modelling incremental costs and incremental economic and clinical benefits of a new antimicrobial into the future, given the uncertainty regarding resistance rates into the future, in particular the challenges of predicting the impact from the non-human health sectors. A key point highlighted in this paper is the need to take a 'One Health' perspective when the cost-effectiveness of an intervention to address antimicrobial resistance is estimated. That is, the costs and benefits to all sectors should be considered, including the human health sector, animal health and the health of the environment. The text and figures from the paper are reproduced in this chapter.

Publication

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Name of Principal Author (Candidate)	Nadine Hillock
Contribution to the Paper	Conducted the literature review, conceived and drafted the manuscript, revised and corrected the manuscript based on co-authors and reviewers' comments
Overall percentage (%)	75%
Certification.	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 14/5/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above).

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Abstract

Due to the increasing threat to public health and the economy, governments internationally are interested in models to estimate the future clinical and economic burden of antimicrobial resistance (AMR) and to evaluate the cost-effectiveness of interventions to prevent or control resistance and to inform resource allocation decision making. A widely cited UK report estimated that 10 million additional deaths will occur globally per annum due to AMR by 2050, however the utility and accuracy of this prediction has been challenged. The precision of models predicting the future economic burden of AMR is dependent upon the accuracy of predicting future resistance rates.

This paper reviews the feasibility and value of modelling to inform policy and resource allocation to manage and curb AMR. Here we describe methods used to estimate future resistance in published burden of disease models, the sources of uncertainty are highlighted, which could potentially mislead policy decision-making. While broad assumptions can be made regarding some predictable factors contributing to future resistance rates, the unexpected emergence, establishment and spread of new resistance genes introduces substantial uncertainty into estimates of future economic burden, and in models evaluating the effectiveness of interventions or policies to address AMR.

Existing reporting standards for best practice in modelling should be adapted to guide the reporting of AMR economic models, to ensure model transparency and validation for interpretation by policymakers.

Key points for decision makers:

The overuse and inappropriate use of antimicrobials, and the consequent impact on the risk of antimicrobial resistance, extends well beyond the individual recipient of the antimicrobials, however the wider consequences are difficult to quantify.
Consideration of the cost-effectiveness of interventions to address antimicrobial resistance must take a One Health perspective and incorporate the costs and benefits to all sectors, including human health care, animal health care and the health of the environment.
Methods and assumptions used to model future resistance rates should be transparently and consistently reported to assist interpretation by policymakers who must determine whether the models are credible and clinically relevant.

Introduction

"All models are wrong, but some are useful".[250] This quote from renowned statistician George Box encapsulates the concept that no mathematical model can perfectly simulate real-life, but some well-structured and adequately populated models may estimate future scenarios with sufficient accuracy to usefully inform decision making.

Cost-effectiveness models are used to inform health care resource allocation by providing decision-makers with quantitative estimates of the future costs and benefits of alternative health technologies and health policies.[251, 252] Cost-effectiveness models constructed to inform funding decisions typically extrapolate health care resource use and health outcomes over an appropriate time horizon, based on the results of clinical trial data or non-trial data (real world data / observational data). Forecasting models are used to estimate the impact of near-term expenditure on interventions that will prevent or reduce future economic burden due to a particular disease or public health concern.[253]

This narrative review examines the methodologies and uncertainties around existing models of the clinical or economic burden of AMR, and reflects on the value and potential role of such models in informing policy and practice. A literature search of peer-reviewed literature (Medline and Embase) was conducted in 2018 and updated in October 2021, and included

search terms 'antimicrobial resistance' or 'antibiotic resistance' (and associated MeSH terms) in addition to any of the following terms: models, modelling, cost of illness, cost-benefit analysis, cost-effectiveness models or economic models. The search was supplemented with searches of the grey literature, and included the websites of both the UK AMR review (https://amr-review.org) and DRIVE-AB (drive-ab.eu), an international collaboration of 12 countries developing economic models to promote antibiotic innovation. Reference lists of relevant papers were searched to identify additional evidence sources. No date limits were set for the literature search.

The potential role of burden of disease models to inform AMR policy and resource allocation

Antimicrobial resistance (AMR) is the natural adaptation of micro-organisms to resist those medicines designed to inhibit their growth.[1] AMR is associated with increased clinical and economic costs due to suboptimal treatment or treatment failure.[9, 254-257] Although it is agreed that AMR is becoming an increasing burden on the healthcare system and society in general, published estimates of the clinical and economic burden vary significantly.[27-29, 31, 158, 256, 258, 259] While modelled estimates of burden would be useful for all levels of government, the ability to do this is constrained by substantial uncertainty about the future evolution of resistance in different bacterial species, and the multifarious nature of the epidemiology and transmission dynamics of antimicrobial resistance, including multidirectional relationships between human and animal health and the environment (Figure 7.1).[6-8, 49]

For Governments to plan their future approach to managing AMR, an accurate estimate of the future clinical and economic burden of resistance could enable better predictions of:

- the cost-effectiveness of policies or programs (such as antimicrobial stewardship (AMS) interventions), infection control procedures, policies regarding animal or environmental use of antimicrobials to curtail the spread of resistance;
- the cost-effectiveness of new rapid diagnostic tests, directing appropriate antimicrobial treatment in a timely manner, and reducing inappropriate antimicrobial use; or
- the cost-effectiveness or "value" of new antimicrobials and other types of pharmacological interventions.

Estimating future resistance - modelling methodology and parameter uncertainty

From the perspective of policy-makers, the validity of the structure of any economic model and it's inputs must be clearly described in order for the model's outputs to be interpreted with clarity in light of any limitations.[252] The scope and perspective of an economic analysis, as well as the type of policy questions requiring answers, are important considerations in determining the type of model required to inform policy.[260] A key aspect of models designed to estimate the future economic burden of AMR, or to compare the cost-effectiveness of difference interventions, is the prediction of future resistance. [261-263]

Although there is a correlation between antimicrobial use and resistance, the emergence of AMR is largely unpredictable and can occur either via spontaneous mutations in the bacterial chromosome, or much more commonly by acquisition of an existing resistance gene or genes via mobile genetic elements or transformation (gene acquisition).[49] Acquisition of multiple resistance genes, either sequentially or bundled within mobile genetic elements, means that exposure to one antimicrobial can enable resistance to other antimicrobials, either of the same class or to an unrelated class, a process that is difficult to predict or model. Transmission dynamics of AMR are complex, with a myriad of factors and multidirectional pathways transferring resistant genes or bacteria between human, animals, food and the environment [6-8, 49] (Figure 6.1).

While the link between antimicrobial use and resistance is complex, the drivers of antimicrobial use and misuse, including the volume and choice of antimicrobials used, are also multifaceted and often unpredictable and includes social, cultural, ethical, economic and political factors. [264] The inter-sector, multi-directional transmission of AMR, is acknowledged in the 'One health' approach by policymakers in addressing the issue, whereby it is recognised that human health is dependent upon and connected to the health of animals and the environment.[265]

Figure 6.1. Epidemiology of antimicrobial resistance
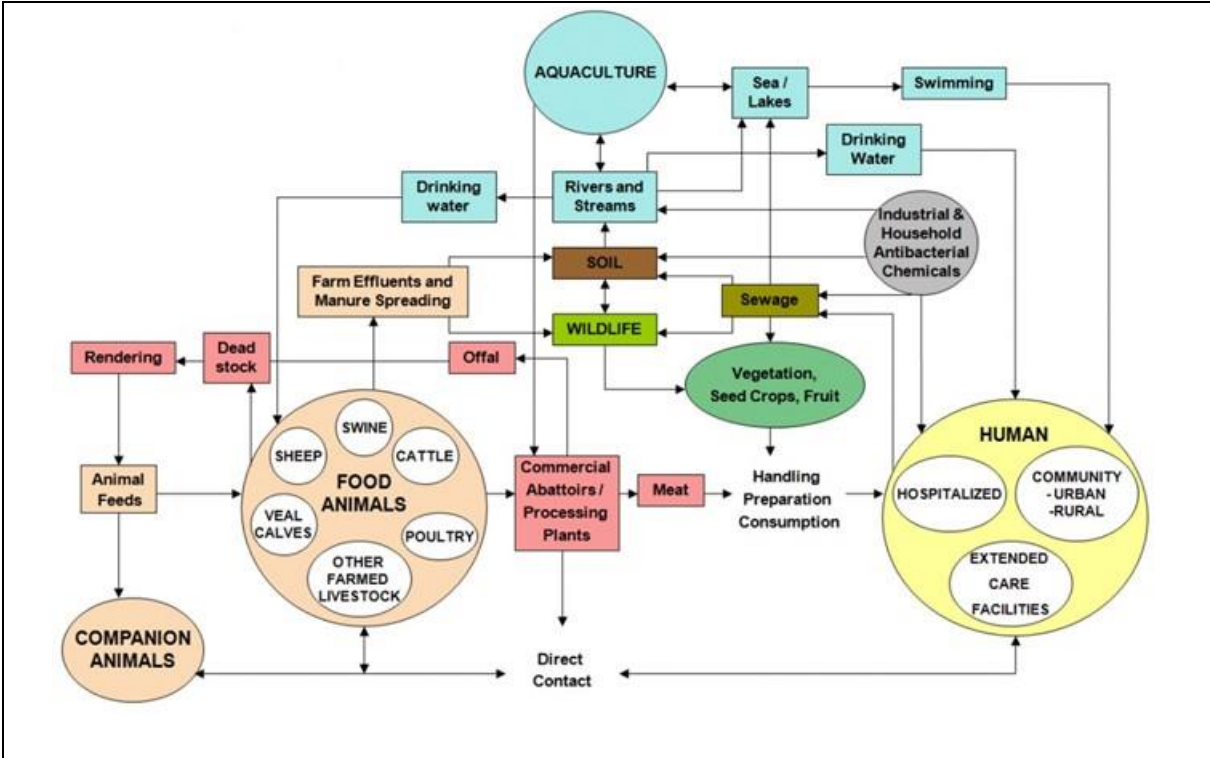
 (Source: ACSQHC, 2013. Reproduced with permission from the author)

Emergent pathogens are also unpredictable and cannot be anticipated with any certainty for the purposes of predictive modelling; their impact on global burden can be illustrated by *Candida auris*, a fungal pathogen which was first isolated from a patient in 2009, but ten years later is a global health threat causing severe invasive infections with reported mortality rates of up to 72%.[266] The exact number of human pathogens is not known, however a comprehensive literature survey identified over 1,400 pathogens of which approximately 40% were bacteria, and of those bacterial species, 10% were considered emerging or re-emerging.[267]

Although deterministic or compartmental models have been developed to conceptualise the emergence and spread of resistant pathogens within certain defined settings, for example, in a ward or a hospital, the complexity of transmission described above means these modelling approaches for long-term predictions of rates of resistance at a population level are highly uncertain.

Published models estimating the current and future economic burden of AMR

For predictive modelling to accurately inform policy and evaluate the impact of various interventions or policies, it is first necessary to establish the baseline expected costs and outcomes without those interventions or policies in place.

A 2016 report commissioned by the UK government to model the future clinical and economic impact of antimicrobial resistance estimated that with increasing resistance to currently available antimicrobials, drug-resistant infections could kill more than 10 million people globally per year by 2050, including 22,000 per year in Oceania.[27] Although widely cited, the methodology used in the study and lack of peer review raised questions regarding the accuracy and utility of this estimate.[268] However, despite the questionable model output, the UK report has been a useful reference to highlight the issue of AMR to governments globally.

A 2018 systematic review of published economic burden studies found only six of the 11 identified studies utilised evidence synthesis – a best practice method for estimating model input parameter values.[269] Two of the identified modelling studies informed the UK *Review on AMR.*[27] RAND Europe, an independent not-for-profit research organisation, and KPMG UK have published overviews of their economic models developed to inform the review.[31, 270] The models projected the economic impact of different future AMR scenarios based on the change in mortality rates and the predicted impact on labour efficiency (productivity) under each scenario with varying resistance rates.

To estimate the impact of AMR on productivity, the authors of both models published their estimates of the reductions in the 'working age' population due to resistance-attributable mortality.[31, 270] The authors of the RAND model stated that AMR-attributable mortality is dependent upon the incidence of infections caused by the included pathogens, as well as current and future resistance rates, but they are not explicit in their calculations. They acknowledged there was limited data to estimate future AMR-attributable mortality which was a limitation of their model. KPMG modelled mortality as a function of infection rate, resistance rate and attributable mortality rate, but justification for the attributable mortality rate was unclear, with the two scenarios for increased resistance rates being arbitrary (40% or 100% resistance across all countries for the 6 pathogens modelled).The uncertainty regarding the

magnitude of these estimates (e.g., confidence intervals) was not provided in either model.[31, 270]

The scope of both models included only three pathogens that are common causes of community and hospital-acquired infections (*E. coli, K. pneumoniae* and *Staph. aureus*), in addition to HIV, tuberculosis and malaria. Future resistance rates were not based on historical AMR data, rather three arbitrary future resistance rates were projected (5%, 40% and 100%) and compared to baseline (0%). The growth rate of resistance was assumed to be a 'one-off step' in year 0 to year 15 for all six pathogens, rather than an increase from baseline over time based on statistical modelling of available surveillance data. Although not stated explicitly, it appears that the models assumed resistance to be defined as non-susceptible to *all* possible available treatment options when used either as monotherapy or combination therapy.

How to model the impact of AMR on the future incidence of infections is also unclear. Notably, both models informing the UK AMR review explicitly excluded costs associated with stewardship and infection control.[31, 270] For the three common hospital pathogens, and for transmissible infections, HIV and TB, two scenarios were modelled in the KPMG model, one where incidence rates remain constant until 2050, and another scenario where current infection rates doubled between 2014 and 2050.[270] The RAND model also assumed no change to future incidence as "there is a lack of agreement among health specialists about the future changes to incidence rates and/or their direction".[31] The potential impact of resistance on the prevalence of HIV and TB was not discussed.[31, 270]

A 2019 systematic review of economic studies reporting the additional burden of antimicrobial resistance identified 12 peer-reviewed studies in addition to the two reports by RAND and KPMG.[271] All 12 studies reported attributable costs associated with AMR from a healthcare system or hospital perspective, rather than from a societal perspective.[271]

Kaier (2012) published a model which aimed to determine the economic impact of the recovery of antibiotic effectiveness, simulating different scenarios to model the burden of AMR as an externality of antimicrobial use (where reduced usage led to a decrease in AMR) [272]. The model was limited to a single hospital setting and was based on the assumption that a reduction in antibiotic use would result in a decline in the frequency of resistant bacteria.

The authors themselves acknowledged that the recovery of antibiotic effectiveness differs between bacterial species; in some cases, even where a reduction in use occurs, an increase in resistance is observed.[272]

In 2017, the World Bank published a report estimating the possible impact of AMR on the global economy from 2017 to 2050.[28] A narrative description of the structure of the economic model is provided in the report, describing it as "dynamic, multi-country, multi-sector, general equilibrium model", with two scenarios described as "low AMR impacts" and "high AMR impacts" however the definition and methodology for these scenarios was not provided. No graphical representation of the model variables and their relationship was provided, nor were any details of the simulations of future resistance rates. The report estimated that without effective containment, AMR will likely reduce annual global GDP by between 1.1 – 3.8% by 2050.[28]

Using current data to estimate future resistance rates and future economic burden

The use of currently available data to inform and forecast the future clinical and economic burden of a disease is a common approach to inform policy decision-making. There are however many gaps in the currently available surveillance data of antimicrobial use and antimicrobial resistance, in humans, animals and the environment. Diverse approaches have been used in published studies to estimate future resistance and reiterated the lack of comprehensive data to inform predictive models.[271]

To estimate the future economic burden associated with AMR, accurate data is needed to quantify the marginal health costs associated with the treatment or prevention of multi-drug resistant infections (compared to treatment of susceptible infections), as well as more comprehensive surveillance data of antimicrobial use and resistance.

Data to inform marginal costs associated with infections due to resistant organisms

Most published studies investigating the incremental costs of resistant infections are hospital-based and have focused on a specific disease or pathogen.[256] Costs assessed in published studies have included additional investigations, drugs costs, costs associated with side effects from more toxic drugs or drug combinations, length of hospital stay and

increased mortality rates. A 2015 modelling study investigated the additional surgical site infections and deaths likely with increasing resistance to antimicrobials used for surgical prophylaxis.[259] To our knowledge there are no studies investigating that model the societal cost impact of scenarios with no effective antibiotics for procedures or interventions where antibiotics are currently used routinely, such as prophylaxis in surgery, to quantify the impact on the workforce or economy due to being unable to perform these interventions safely.

In 2014, the WHO conducted a systematic review of evidence relating to the health and economic burden of three multi-resistant organisms: *Escherichia coli* (*E coli*) resistant to 3rd generation cephalosporins and fluoroquinolones*, Klebsiella pneumoniae* resistant to 3rd generation cephalosporin and carbapenems and *Staphylococcus aureus* resistant to methicillin (MRSA).[8] The review found there was a lack of published studies collecting health-care resource consumption concurrently with clinical outcomes, for *E. coli*, and none for *K. pneumoniae*. Limitations in the methodology used to capture cost data were identified: data collection on health-care resource use were mostly retrospective, often not done at the same time as the collection of clinical data, and limited to an estimate based on length of stay in hospital and the proportion requiring treatment in intensive care.[8] The magnitude of marginal costs associated with resistance to is likely underestimated due to the paucity of definitive cost evidence available, especially with regards to global and regional impact of specific multi-resistant pathogens.[8]

A 2019 systematic review found data were available to allow justifiable estimates of the AMR-associated economic burden for healthcare-associated *Enterobacteriaceae* and methicillin-resistant *Staphylococcus aureus* bloodstream infections. For all other infections, and settings, there was insufficient data to generate accurate estimates of the costs attributable to resistance.[271]

Resistance and usage data to inform statistical forecasting models

Extrapolating future resistance rates from available surveillance data has been used as a method to forecast health and economic burden of resistance.[262, 273, 274] Statistical modelling methods such as interrupted time series regression are a practical modelling method using historical data and current observations to investigate the relationship between

antimicrobial utilisation and resistance over time. However this method is also limited by the comprehensiveness and completeness of available surveillance data. In addition to data gaps regarding emergence and transmissibility, there is also a lack of standardisation regarding defining and measuring AMR, further complicating the interpretation of the data that is available.[275]

A recent statistical modelling paper suggested that an autoregressive linear model with consumption as an independent parameter, was the most appropriate approach to a predictive model of future resistance.[276] Further validation of this model is required using different 'drug-bug' combinations, as it is not always clear that the relationship between antimicrobial use and resistance is linear for different 'drug-bug' combinations. Emerging research suggests a non-linear relationship is more probable, with selection pressure increasing once antimicrobial use exceeds a certain threshold.[277] Non-parametric time-series models using historical surveillance data have been used to identify non-linear relationships between population antimicrobial use and resistance burdens.[277] These methods may enable prediction of thresholds of antimicrobial consumption above which resistance to particular pathogens increases. Validation of these methods may enable improved estimates of burden in the future, in addition to setting targets for reductions in antimicrobial use.

Dynamic transmission models and incorporation of antimicrobial consumption as an externality

Dynamic modelling methods are used to develop mathematical representations of non-linear systems, incorporating feedback loops and multiple interdependent variables that evolve over time.[278] Dynamic models can be used to simulate the impact of an intervention at a systems level and are used increasingly to inform policy making.[279-281] They provide an explicit method to synthesise available evidence regarding the effectiveness and costs of alternative healthcare interventions or strategies.[282] A 2018 scoping review investigate the range of published studies that used dynamic models to analyse the problem of AMR, identifying 81 studies in relation to human or animal use.[283] Only two of the 81 studies incorporated multiple host species in a shared environment, highlighting the lack of "One Health" approach to modelling in the literature. The use of an antimicrobial in an individual person, a human population, or multiple animal species, potentially impacts the risk of drug-

resistant pathogens in that individual, or in other human or animal populations. Ideally dynamic modelling of AMR needs to include consumption as an 'externality', that is, a cost or benefit associated with one person's activity (e.g. consumption of an antimicrobial) that impacts the population who did not choose to incur that cost or benefit.[284] For example, stewardship interventions that result in prescribers utilising narrower-spectrum antimicrobials instead of broader spectrum ones, may potentially reduce the selection pressure for resistant organisms in the population.

Discussion

Very crude models of future economic burden, using hypothetical scenarios of future resistance rates lack the accuracy to adequately inform governments seeking optimal allocation of resources to limit AMR. Governments globally are seeking 'better models' for a more accurate estimate of country-specific future burden, however it is questionable whether sufficiently accurate estimates are possible given the substantial uncertainties regarding the transmission dynamics of AMR. The National Institute for Health and Care Excellence (NICE) in the UK are currently undergoing wide consultation in order to seek consensus among stakeholders on other methods and models for evaluating antimicrobials given the limitations highlighted here.[285]

As illustrated in this review, the feasibility and accuracy of estimating long-term cost-effectiveness of new antimicrobial drugs or stewardship interventions is dependent upon being able to correlate the effect of that drug or intervention with long-term effects on resistance rates, and therefore on public health. Compared to other medication use, antimicrobial treatment is unique in that its use generates a negative externality, antimicrobial resistance, reducing the effectiveness of that drug into the future.

At a national level, antimicrobial utilisation has been used as a surrogate outcome measure for policy or stewardship interventions, with the assumption that reduced antimicrobial consumption will lead to a reduction in future resistance rates and therefore reduce the risks of treatment failure and improve clinical and economic outcomes. Comprehensive surveillance data measuring consumption across all sectors (human, animal and the environment) is required to reduce the uncertainty regarding the correlation between usage and future resistance rates. The Global Antimicrobial Resistance and Use Surveillance System

(GLASS) has grown from 729 surveillance sites when it was established by the WHO in 2015, to 24803 surveillance sites in 70 countries.[286] As surveillance data improves, the precision of statistical forecasting models will improve, allowing further exploration of non-linear relationships between use and resistance, as well as further research to identify possible thresholds of usage at which resistance emerges.[277]

While broad assumptions can be made regarding some predictable components of resistance rates, the unexpected emergence, establishment and spread of new resistance genes limits the feasibility of models to provide governments with accurate predictions regarding the long-term cost-effectiveness of AMR policies or interventions. While models may crudely predict the immediate clinical and economic impact of antimicrobial failure in a particular clinical area, the complexity of AMR limits the utility of dynamic models in predicting future resistance rates. Even if more comprehensive antimicrobial usage and resistance surveillance data were available, there are multiple unpredictable behavioural and social factors that introduce uncertainty into dynamic models of future AMR, such as patient compliance with antimicrobial treatment and compliance with infection control methods.

The COVID-19 pandemic has illustrated how models estimating the future economic burden of a particular disease can divide political opinion, resulting in contrasting policy decisions, based on political trade-offs between economic and health outcomes. Like COVID-19, future AMR risks at a patient and population level are dependent upon both policies implemented by governments but also by human compliance and behaviour. However the COVID-19 pandemic has also illustrated that complex models that incorporate behavioural and social factors can be developed.[287] Improved surveillance may reduce the uncertainty in statistical forecasting of resistance, which in turn could be used as inputs into dynamic models in the future. Expert elicitation methods have been investigated to address the fundamental challenges of predicting future resistance, with experts demonstrating relevant knowledge not captured in statistical forecasts.[288] Future modelling frameworks could employ such methods to (a) design parsimonious model structures and (b) to estimate uncertain parameters.

One issue that can be fairly easily addressed is that the methods and assumptions used in models to estimate the burden of AMR, or in cost-effectiveness analyses, should be transparently reported. Without these, the policy maker is unable to judge whether the assumptions and inputs used to inform the model are credible and clinically relevant. Existing reporting standards for best practice in modelling should be adapted to guide the reporting of AMR economic models.[252]

Without consistency in reporting and transparency regarding the level of uncertainty about future resistance rates and transmission dynamics, and the future incidence of drug-resistant infections, the value of modelling to guide decision-making on which interventions will be the most cost-effective use of resources for managing AMR is limited.

Declarations

Conflict of Interest: None of the authors have any conflicts of interest to declare.

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*****End of published paper*****

Chapter synopsis

This chapter provides an overview of the challenges associated with forecasting resistance into the future, which also has implications for estimating the benefits of new antimicrobials entering the market. Estimating the future burden (both clinical and economic) associated with AMR is highly uncertain using current methods, as the consequent impact of inappropriate use of antimicrobials extends well beyond the individual. For policy decisions regarding public funding of antimicrobials, better estimates of cost-effectiveness are needed and better ways of linking public funding decisions to the likely impact of an antimicrobial to the population, not just the individual. This is further explored in the next chapter on stakeholder views.

CHAPTER SEVEN
Exploring alternative funding models

Preface

This chapter is the first of two publications resulting from a qualitative study exploring the Australian stakeholder perspective regarding the current framework for antimicrobial access in Australia, their opinions on alternative models of registration and reimbursement, and potential issues or factors to consider to ensure sustainable supply of effective antimicrobials in Australia. This article resulting from the stakeholder interviews has been published in the *Journal of Antimicrobial Chemotherapy – Antimicrobial Resistance* and examines the perspectives of both policymakers (including individuals involved in regulation and funding of pharmaceuticals in Australia) and the pharmaceutical manufacturers regarding the system, processes and reform required to separate funding from the volume of antimicrobial sales in Australia. The second publication resulting from the stakeholder interviews, which focuses on their perspective of antimicrobial value assessment, is reproduced in chapter 8 of this thesis.

Publication

Statement of Authorship

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Name of Principal Author (Candidate)	Nadine Hillock
Contribution to the Paper	Conducted the background literature search, wrote the study protocol, interviewed participants, coded the transcripts and conducted the thematic analysis, interpreted the data and drafted the manuscript
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 14/5/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i.   the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Contributed to the coding framework and thematic analysis, and data interpretation, and reviewed the manuscript
Signature	Date 16/5/2022

Abstract

Background: There is a disparity in the economic return achievable for antimicrobials compared to other drugs because of the need for stewardship. This has led to a decline in pharmaceutical companies' willingness to invest in the development of these drugs and a consequent global interest in funding models where reimbursement is de-linked from sales.

Objective: To explore the perspective of stakeholders regarding the feasibility of de-linked reimbursement of antimicrobials in Australia.

Methods: Semi-structured interviews were conducted with 18 participants sourced from the pharmaceutical industry and individuals representing public-sector payers or regulators. Interviews were transcribed verbatim, coded and thematically analysed using the framework method.

Results: Five key themes were identified in the interviews: Funding silos are a barrier to de-linking reimbursement, varying levels of supporting evidence are (currently) required for funding depending upon setting, funding status or cost is used as a stewardship tool, a de-linked model may cost more, and there are concerns regarding governance and access to antimicrobials in the private sector.

Conclusions: Australia's current multi-tiered funding of medicines across different levels of government was perceived as a barrier to de-linked reimbursement. Participants felt that the responsibility for antimicrobial funding and stewardship should be integrated and centralised. Implementing a nationally-funded de-linked reimbursement model for new antimicrobials would require a review of funding decision-making criteria, given that most multi-drug resistant infections are off-label indications and could not then be funded through the Australian Pharmaceutical Benefits Scheme. Findings from this study could be applicable to other countries with reimbursement frameworks similar to Australia.

Introduction

Overuse and inappropriate use of currently available antimicrobial drugs is the leading cause of worsening antimicrobial resistance (AMR). Globally there is growing concern about the lack of new antimicrobial drugs in clinical development to treat multi-drug resistant infections. While it is widely acknowledged that the current volume-based model of reimbursement is broken, there is uncertainty around how countries can adapt their regulatory and funding processes for antimicrobials in order to maintain a viable business model for manufacturers without inadvertently promoting overuse.[1, 2] For pharmaceutical companies, the return on investment to shareholders is higher when prescription volumes are high. With AMR becoming a global threat to healthcare, interventions to reduce antimicrobial use and limit the risk of AMR have directly impacted the potential profit a company can make from marketing an antimicrobial drug. This has led to a marked decline in new antimicrobials being developed.

De-linking reimbursement from the number of units sold has been proposed internationally to reduce the incentive for companies to promote inappropriate sales.[3-6] The Australian Government has acknowledged that opportunities to support antimicrobial development need to be explored.[7] Various alternative reimbursement models have been proposed, including fully de-linked models where companies are reimbursed in pre-agreed lump sum payments to the company irrespective of the number of prescriptions filled (Figure 7.1). Partially de-linked models have also been suggested. These include lower lump sum market-entry rewards combined with some performance-based income, allowing future contractual payments to be linked to meeting certain predefined stewardship goals in addition to supply chain security.[8-11] Sustainable solutions need to be a collaborative negotiation between manufacturers, regulators and payers. For manufacturers, economic reward for shareholders is the motivational goal, whereas for governments the aim is to allocate funding and resources to achieve maximum benefit for the population.

Australia has a universal health care system which is financed through a complex combination of Federal and State Government funding, in addition to private insurance and individual patient funds.[12] The proportion each contributes to the healthcare costs for an individual depends upon the healthcare setting (e.g., inpatient or outpatient), the clinical

indication of the patient and the healthcare services provided. Medicines for patients in the community (non-hospital setting) are funded by the Federal Government via the Pharmaceutical Benefits Scheme (PBS).[13] Medicines administered to public hospital inpatients in Australia are funded by the state or territory governments, whereas medicines supplied to private hospital inpatients are funded by a combination of federal funding (for PBS-listed medicines), health insurance and patient funds. The complexity of funding sources for antimicrobials in Australia is illustrated in Table 7.1.

Figure 7.1. Simplified illustration of alternative reimbursement models
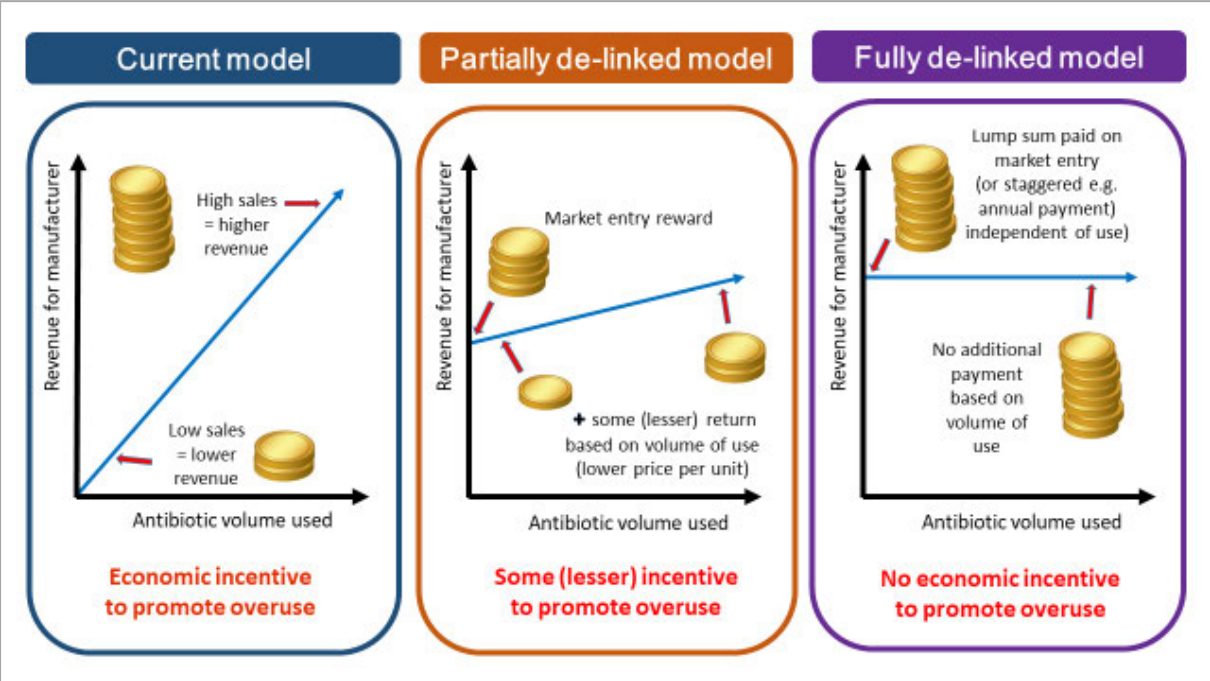
Table 7.1. Funding sources for antimicrobials in Australia

Setting	Funding of antimicrobial treatment
Public hospital inpatient	*State funded* via hospital budget
Private hospital inpatient	· If PBS*-listed indication: *Federally funded*; · If antimicrobial registered in Australia but not PBS-listed indication → *Health-insurer funded* or *patient funded*; · If antimicrobial not registered in Australia → *Patient-funded*[5]
Outpatients / community setting	Oral antimicrobial treatment: · If PBS-listed indication → *Federally funded* with *patient co-payment* (Note: Patient pays full cost where the cost of the antimicrobial is less than the set co-payment fee[6]) · Non-PBS-listed indication (including off-label indications or unregistered antimicrobials) → *patient funded*, or *state funded* (hospital budget) if prescribed on hospital discharge or in outpatient clinic Outpatient Parenteral Antimicrobial Therapy (OPAT): · *State funded* (hospital budget), with *federal reimbursement* of the antimicrobial if PBS-listed indication

* PBS = Pharmaceutical Benefits Scheme

Recently there has been increased global investment ('push incentives') in research to discover potential new antimicrobials and repurpose older agents. Despite this increased investment, based on the current pipeline of drugs in various stages of research and development, it is estimated that no more than one new innovative drug active against a 'WHO priority pathogen'[14] will reach the marketplace in the next five years.[15] Investing in human trials to establish clinical evidence of efficacy and safety for a new antimicrobial is considered a commercial risk, given that potential revenue will be limited by prescribing restrictions to minimise the risk of resistance. International research into methods to reinvigorate antimicrobial development has recommended that governments focus on

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[5] Most health insurance companies do not cover unregistered drugs although some may cover inpatient treatment with unregistered antimicrobials depending on the policy

[6] http://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee

regulatory and funding mechanisms ("pull incentives") to ensure industry has economic certainty once an antimicrobial is marketed.[15]

Although de-linked business models are a theoretical solution, implementation remains practically challenging particularly given the global co-operation required. The UK national AMR plan includes the intention to explore de-linked funding of antimicrobials.[16] Practical details regarding implementation of the UK subscription payment model remain unclear.[16,17] Concerns have been raised that lump-sum payments, irrespective of use, may facilitate distribution of public resources for private gain based on possibly over-inflated estimates of 'value' advocated by manufacturers.[6]

Any new funding model needs to guarantee availability of the antimicrobial when needed, as patient outcomes are dependent on timely administration, particularly for life-threatening infections. Lack of economic return has been cited as an underlying causative factor in the increasingly frequent problem of antimicrobial shortages both in Australia and globally.[19, 20]

Medicines 'formularies' are used by Australian hospitals to ensure constancy of supply and contain procurement costs of medicines.[21, 22] Hospital formularies are typically managed by multi-disciplinary drug and therapeutics committees. Formulary decisions should ideally consider cost-effectiveness but are typically motivated by budget impact i.e. a local reduction in medicine costs, and may fail to adequately assess system-wide clinical benefits or cost-reductions.[23, 24] Some states in Australia have moved to state-wide formulary decision-making to improve equity of access and standardise care between hospitals.[25-28]

This study was designed to explore the feasibility and practicalities of implementing a de-linked funding model for antimicrobials in Australia, from the perspectives of policy-makers/payers and the pharmaceutical industry.

Methods

Design and setting

The context of this study was the Australian healthcare system, a universally funded public health system sitting alongside a privately funded health sector. The Australian setting was

chosen as a case study, to provide the context of a high-income country with multi-tiered healthcare funding, and a relatively small economic market globally. A qualitative approach using in-depth semi-structured interviews was chosen to explore nuances within and between the views of participants.[28] Interviews followed an interview guide (Appendix 4) based upon a search of published and grey literature, with open-ended questions allowing participants to determine the nature of their responses, enabling additional explanation or provision of examples. Interviews were conducted by the first author, either face-to-face or via video or phone conferencing.

Recruitment of participants

Nine participants from the pharmaceutical industry and nine policy-makers were recruited between July and December 2018. Recruitment was initially purposive to select key stakeholders, with additional participants recruited by snowball sampling[200, 289] until thematic saturation was achieved; that is, until no new themes pertaining to the study objectives were identified within the final interviews.[202, 290] Stakeholders from the pharmaceutical industry represented six companies, ranging from large multi-national companies to small-medium companies, in addition to a representative from Medicines Australia.[291] Industry participants were senior employees working in managerial or policy roles within companies currently developing or marketing antimicrobial medicines in Australia, as well as medical managers and market entry specialists. Policy-makers included federal government policy-makers, state government employees involved with state-wide formulary decision-making, and members or ex-members of the Australian Pharmaceutical Benefits Advisory Committee (PBAC) or advisory committees to the Australian regulator, the Therapeutic Goods Administration (TGA).

Analysis

Interviews were recorded and transcribed verbatim, speech idiosyncrasies (such as 'you know', 'sort of' or 'um') removed for ease of reading. Names were de-identified at the point of transcription and replaced with a study number to anonymise the individual and their workplace or associated role. Data collection and analysis were conducted simultaneously, with deductive (predefined) as well as inductive coding with creation of new codes when required.

The transcripts were coded and thematically analysed using NVivo® software (version 12, QSR International Pty Ltd) in accordance with the framework method of qualitative data analysis.[35] Transcripts were read and re-read by the first author to allow familiarisation with the data and an initial coding framework developed following the initial interviews in consultation with two other authors. These initial codes were categorised into potential themes, which were refined with the addition of new data. Minor themes linked by a common distinct idea or subject were grouped together as a major theme. Any differences in interpretation were resolved through discussion amongst the authors.

Ethics

This research was approved by the University of Adelaide Human Research Ethics Committee (Approval H-2018-136). Participants were provided with written information regarding the study and informed consent was obtained.

Results

Themes

A dominant theme addressed the issue of how to translate the clinical value of an antimicrobial into a monetary value, and this is discussed elsewhere (N Hillock, T Merlin, J Karnon, J Turnidge, J Eliott, unpublished data). Five further themes drawn from the data, and pertaining to alternative methods of reimbursement, are discussed below.

Theme 1: Funding silos for medicines and healthcare are a barrier to de-linking reimbursement

Many participants were aware of de-linked funding models proposed internationally but most agreed that implementation would be challenging, citing the complexities of multiple funding sources for medicines in Australia as a barrier.

The divide between the perceived responsibilities of different levels of government was evident in the responses from both policy-makers and stakeholders from industry (Table 7.2).

Table 7.2. Quotes illustrating division in perceived responsibilities of level of government

In general in health across Australia we've got problems with multiple silos and multiple different areas of funding and almost sort of stealing money from one area. A lot of it is false economics where the big picture is you've got a certain amount of money, and whether it's Commonwealth money or state money. (State policy-maker)

Antimicrobials that are for emerging resistant organisms are in smaller groups and it could be hospital only, so therefore it may be a state budget thing more so than a Commonwealth budget matter. (Federal policy-maker)

There is a bit of divide between what happens in the commonwealth-funded space in terms of prevention [of resistance] versus what can kind of happen at the hospitals. I think it is going to become an increasing problem and I think we probably do need to relook at the funding models of some these [interventions] … taking into account the increasing complexity of patients and their conditions they have. (State government policy-maker)

So that is where I think it gets really difficult, because as it stands most of the antibiotics we are talking about the government are not paying for. The state hospitals are paying for it. (Pharmaceutical industry stakeholder)

There is always that tension between the state and federal budget, and if Pharma comes to the federal and says "please pay us money for new antibiotics, and you are currently not paying anything but we want some money", so you know, we will never win that battle on our own. (Pharmaceutical industry stakeholder)

In general, participants felt a more centralised funding of antimicrobials would be beneficial, particularly industry stakeholders who were generally in favour of federal funding of hospital antimicrobials. Most policy-makers agreed, suggesting that centralised funding of antimicrobials, similar to the funding of vaccines or blood products, may remove cost-shifting incentives: "It would be a lot simpler if the funding was less split between the states and the federal [government]".

Some industry stakeholders acknowledged that with hospital or state-based tendering, there can be marked variation in antibiotic prices between hospitals and states, and that a nationwide tendering system may remove price differentials between states. State policy-makers favoured centralised tendering for generic antibiotic supply, stating "It would make

sense that we've all got the same price". There was concern, however, about awarding a tender to a single supplier due to possibly increasing the risk of shortages:

> You offer a 100% to that company, but then you run that risk … where that one company can no longer supply and then you get into shortages and unavailability because the other players that in a competitive market are there, have just gone away and they don't do it at all anymore (PBAC member)

Some participants felt that federal management and funding of generic antimicrobials would prevent local stockpiling if there was a shortage, "because then you're removing the free-for-all that happens when something goes out of stock".

Opinions varied regarding centralisation of funding and supply for new drugs. Some participants felt there was a need for local hospital management to allow for flexibility in rare or complex infections:

> In principle a common formulary is good; the time bringing it all together and the need to have flexibility in certain circumstances are an impediment. (Federal policy-maker)

Theme 2: Varying levels of evidence (currently) required for funding depending upon the setting

A further perception was that new antibiotics were generally destined for use in the hospital system, and that access to funding in the public hospital system was a less rigorous process than for federal funding of these medicines through the PBS, where evidence of value for money (cost-utility) is required (Table 7.3):

Table 7.3. Illustrative quotes – varying levels of evidence required for funding depending on payer

The lack of cost-effectiveness constraints around the non-PBS marketplace increases the chance that manufacturers would license a drug with the TGA irrespective of whether they put it forward for the PBS or not. (Ex-PBAC member)

Because you're not going down the PBS road … they're (public hospitals) freer to use what they need to use. (Industry representative, policy role)

If you get regulatory approval, it's based on whatever trials you've got, whereas a lot of those drugs are used off-label. (Industry representative, market access)

Participants agreed that it would be difficult for new drugs targeting multidrug-resistant infections to attain the level of evidence required to support a regulatory (market approval) decision, and, without regulatory approval, access to federal subsidy for the medicine is not possible in Australia. One industry participant emphasised the challenges with obtaining clinical trial evidence for treatment of multidrug-resistant infections and the ethical issues arising if a patient is randomised to "standard of care" when there is a risk the infection may be resistant to current treatment options:

> Let's say multi-drug resistant *Acinetobacter baumannii*, right? That's an area with great unmet need. If trials were to be done on new agents, then they would want to have not a trial against susceptible *Acinetobacter* because that's not where they want to use it. (Pharmaceutical industry stakeholder)

One policy-maker acknowledged the difficulties regarding changing resistance patterns affecting efficacy: "we have trial data that's generated … we can approve it at a point in time and the difficulty is it may be difficult to replicate these studies at a later time."

Industry stakeholders believed government had a role to assist with collection and assessment of outcome data: "I think we have a good commitment to generating real world data and to supporting clinician-generated data. But should the responsibility be totally on Pharma?". Policy-makers were generally supportive of clinical outcome registries, but were more cautious regarding fast-tracking reimbursement processes "We've got examples in other areas where fast-tracking of drugs has actually led to quite poor outcomes".

New drugs targeted at an unmet need were likely to be high cost, but participants felt they would likely be approved for individual patients at hospital level despite this:

> You are going to have some extremely high-cost antibiotics, extremely costly antibiotics that you will have extremely tight restrictions on … while clearly for an antibiotic you would expect it to be almost instant approval but it may still necessarily rely on some central level of approval. (PBAC member)

Theme 3: Funding status used as a stewardship tool

A further theme, particularly among policy-makers, was that the current 'user-pays' funding model allows cost to be used to control use. As one participant put it, 'paying for something does act as a suitable disincentive for overuse as well'. Some policy-makers felt that having hospitals pay for antimicrobials is a good incentive to keep utilisation rates down, particularly for high-volume generic drugs. Some industry participants also recognised that not being funded on the PBS prevented inappropriate use in the general practice (GP) setting. One industry participant used the example of oral linezolid, "If a GP could prescribe it …, potentially that leads to some misuse of a drug that should be reserved". Some participants felt that separation of payment from use (de-linking) would remove the cost barrier that can be used to prevent overuse.

Although cost could be currently used as a tool to prevent overuse, other participants pointed out that the appropriateness of antimicrobial use can be adversely influenced by the cost, because some of the least appropriate antimicrobials are often the cheapest. "So it might be the right drug to use in that patient, but because it's too highly priced then they will look for another option". Antimicrobial drugs are not priced according to their impact on resistance selection, and sometimes the broader spectrum drugs are cheaper than the narrower spectrum ones:

> At the moment ... the hospital pharmacy budget pays for antimicrobials. So if you have the choice between hypothetically a new agent, which may be more appropriate from a stewardship perspective, or something which is cheap, both of which is going to work in that patient, but one has a higher societal cost, ... they

would have to go with the cheaper agent, because that's the precedent for their hospital budget. (Pharmaceutical industry, medical manager)

Theme 4: Concerns about a de-linked model costing more

Non-industry participants expressed concerns that a de-linked method of reimbursing companies for antimicrobials would cost more than the current funding of antimicrobials in Australia. To fund antimicrobials via a de-linked model and still incentivise new products, payment is made even if the drug is not used. One policy-maker gave an analogy, "a bit like the EU paying farmers not to farm". Uncertainty about the amount a country should pay, and how a new product would be assessed for value to that country's population, was a prominent theme. Participants felt that the impact Australia could have on incentivising antimicrobial development was insignificant in a global context due to its small market size.

There was general agreement across stakeholders that increasing antimicrobial resistance will mean increasing costs associated with infections that are more difficult to treat, but drug procurement costs seemed more visible to payers than the consequences of resistance in the future.

> I think the problem with the de-linked model I guess is finding … a cost-efficient price, and so we could end up just paying a lot more for antibiotics with little benefit. (PBAC member)

Theme 5: Governance of, and access to, antimicrobial use in the private hospital or community sector

Most stakeholders believed that the current funding of medicines in Australia results in inequity of access in the private hospital sector (Table 7.4). Participants agreed that in private hospitals there is an incentive to preference PBS-listed antimicrobials over non-PBS antimicrobials, because they are federally funded, particularly if a health insurer does not cover the cost.

Table 7.4. Illustrative quotes – inequity of access in the private sector

Inequity of access—once you start quoting costs like that then it really comes down to a decision of a bunch of people sitting around a table at each hospital or Network (Local Health Network) as to whether the Network will bear that cost, and in the private system there's a much more defined accounting system. (Ex-PBAC member)

The biggest difference we see between public and private, is private is a lot more restricted in terms of what they spend. (Industry representative)

The PBS, non-PBS thing … again could potentially be an issue with, for the patient, because if they're presented with a perhaps not the most appropriate medication that's going to cost them $6, versus the most appropriate medication which might cost them $100, then that's going to be a barrier to appropriate prescribing. (Pharmaceutical industry, policy manager)

Participants believed that if a patient needed a high cost, non-PBS-funded antibiotic, they would need to be transferred to the public sector for hospital-funded access:

> I think most patients who need high cost antibiotics, they end up accessing it one way or another …, and if it can't happen through the private sector, potentially a lot of that gets transferred into the public sector. (PBAC member)

It was felt that the only way to ensure equity of access to new antimicrobials in the private hospital setting would be for antimicrobials to be federally funded across all settings:

> Clearly if the PBS found a way to approve the use of drugs under specific indications and clearly that's a role that may occur in the private sector … that would definitely improve access in terms of those that saw a way to get approved. (Ex-PBAC member)

Discussion

New antibiotics are destined predominantly for the public hospital setting which is funded by the state governments in Australia, where the level of evidence required to obtain funded access is lower than required for federal reimbursement on the PBS. In addition to challenges assigning a monetary value to a lump sum payment for an antimicrobial, most participants in this study felt that hospital or state budgets were insufficiently flexible to accommodate negotiating either a fully delinked lump sum payment or market entry reward

as part of a partially-delinked model. Federal funding of all antimicrobials was considered an alternative model (a federally-funded national formulary), which participants felt could assist with market stability and remove price discrepancies between the states, but they raised some concerns regarding flexibility and the ability to cater for local differences in antimicrobial epidemiology.

Although current funding of healthcare in Australia is multi-tiered, there are examples of nationwide funding of some resources, such as the of blood products through the National Blood Authority (NBA). The NBA is federally funded with a national inventory system that allows local health services to enter their inventory levels, to limit waste and ensure the product is available where it is needed.[36]

Concern about increased costs were expressed by non-industry participants. Participants in this study also raised concerns about equity of access and the governance of stewardship in the private hospital setting currently, and agreed that federal oversight and funding could improve equity.

Limitations

Our sample of policy-makers included funding decision-makers at Australian federal and state level, but only two states were represented, despite attempts to recruit participants from two other states with state-wide formulary processes. States without a state-wide drug formulary were not represented. While the majority of participants were recruited by purposive sampling to ensure a representative sample, some participants were recruited by snowball sampling which may increase the risk of selection bias.

Conclusion

The adoption of a de-linked reimbursement model for antimicrobials in Australia would require a system-wide transformation of funding. Fragmented silos of funding and split responsibility for consequences of future resistance were highlighted by stakeholders as a significant barrier to implementing a de-linked reimbursement model. With current funding silos, there is not one single 'funder' responsible for the patient outcome, nor the outcome regarding the impact on AMR in the future. The economic burden of multi-drug resistant infections sits largely with hospitals as patients with these infections are predominantly

treated in the hospital setting. Hospitals have antimicrobial prescribing policies aimed at reducing resistance, however there is no economic incentive to consider the long-term impact of formulary decisions on future resistance and the consequent economic burden in future decades; the economic drivers for hospitals are to keep current medication costs at a minimum and enable patient discharge as soon as possible. De-linking reimbursement from sales would require moving towards a more centralised (federal) funding model to remove silos of responsibility regarding the management of AMR, including the funding of antimicrobials. Increased federal governance over the access and use of antimicrobials in the private sector would also be required.

In addition, to implement a nationally-funded de-linked reimbursement model for new antimicrobials, the evidentiary support for reimbursement would need to be more flexible than current PBS requirements, given that many multi-drug resistant infections are off-label indications (i.e. medical conditions not approved by the national drug regulatory body). Governments need to consider adaptive methods of collecting sufficient evidence for federal reimbursement of novel antimicrobials, or for reimbursement of older antimicrobials for novel indications, with consideration of the wider public health impact.

This study provides a unique insight into the perspective of stakeholders regarding the feasibility of an alternative de-linked model of reimbursement for antimicrobials in Australia. While the larger markets of the USA, Europe, Japan and China are driving the public investment into antimicrobial development, the methods of reimbursement and regulatory controls regarding usage differ among these large market players. Australia is representative of smaller, high-income countries with complex, multi-tiered reimbursement structures for medicines. Findings from this study could be applicable to other countries with reimbursement frameworks similar to the Australian model. De-linked funding for antimicrobials requires a collaborative international approach which will necessitate significant policy and funding reform within countries in order for it to succeed globally.

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Transparency declaration

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Chapter synopsis

To summarise, this chapter has provided the perspectives of both the pharmaceutical suppliers and policymakers with regard to alternative funding approaches for antimicrobials in Australia. In exploring the opinions of stakeholders the chapter addresses the question of feasibility and whether a de-linked model of funding is viable within Australia. Stakeholders highlighted a number of challenges specific to the Australian context as well as to the wider global context. Further research or policy action would be required to identify the many funding pathways across various healthcare settings in Australia that could be utilised, should a de-linked funding model be implemented. Particular areas of uncertainty were highlighted by stakeholders, in particular, the optimal approach to value assessment, which is further explored in the following chapter.

CHAPTER EIGHT
Understanding Value

Preface

This chapter contains the second of two publications resulting from a qualitative study investigating the Australian stakeholder perspective. The first publication resulting from the stakeholder interviews, which focused on the feasibility of a delinked reimbursement model in Australia, is reproduced in chapter seven of this thesis.

The text, tables, figures and appendices from the second publication are reproduced in this chapter.

Publication

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Contribution to the Paper	Conducted the background literature search, wrote the study protocol, interviewed participants, coded the transcripts and conducted the thematic analysis, interpreted the data and drafted the manuscript		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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By signing the Statement of Authorship, each author certifies that:

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    ii.   permission is granted for the candidate to include the publication in this thesis; and

    iii.   the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Abstract

Background: The frameworks used by Health Technology Assessment (HTA) agencies for value assessment of medicines aim to optimise healthcare resource allocation. However, they may not be effective at capturing the value of antimicrobial drugs.

Objective: To analyse stakeholder perceptions regarding how antimicrobials are assessed for value for reimbursement purposes and how the Australian HTA framework accommodates the unique attributes of antimicrobials in cost-effectiveness evaluation.

Methods: 18 individuals representing the pharmaceutical industry or policy-makers were interviewed. Interviews were transcribed verbatim, coded, and thematically analysed.

Results: Key emergent themes were that reimbursement decision-making should consider: the antibiotic spectrum when assessing value, risk of shortages, the impact of procurement processes on low-priced comparators, and the need for methodological transparency when antimicrobials are incorporated into the economic evaluation of other treatments.

Conclusions: Participants agreed the current HTA framework for antimicrobial value assessment is inadequate to properly inform funding decisions, as the contemporary definition of cost-effectiveness fails to explicitly incorporate the risk of future resistance. Policy-makers were uncertain about how to incorporate future resistance into economic evaluations without a systematic method to capture costs avoided due to good stewardship. Lacking financial reward for the benefits of narrower spectrum antimicrobials, companies will likely focus on developing broad-spectrum agents with wider potential use. The perceived risks of shortages has influenced the funding of generic antimicrobials in Australia, with policy-makers suggesting a willingness to pay more for assured supply. Although antibiotics often underpin the effectiveness of other medicines, it is unclear how this is incorporated into economic models.

Introduction

There is much debate in the literature regarding what constitutes 'value' in healthcare and how to measure it.[122, 292-296] The value of a medicine or health technology can be described as a multidimensional concept which incorporates utility (the health and wellbeing benefits to an individual and/or society) as well as the costs.[297] The assessment of value of a healthcare intervention can be impacted by the level of importance placed on particular attributes of the intervention.[292, 297]

Health Technology Assessment (HTA) is the systematic process of synthesising evidence to assess the value of a medicine or health technology.[132] The value assessment includes an evaluation of the safety, efficacy, effectiveness and cost-effectiveness of a technology as well as wider health system and societal impacts, compared to currently available therapies using a predefined framework to ensure transparency and accountability.[121, 298, 299] The purpose of HTA is to inform policy and funding decisions in healthcare, including, how to best allocate taxpayer funds. From the health economic perspective, value is typically measured using cost-effectiveness analysis (CEA) or cost-utility analysis (CUA).[292] The cost-effectiveness of a new medicine is determined by the incremental cost-effectiveness ratio (ICER), an estimate of the relative benefits and costs of a new medicine over currently available treatment options.[300] In a cost-utility analysis, benefits are measured from the perspective of the health system using the Quality-Adjusted-Life-Year (QALY). Frameworks for assessing value using just the QALY have been criticised for not incorporating other aspects of value.[293] Appropriate selection and use of antimicrobial drugs to minimise future resistance has a public health value that is challenging to quantify. While modelling methods generally enable accurate predictions of costs and benefits over a time horizon for most drugs, the utility of models to estimate the impact of a new antibiotic (beyond the resolution of the infection) is low, due to the high degree of uncertainty around future antimicrobial resistance and the complexity of modelling required.

With increasing antimicrobial resistance (AMR), there is global concern about the lack of new antimicrobials currently in clinical development to meet the increasing need.[9, 130] Non-antimicrobial drugs (e.g. oncology drugs) are much more profitable for manufacturers as

they are valued more highly by funders. To incentivise companies to invest in developing new antibiotics, alternative methods of assessing their value have been proposed.[130, 301]

Although antimicrobials have attributes that make them unique compared to other classes of medicine, they are currently evaluated using the same methodological framework to assess their cost-effectiveness and value to society. A review of HTA reports for the 10 years to June 2016 in 11 countries (the 10 largest European Union economies plus Norway) found that in some evaluation reports additional values such as 'insurance value' were mentioned but not explicitly included in recommendations.[129]

Restricting the use of broad-spectrum antimicrobials is an essential strategy of antimicrobial stewardship, so as to limit the spread and rise of antimicrobial resistance.[302, 303] Future resistance to antibiotics is unpredictable, and many factors impacting future resistance are not related to the drug itself but attributable to other factors such as suboptimal infection control practices. However there are factors that are intrinsic to the drug, such as the spectrum of activity, which may impact future resistance.

A notable difference between antibiotics and other medicines is that the usage of an antibiotic in one patient potentially has an impact on the future efficacy of that drug in that patient, as well as in other patients to whom resistant bacteria have been transferred. As resistance genes can be transferred between different bacteria the effectiveness, and consequently the cost-effectiveness, of one or more antibiotics can change depending on usage. In addition, any 'real world' factors influencing usage of a particular drug (e.g., regulatory policy, funding decisions, shortages of other drugs) can impact future resistance rates, and, as a consequence, therapeutic effectiveness and patient outcomes. Economic evaluation is therefore challenging with antibiotics, as resistance rates (and efficacy of the treatment in future patients) will vary over time for the medicine under evaluation, as well as for the comparator. These 'real world' factors which impact resistance rates and patient outcomes should be included in cost-effectiveness analysis but, with wide margins of error, these estimates of future resistance are largely speculative.

In Australia, funding decisions for medicines occurs both at the federal and state level. The Pharmaceutical Benefits Advisory Committee (PBAC) evaluates medicines for federal funding via the Pharmaceutical Benefits Scheme (PBS), whereas decisions regarding the funding of

medicines for public hospital inpatients in Australia are largely controlled by state-wide formulary committees or hospital drug and therapeutics committees (DTCs).

Value-based pricing for antibiotics is being considered in the UK, though regulatory bodies are grappling with how to measure 'value'.[304] Many factors other than QALYs have been identified as important considerations when assessing value, including the burden of disease and wider social impacts.[305] For any medicine that is publicly funded, there needs to be agreement between governments and manufacturers about how much will be paid for that medicine. While manufacturers require adequate reimbursement for investment into a new medicine, the cost of new medicines must be affordable for governments and patients.

As part of a research project investigating alternative methods for regulating and funding antimicrobial drugs, this qualitative study was designed to elicit and analyse the perspectives of policy-makers and pharmaceutical industry representatives regarding how antimicrobials are assessed for value for the purposes of reimbursement. The study explored stakeholder perceptions of how the framework for HTA in Australia accommodates the unique attributes of antimicrobials in cost-effectiveness analyses.

Methods

Design and setting

A qualitative approach using in-depth semi-structured interviews was chosen to explore nuances within and between the personal opinions of stakeholder participants.[306] Interviews followed an interview guide which was based upon a search of published and grey literature. Medline and Econlit databases were searched for published health policy or economic studies investigating alternative business models for antibiotics; HTA agency websites were searched for public summary documents for antimicrobial drugs; and government websites were searched for policies or other documents referring to medicines regulation, reimbursement and supply chain management. Open-ended questions allowed interviewees to determine the nature of their responses, and the interviewer to probe or seek clarification (Appendix 4). Interviews were conducted by the first author, either face-to-face, or via phone or video conference.

Recruitment of participants

Pharmaceutical industry representatives and regulatory or funding decision-makers at a federal or state level were recruited, initially by purposive sampling to select key stakeholders, with additional participants recruited by snowball sampling.[200, 289] Senior employees working in managerial or policy roles within pharmaceutical industries currently developing or marketing antimicrobials in Australia, as well as medical managers and market entry specialists, were included. Policy-makers included state government employees involved with formulary funding decisions at a state-wide level, federal government policy-makers, members or ex-members of the national Pharmaceutical Benefits Advisory Committee or Therapeutic Goods Administration (TGA) advisory committees. Recruitment continued until thematic saturation was achieved; that is, until no new codes or themes pertaining to the study objectives were identified within the final interviews.[202, 290]

Analysis

Interviews were transcribed verbatim (with speech idiosyncrasies such as 'you know' removed for ease of reading), coded, and thematically analysed using NVivo® software (version 12, QSR International Pty Ltd) in accordance with a qualitative framework method.[307] At the point of transcription all names were replaced with a study number to de-identify the participant and their workplace or associated role. Transcripts were then read and re-read to allow familiarisation with the data and an initial coding framework developed. Data collection and analysis were conducted simultaneously, with deductive (predefined) as well as inductive coding, with new codes introduced when required. Initial codes were merged into more focussed codes on agreement between three authors (NH, TM and JE), which were then refined into emergent themes. Once themes and codes were agreed, all authors were involved in discussion around the data interpretation. Participants were consulted via email to clarify uncertainties in the analysis of individual transcripts.

Ethical considerations

This study was approved by the University of Adelaide Human Research Ethics Committee (H-2018-136). Written information on the purpose and method of the study was provided to participants prior to the interviews, and informed consent was obtained.

Results

Participants

Eighteen participants (nine pharmaceutical industry representatives and nine policy-makers) were interviewed between July and December 2018. The industry stakeholders were individuals in senior roles, including medical managers/directors (n = 2), chief development/commercial officers (n = 2), manager/director of regulatory policy (n = 2), a CEO, a national sales manager, and a market access analyst. Policy-makers included state government employees (n = 3), federal government employees (n = 2), members or ex-members of the PBAC (n = 3), and a member of a TGA advisory committee. Individuals representing state governments were directly involved with formulary funding decisions at state-wide level. All other policy-makers were involved in regulatory or funding decisions at a federal level. Interviews lasted between 22 and 60 minutes.

Themes

A dominant theme pertained to the method of reimbursement and the feasibility of de-linking payment from sales volumes and this is discussed elsewhere.[308] Four key themes were derived from the analysis regarding the value assessment or cost-effectiveness evaluation of antimicrobials (see Table 8.1).

Table 8.1: Illustrative quotations for identified themes

Theme	Illustrative quotes
Consideration of antibiotic spectrum in value assessment	"There is that sort of external and difficult to quantify cost which is that if we end up using better and broader spectrum antibiotics, then in the longer term those broader and longer term, broader spectrum antibiotics will become less effective over time" (PBAC member)
	"you can get a very effective antimicrobial for less than narrow-spectrum antimicrobial, so almost the calculation is almost back-to-front in that regards" (State-wide policy-maker)
	"going back to some of the decisions we've had to make, it's very hard to think about QALYs, to think about additional life gained in terms of stewardship" (State-wide policy-maker)
	"I think the general idea that we should be implementing policies or models that make it more favourable to preserve narrow-spectrum antibiotics is a good one but in terms of quantifying exactly how much more we should be paying I think it's very hard to do" (PBAC member)
Consideration of shortages in funding decision-making	"definitely in terms of insurance against shortages, we take that into account" (State-wide policy-maker)
	"Having that available, that extra drug available and diluting the use of, or deducing the use of the drug which was in shortage, was an important factor" (State-wide policy-maker)
	"I think guaranteed supply has to be part of the equation and sometimes that is definitely worth a bit more money" (State-wide policy-maker)
Comparators are cheap and procurement processes are devaluing them further	"There is this sort of connection between the low cost and the generic sort of antibiotics and any newer antibiotics … we need to still make it attractive and profitable for companies to produce and market the generic antibiotics" (PBAC member)
	"we've sort of said for a long time that maybe vancomycin gets used more than it should, just because it's so cheap" (Industry stakeholder)

Recognition that antibiotics underpin the effectiveness of other medicines (need for transparency regarding how antimicrobials are incorporated into the economic evaluation of other medicines)	"people dying of infections, that's invisible, because most of the time it doesn't happen" (Industry stakeholder, Global regulatory policy)
	"I was at an infections in cancer workshop for an entire day, and they were presenting all of the new cancer therapies and what the consequences are for patients who get, or what infections they get" (Industry stakeholder)
	"People don't actually die from cancer … I mean they do … But a lot of them actually die from the infections" (Industry stakeholder)

Theme 1: Consideration of antibiotic spectrum in value assessment

Stakeholders agreed that current cost-effectiveness approaches to assessing value of antimicrobials preclude consideration of relevant factors impacting future resistance, in particular, spectrum of activity. Policy-makers in funding-decision making roles were open to the idea of incorporating other stewardship factors into the value assessment of antimicrobials, for example, stating "I would be willing to find a way of incorporating some of these other things into it which may not be captured by cost per QALY".

To illustrate difficulties in considering comparative spectrum of activity in funding decisions, several stakeholders raised the example of intravenous amoxicillin-clavulanate (IV amoxiclav). IV amoxiclav has been available in many countries since the 1980s, but in Australia, only the oral dosage form was marketed until 2017 when a generic brand was launched. Another broad-spectrum penicillin, piperacillin-tazobactam (piptaz) is the most commonly used IV penicillin/β-lactamase inhibitor in Australian hospitals [309]. The antimicrobial spectrum for both drugs are similar, but piptaz is active against additional pathogens, most notably Pseudomonas aeruginosa [310]. Global patents on both drugs have long expired and they are relatively cheap globally; however, IV amoxiclav is significantly more expensive than piptaz in Australia (AUD $28-29/day compared to AUD $12-16 based on usual daily doses in adults).

> We were looking at the marginal costs, marginal additional costs of IV Augmentin
> (amoxiclav) vs IV piptaz, and then the data to show you saved resistant cases is non-
> existent, so then it becomes a conceptual discussion about is spending $500,000

more or spending a million dollars more to have a narrow-spectrum drug, is that cost effective?

Decision-makers rely on cost-effectiveness analysis to make decisions about future costs and benefits of funding a new drug, yet because the ICER does not capture the impact of antibiotic spectrum on future resistance rates, it is difficult to incorporate into funding decisions:

> That's where we really got stuck with, with IV Augmentin. We knocked it back a few times and that was just because members couldn't quite understand why we would need to pay so much more for something that we already have an option for. And they understand antimicrobial resistance … you can't say that it's going to give x-patient you know, 3 months more life, and that's how they always think about in terms of cost effectiveness.

Policy-makers expressed difficulty in conceptualising the opportunity cost of paying more for narrower spectrum:

> When trying to have the members of our various panels think about it, we put it in terms of the cost of an additional, the opportunity cost for an additional ID (Infectious Diseases) Physician, or how much it might cost for a resistant Pseudomonas case but it's all still very guestimate kind of discussions.

Despite general consensus among policy-makers that there is additional 'value' in using the narrowest spectrum possible to treat an infection, one policy-maker felt it might be futile to pay extra for narrow-spectrum unless other countries do as well:

> Global responsibility, even if we pay a premium for narrower spectrum, if other countries don't take steps to limit resistance, the extra money we pay for narrower spectrum is not worth it. So it may be that we pay a higher price for narrow-spectrum antibiotics and we restrict the use of the broader spectrum antibiotics but we still pay the price of worsening antimicrobial resistance.

Without an economic incentive to develop narrow-spectrum antimicrobials, manufacturers may only focus on broad-spectrum agents. Developing broader spectrum drugs potentially reduces economic risk for companies due to more potential indications for the drug in the

future. In contrast, a narrow-spectrum drug may only have a single indication, often with a relatively low incidence. Some policy-makers felt it would be difficult to financially reward companies for developing narrow-spectrum agents, "I think there will be some merit in that perhaps but yeah, it will be a difficult one". Fidaxomicin was raised as an example of a narrow-spectrum drug with a single indication (treatment of Clostridium difficile) that was considered too expensive compared to currently available broader spectrum options:

> The best example of that is fidaxomicin with C diff? So in theory, the most narrow-spectrum antibiotic ever because it only treats one condition and is a cure but when they brought it in it was $2000.

Decision-makers found it challenging to consider the impact of the spectrum of activity on future resistance compared to other factors that may impact resistance (table 1). Participants frequently referred to modelling to estimate future economic burden, but when asked to elaborate, most recognised that the substantial uncertainties associated with future resistance would result in very wide margins of error. One participant involved with hospital formulary funding decisions at a state-wide level expressed the dilemma for decision-makers:

> I think some of our decision-makers may be a bit disheartened if that's the right word about what impact they can actually make in some of these, their decisions in some of these areas. I think a lot of the time it seems like it's out of their control and even if they do make these small changes, the impact is going to be so small, is it worth considering?

Theme 2: Consideration of shortages in funding (formulary) decision-making

Participants agreed that shortages negatively impact clinical and economic outcomes, particularly when there is a need to initiate antimicrobial treatment immediately. Assurance of access was considered valuable, "I think guaranteed supply has to be part of the equation and sometimes that is definitely worth a bit more money". The risk of shortages was incorporated into funding decision-making at state level, "definitely in terms of insurance against shortages, we take that into account".

Industry stakeholders attributed shortages to low prices paid by government:

Shortages occur due to market conditions and policies that deflate the price of generic medicines below reasonable levels. If price falls below the break-even point, the most efficient manufacturer may have to exit the market, leading to a loss in supply.

Shortages can directly impact the clinical outcome of an individual, but can lead to use of broader spectrum alternatives, which may impact future resistance rates and future antibiotic effectiveness in other patients: "if we make those antibiotics too cheap … the price we pay is that they are no longer available and people will inevitably get pushed to using broader spectrum antibiotics, yeah".

Policy-makers argued that increasing prices paid on the PBS would increase the reliability of supply: "a lot of [antimicrobials] are covered on the PBS anyway, and that's where we may want to be paying a bit more, to make it profitable for companies to continue to produce them". They recognised, however, that at a hospital level, under the fixed-budget model for procurement, there is little capacity to pay more for antibiotics, and tendering drives antibiotic prices down further, "it's a race to the bottom to win a tender".

Theme 3: Comparators are cheap and procurement processes devalue them further

Because most currently-used antibiotics are cheap, it is impossible for companies to develop new drugs that are cost-effective in comparison, for infections that are not yet resistant to current options. Comparator drugs are in most cases generics and often very cheap, so that even if they are the inferior choice of treatment for a patient from a stewardship perspective, they may be used due to tight budget constraints on hospitals: "Ceftriaxone IV costs $1 a vial. So they use ceftriaxone all the time". This quote illustrates that the comparator drug may be very cheap, and while often equally effective at resolving an infection, may be less appropriate than narrower spectrum drugs that are more expensive in Australia, such as benzylpenicillin.

Some participants referred to the PBS price-reduction policy to illustrate the declining prices of generic antimicrobials:

So the price crashes down. There is actually no mechanism for the price ever to go up. And the reality of life is all costs go up over time, all costs. Petrol cost, freight costs, input costs, raw material costs.

Theme 4: Need for transparency about how antimicrobials are incorporated into the economic evaluation of other medicines

Stakeholders agreed that effective antimicrobials are essential in many therapeutic areas where the disease or treatment reduces that patient's natural immune defences. As one participant framed it, "it underpins like some of the more profitable therapeutic areas".

Multiple participants cited the price of oncology drugs to illustrate the price gap between antibiotics and more lucrative medicines. There was general agreement that governments are willing to pay higher prices for oncology drugs, particularly where there is an unmet need. There was disagreement, however, that companies specialising in oncology or other immunosuppressive drugs should subsidise antibiotic development despite acknowledgement that patients on immunosuppressive drugs were more likely to require antibiotics. One industry participant stated, "I don't really think that would be palatable … I don't think we should be necessarily forcing companies to invest where they don't want to invest".

A state government participant understood that the PBAC incorporates adverse effects and co-therapy into their economic evaluation of oncology drugs, but was unclear whether concurrent or consequential antimicrobial treatment was similarly accounted for:

> I don't think that it's transparent and it's not explicit in what they are taking into consideration. I think it has to be a part of the full conversation about cost-effectiveness and whilst I'm pretty sure that it is, it will be nice to make it more clear, so that the allocation of money or the savings be attributed to where it needs to go.

Discussion

This study provides an insight into the complexities involved with placing a monetary value on antimicrobial drugs. Participants agreed there was a notable disparity between prices paid for new antibiotics compared to other new drugs such as oncology drugs, and acknowledged this is the reason many companies have abandoned research and development of antimicrobials. Most participants, particularly those from pharmaceutical companies, expressed the view that the price should be higher to reflect additional public health benefits, such as in the value ascribed to vaccines. This view is in accordance with

other authors who have suggested that current value assessment frameworks utilised by HTA agencies globally "may not capture the broader public health benefits of antibiotics, including the value of tackling AMR".[130] However, although the unique properties of antimicrobials lends weight to their argument that the HTA methodology for reimbursement should have a specific framework for antimicrobials, the negative impacts of introducing even broader acting, new antimicrobials into clinical practice has not been addressed.[130]

The spectrum of activity and how to incorporate it in the value assessment of antimicrobials was a dominant theme in this study. Overuse of broad-spectrum drugs can cause harm with regard to the impact on resistance rates in the population, and in general participants agreed that it is difficult to incorporate stewardship towards narrower spectrum drugs in funding decisions because the future impact on resistance is difficult to quantify. Ideally, an estimate of the current economic burden of AMR and an extrapolation of the burden in the future would be informative to decision-makers. Understanding the relationship between human, animal and environmental use of antimicrobials is limited by a lack of available, meaningful data. In addition, the AMR burden of an individual country is not independent of the burden in other countries (and the policies and consumption rate of antimicrobials in those countries).

While broader deliberative processes in HTA frequently consider less-readily quantifiable factors to inform funding decision-making (for example, public health issues), the methods for considering the development of pathogen resistance (to either the new drug, the comparator drug(s), or to multiple drugs in clinical practice) are not explicit.[121] The current frameworks for value assessment of new antibacterials do not reward narrow-spectrum agents; rather, there is greater incentive for manufacturers to develop and market broader spectrum agents with more potential future indications. This is not to argue that broad-spectrum drugs are not valuable per se. The "value" of the antibiotic spectrum for an individual agent is correlated with certainty of the diagnosis; for example, for empirical treatment where the causative organism has not been confirmed, a broader spectrum drug is more likely to have activity against the pathogen. However, once a pathogen has been identified, a narrower spectrum agent targeting that pathogen would have less impact on other commensal organisms, carry less risk of antimicrobial resistance, and therefore would have more societal value. Future research into modelling methods to capture the impact of

spectrum on resistance could potentially involve the integration of a non-fixed antimicrobial spectrum variable. Nonetheless, public hospitals in Australia operate under a fixed-budget procurement model, and this may constrain their capacity to pay more for narrow-spectrum antibiotics even if the beneficial impact on future resistance could be proven.

Shortages of antimicrobials was another prominent theme in this study with many participants attributing the problem to insufficient reimbursement. Participants representing state-wide decision-makers felt that assurance of supply was 'valuable' and suggested a willingness to pay more to avoid shortages (see Table 8.1). Patient outcomes with antimicrobial treatment are impacted by the expeditiousness of treatment initiation and delays in accessing the appropriate antimicrobial can be detrimental to the patient or result in substitution with an inappropriate agent. A number of studies have highlighted the clinical and economic impacts of antimicrobial shortages.[311] Shortages can result in the use of more toxic antimicrobials, broader spectrum antimicrobials, longer hospitalisations, and long-term morbidity from inadequate treatment of infections, in addition to the opportunity cost of pharmacy clinical services when pharmacists spend significant time procuring alternative, and often less optimal, treatment to replace an antimicrobial that is unavailable.[146] How assurance of supply is incorporated into the accepted price hospitals are willing to pay is unclear; however, policymakers in this study emphasised that shortages contribute to the inappropriate use of broader spectrum drugs which may adversely affect resistance rates.

Limitations

Our sample of policy-makers included funding decision-makers at Australian federal and state level, however only two states were represented. Attempts were made to recruit participants from the other two states that currently have a state-wide formulary process, without success. States that do not have a state-wide drug formulary process were not represented. This study was limited to Australian stakeholders therefore only pharmaceutical companies with an interest in the Australian antimicrobial marketplace were included.

Conclusions

These study results illustrate that the current framework for value assessment is considered insufficient to fully inform funding decisions for antimicrobials, as contemporary methods for the analysis of cost-effectiveness fail to explicitly incorporate the attributes of antimicrobials that contribute to future resistance. Future resistance is difficult to predict leading to significant uncertainty in economic evaluations, however there is a need for a systematic method to illustrate to decision-makers the costs avoided due to good stewardship through the funding of narrow spectrum antibiotics (and the consequent reduced risk of resistance).

Currently there is no financial incentive for companies to develop narrow-spectrum drugs that are less likely to drive resistance, so companies are likely to focus on developing broad-spectrum agents with wider potential use, thereby exacerbating the burden of resistance long-term. Future research could explore the incorporation of spectrum of activity into cost-effectiveness evaluation, which would provide a weighting in favour of a drug less likely to cause resistance over one that is more likely to do so. Initial steps to establish a 'spectrum-index' based on the spectrum of activity against clinically relevant pathogens has been developed [312], but currently there is no internationally-agreed 'measure of spectrum'.

The 'value' of a drug is essentially the amount the market will bear to pay and therefore it is in the interest of industry to advocate for other measures of value in addition to QALYs. Higher prices alone are not a sustainable solution; with the current sales-based model of funding (where the profit for the manufacturer is proportional to sales), higher prices may further incentivise pharmaceutical companies into promoting inappropriate sales. Different mechanisms of reimbursement of antimicrobials are being explored globally such as market-entry lump sum payments delinked from sales.[43, 45, 75] The feasibility of delinking reimbursement from sales in the Australian healthcare system, also part of this research, is discussed elsewhere.[308]

In Australia, the HTA framework for federally-funded antimicrobials (via the Pharmaceutical Benefits Scheme) explicitly considers antimicrobial resistance; however, it is not clear how the risks or implications of this are considered.[121] Most new antibiotics are destined for use in the hospital setting where the processes for medicine evaluation are less rigorous and lack

a structured HTA framework. Although many factors limit the ability to accurately predict or model future resistance, methods to include the impact of antimicrobial spectrum of activity into deliberative HTA frameworks should be explored. Finally, HTA frameworks globally should include transparent and explicit guidance on how the risks and treatment of multi-drug resistant infections consequent to immunosuppressive treatments are incorporated into the economic evaluation of those immunosuppressant agents.

*****End of published paper*****

Synopsis of chapter

This chapter presents further insight into the various factors to be considered in any alternative funding model going forward, with particular focus on determining the benefits or value of an antimicrobial to both patient care and to society. Although the optimal methodology has not yet been determined, the incorporation of spectrum of activity into the value assessment of antimicrobials could provide a mechanism to incentivise the development of narrow spectrum antimicrobials.

The findings of both this chapter and the previous one provided justification for the selection of economic and non-economic attributes in the following study which aimed to identify key factors that health practitioners value at the point of care and how those factors influence decision-making.

CHAPTER NINE
Understanding Choice

Preface

This chapter contains the text, tables, figures and appendices for the final manuscript for this thesis. This study follows on from the qualitative component of this thesis (Chapters seven and eight) which highlighted the challenges faced by funding decision-makers when attempting to quantify the potential impact an antimicrobial may have on the risk of antimicrobial resistance in microbes in the individual and the environment. The objective of this study was to understand the attributes of antimicrobials that healthcare practitioners consider most valuable in a new antimicrobial treatment, with consideration of patient outcomes and the impact on antimicrobial resistance. A discrete choice experiment was undertaken to estimate healthcare providers' willingness-to-pay for specific antimicrobial attributes, including narrow spectrum of activity which would minimise the risk of future resistance. This research is aimed at identifying the factors (economic and non-economic) that may influence antimicrobial choice by healthcare practitioners at the point of care, and therefore could be considered by policymakers to improve the utilisation of these medicines.

Manuscript

Hillock NT, G Chen, J Turnidge, T Merlin, J Louise, Karnon J. Is it worth the money? Healthcare practitioners' willingness to pay for narrow spectrum and other attributes of antimicrobials (unpublished manuscript).

Abstract

Background: The price of an antimicrobial may affect the antimicrobial choice of prescribers. Narrower spectrum antimicrobials are sometimes more expensive than broader spectrum drugs.

Objective: To determine health practitioners' willingness to pay for narrower spectrum antimicrobials, and to estimate the influence of other factors on treatment choice including patient co-payment, the source of funding, route of administration and whether the antimicrobial is a novel class.

Method: Two discrete choice experiments (DCEs) were administered via an online survey to Australian infectious disease (ID) physicians and/or clinical microbiologists, and hospital pharmacists. Preferences regarding six clinical and economic attributes of a hypothetical new antimicrobial were measured. Both DCEs provided the same clinical scenario, but varied by the number of patients requiring treatment. A conditional logit model was used to investigate preferences for the new antimicrobial.

Results: All but one of the included attributes significantly affected the preferred antimicrobial, including price, whether it was PBS-funded, spectrum of activity, patient co-payment and route of administration. Whether the drug was a novel class of antimicrobial or not did not significantly impact choice. As the price of a narrow spectrum antimicrobial increased, it became less preferred by participants compared to a broad-spectrum cheaper alternative.

Conclusion: The antimicrobial choice of health practitioners with expertise in antimicrobial stewardship is significantly influenced by drug price, the source of funding and patient co-payment. In order to effectively steward appropriate antimicrobial use, the economic factors that drive the antimicrobial choices of healthcare providers must be addressed.

Introduction

With the renewed global investment in the discovery of new antibiotics, there is also an accompanying debate about what a new antibiotic is "worth" to an individual and to society. Drug companies wanting to provide good returns to their shareholders aim to charge as much as they can for new medicines, and governments have in turn developed frameworks to ensure equity of access to the most cost-effective medicines, without ongoing excess fiscal strain on health budgets. For antibiotics, there is the wider public health value of having access to effective medicines, but also ensuring that access does not lead to excess use and therefore negative impacts on public health.

Cost-effectiveness analysis is an established method used to rank the desirability of using two or more medical interventions based on their comparable cost and effectiveness.[313] Cost-effectiveness is a key deciding factor for public funding of new drugs in many countries, including Australia. Current value-based frameworks, when applied to antimicrobials, frequently do not incorporate stewardship or risk factors for future resistance.[314] This has implications for the reimbursement of new antimicrobials and the sustainability of antimicrobial research and development.

Cost is an important factor to consider when prescribing antimicrobials. Formulary decisions in the hospital setting are predominantly based on antimicrobial stewardship, however procurement prices may also affect decision-making.[308] Decisions may be a compromise between the most appropriate antimicrobial, from a stewardship perspective, and the most cost-efficient choice for the hospital. Narrow-spectrum antimicrobials are less likely to drive resistance, but are less attractive for development by manufacturers due to the smaller potential market, and economic return. There is no systematic and transparent method of incorporating the benefits of a narrower spectrum of activity into funding decisions.

Discrete choice experiments (DCE) are a stated preference elicitation method that have been increasingly utilised in health economics to elicit patient preferences and to evaluate the relative importance of attributes that inform policy decision-making.[205-208, 315] DCE methodology is founded on the characteristics theory of demand, which states that individuals attain utility not from the goods themselves, but from the "characteristics of the goods from which utility is derived".[210] Individuals in a DCE are requested to choose

between two options, with each option defined by a set of attributes (or characteristics), and each attribute varying over several levels.[211] DCE methodology assumes that participants will respond in a 'utility-maximising' manner based on the particular attributes in each scenario.[205] Random utility theory (RUT) assumes the underlying utility being estimated is a function of the different attributes and their levels and that there is also a random component or preference variation.[205] The methodological technique involves presenting a series of two alternatives, with differing levels of each attribute to assess the willingness of an individual to relinquish levels of one attribute in order to increase levels of another attribute. DCEs provide a framework for evaluating both non-health related outcomes and health related outcomes. Although the majority of published DCEs in healthcare research focus on the valuation of the patient experience, DCEs have also been used to investigate individual preferences from the decision-maker perspective regarding the allocation of public funding and how different stakeholders may value outcomes.[208, 212]

The aim of this study is to determine health practitioners' preferences for novel antibacterial drugs based on various clinical and economic attributes, including spectrum of activity, out-of-pocket costs to the patient and whether the drug is federally funded in Australia.

Methods

Design of experiment

A hypothetical clinical scenario was posed to participants whereby a patient presented with a multi-drug resistant gonorrhoeal infection, resistant to all currently available antimicrobial drugs. Participants were asked to choose between two hypothetical new drugs that they would prefer to treat the patient. The causative pathogen, *Neisseria gonorrhoeae*, is deemed by the World Health Organization to be a priority pathogen for which new treatment options are urgently needed due to the emergence of increasingly resistant strains.[82] *N. gonorrhoeae* is the most commonly reported critically-resistant pathogen in the community setting in Australia.[15] The hypothetical scenario posed to participants was set in an outpatient clinic of a 500-bed tertiary hospital, with 100 patients requiring treatment per annum in the first DCE and 1000 patients in the second DCE.

In making their choices, participants were instructed to assume the following:

- *Neisseria gonorrhoeae* has 100% susceptibility to both drugs

- A course of either hypothetical drug is a single dose only

- The patient is to be treated as an outpatient (not admitted to hospital)

- Resistance is assumed to all other available antimicrobials used to treat gonorrhoea

- Except for potential injection site pain or redness, assume both drugs have similarly low risk of side effects

- The definition of "broad-spectrum" refers to a similar spectrum to that of a 3rd-generation cephalosporin

- If the antibiotic is a new class of drug with a novel mechanism of action, it may help existing antibiotics to remain effective against other pathogens by reducing selection pressure

- Patient co-payment on prescriptions would be a maximum of $41.30 (or $6.60 for concession card holders)

- The choice of drug is for treatment of a non-pregnant patient, with normal renal and hepatic function

The hypothetical antimicrobial drugs in each choice set were described using a bundle of clinical and economic attributes (Table 9.1).

Defining the attributes and levels

The six clinical and economic attributes were selected on the basis of semi-structured interviews with expert stakeholders from the pharmaceutical industry and government.[314] The attributes included spectrum of activity, price per treatment course, novel pharmacological mechanism of action, route of administration, the source of funding (hospital or national insurance scheme (PBS)) and patient co-payment. The justification for including each attribute, and the levels assigned to them, are provided in Table 9.1.

Selection of discrete choice tasks

In a full factorial design, given the six chosen attributes and their levels, 256 plausible profiles for a hypothetical antimicrobial are possible ($2^4 4^2$). To pose all possible choice questions, with choice sets of two alternatives, each participant would be shown an impractically large number of combinations [256 x (256-1)/2].[206] The design of a DCE is considered efficient if the design yields data that enables the parameters to be estimated

while minimising the standard error.[215] 24 binary choice sets (Fig 9.1) were generated using Ngene® software, in accordance with a D-efficient design (D-error = 0.230749). Participants were randomised to one of three blocks of eight binary choice sets, in addition to a single fixed task (Table 9.2) to check for non-attendance to the questions. After a multiple-choice question, participants were randomised again to a further block of eight binary choice sets.

Figure 9.1. Example choice set

	Broad	Narrow
Spectrum of activity	Broad	Narrow
Price	AU$ 100	AU$ 2000
New class of antibiotic / novel mechanism of action	Yes	Yes
Route of administration	Parenteral	Parenteral
PBS *or* hospital-funded	Funded on the PBS	Funded on the PBS
Cost to the patient (co-payment)	No	Yes
	○	○

Table 9.1: Attributes and levels

Attribute	Levels	Definition	Justification for inclusion in DCE
Spectrum of activity	1. Narrow 2. Broad	'Narrow' – bactericidal against target pathogen but little/no activity against other bacteria &/or normal flora 'Broad' – bactericidal against wide variety of bacteria including normal flora	Overuse of broad-spectrum antimicrobials is a key driver of antimicrobial resistance, however sometimes the broader spectrum drug may be cheaper. Uncertainty regarding the relative impact of antibiotic spectrum on future resistance makes it difficult to assign a monetary value to the additional long-term societal benefit of preferring a narrow-spectrum drug over a broad-spectrum one.
Price of antimicrobial per treatment course	1. AU$ 100 2. AU$ 500 3. AU$ 1000 4. AU$ 2000	Cost of antibiotic course of treatment. Does not include additional hospital costs.	Antibiotics are commonly considered to be readily available and cheap.[316] The lack of new antibiotics entering the market has been attributed to lower prices achievable by developers relative to the economic return for other therapeutic agents.[43, 316]
New class of antibiotic / Novel mechanism of action	1. Yes 2. No	New class of antibiotic with a novel mechanism of action. Or alternatively, a new antibiotic in a current antibiotic class.	A novel mechanism of action, or a new class of antibiotic, may potentially have a reduced risk of cross-resistance from existing classes of antibiotics, and therefore increased societal value.
Route of administration	1. Parenteral 2. Oral	Administered by injection, or taken by mouth as a capsule or tablet	Oral administration is less invasive for the patient, but historically more difficult for companies to develop. Parenteral administration is associated with increased costs associated with hospitalisation, more nursing and pharmacy resources required, and increased adverse effects associated with IV lines.[317-319]
PBS or hospital-funded	1. Funded on the PBS 2. Hospital funded	Hospital budget (state-funded) or funded via the federal government (on the Pharmaceutical Benefits Scheme (PBS))	The impact on the hospital budget is dependent upon whether a drug is federally funded (listed on the PBS) and the expected number of patients annually. Inclusion of the payer aimed to determine whether participants were willing to tolerate a higher price if the cost was not borne by the hospital
Patient to pay co-payment	1. No 2. Yes	Out-of-pocket cost to the patient for a prescription ($41.30, or $6.60 for concession card holders)	Following the pilot of the survey, some clinician respondents provided feedback that they felt they needed to know whether there was any patient cost when making their drug selection.

The fixed task (Table 9.2) to test for task non-attendance assumed that participants (given their expertise) would rationally choose the dominant option. Choice 1 was the rational choice, given the narrower spectrum, lower cost to the healthcare system, no cost to the patient, and equivalent other attributes (PBS-listing, route of administration, and novel class).

Table 9.2. Dominant choice fixed-task test for nonattendance

Concept	Spectrum	Price	Novel class or mechanism	Route of admin	On PBS	Cost to Patient
Choice 1	Narrow	$100	Yes	Oral	Yes	No
Choice 2	Broad	$2,000	Yes	Oral	Yes	Yes

Survey administration

The survey instrument was constructed and administered using the online QuestionPro® platform. The design flow of the survey and DCE participation is illustrated in Figure 9.2. Participants were administered two blocks of 8 choice tasks, a fixed task for non-attendance, two multiple-choice questions, and 6 demographic questions (Appendix 6).

Pilot survey

Before launching the survey, it was piloted with 4 pharmacists and 3 medical practitioners from a similar demographic to the intended participants. As a result of the pilot, an additional attribute (patient co-payment) was introduced to the DCEs. Additionally, feedback on the QuestionPro® survey tool was sought. Participants in the pilot felt the number of DCE tasks were appropriate.

Figure 9.2: Design flow of survey and DCE participation


```
         Survey emailed to an estimated 800 ID/micro and 400 pharmacists

                          Introduction & consent

                     Consented to participate:
                     81 ID/micro and 120 pharmacists          Discontinued:
                                                              19 ID/micro
                     Randomisation  (n=155)                   27 pharmacists

DCE 1:
100         Block 1:            Block 2:            Block 3:
patient     9 tasks (1 fixed)   9 tasks (1 fixed)   9 tasks (1 fixed)
scenario

                     Multiple choice question
                                                              Discontinued:
                                                              11 ID/micro
                     Randomisation  (n=131)                   13 pharmacists

DCE 2:
1000        Block 1: 8 tasks    Block 2: 8 tasks    Block 3: 8 tasks
patient
scenario

                     Multiple choice question

                     Demographic questions
```

Selection of participants

Healthcare practitioners who typically participate in, or coordinate, hospital antimicrobial stewardship (AMS) committees were the target of this study, specifically hospital pharmacists and infectious disease (ID) specialists or clinical microbiologists. The survey was emailed to an estimated 800 ID specialists/clinical microbiologists who were current members of ASID (Australian Society of Infectious Diseases) and approximately 700 pharmacists. Pharmacists were either members of the SHPA (Society of Hospital Pharmacists) ID interest and/or specialty practice group, AMS pharmacists registered with the National Antimicrobial Utilisation Surveillance Program (NAUSP), or pharmacists belonging to the SHPA leadership and management interest and/or practice groups. (The exact number of pharmacists was unclear as some pharmacists were likely to be included in more than one of the email distribution lists). The survey was distributed over a three-and-a-half-month period between the 18th July 2021 and the 4th November 2021.

Statistical analysis

Preference data from the DCEs data were analysed using the random utility framework, which makes the assumption that a participant *i* maximises their utility when choosing between *j* alternatives.[211, 221] A conditional logit model was used to investigate preferences for a new antimicrobial:

$$V_{ij} = \beta_1 spectrum_{ij} + \beta_2 price_{ij} + \beta_3 novel_{ij} + \beta_4 route_{ij} + \beta_5 PBS_{ij} + \beta_6 Patcopay_{ij} + \varepsilon_{ij}$$

where $i = 1,…, I$ participants

$j = 1,…, J$ choices

V_{ij} = the utility that participant *i* obtains from choosing alternative *j*

X_j = attributes of choice *j*

β = preferences for observed choice attributes

ε_{ij} = random ('unexplained') component of the utility associated with any choice *j* for participant *i*

The error term, ε_{ij}, captures the unobserved characteristics or influences on the participant's choice. In some situations, a participant's choice may truly be random, or they may not be fully aware of the benefits or otherwise of each attribute. Any interaction between any of the attributes that is not apparent may also be captured by the error term.[221]

A conditional logit model was fitted for the first DCE (100 patient scenario), then the second DCE (1,000 patient scenario), and then for the data from both DCEs together. The data were then analysed again including only those participants who completed the fixed task correctly.

Sensitivity analysis

To overcome a limitation of the conditional logit model (that is, the assumption that respondents have homogenous preferences), a sensitivity analysis using mixed logit

modelling (allowing coefficients in the model to vary between participants) was undertaken to examine whether results changed if the model allowed for heterogeneity of preferences.

Marginal preferences and willingness to pay

Marginal rates of substitution for the different economic and non-economic variables were calculated using the negative of the ratio of any two coefficients.[224]

Marginal rate of substitution = $\frac{-\beta_k}{\beta_m}$ where β_k is the coefficient for attribute k and β_m for the attribute m.

Willingness to pay (WTP) estimates provide a monetary value for each of the attributes. To calculate the marginal willingness to pay (WTP) for a change in the level of an attribute (where everything else was equal), the price coefficient as a continuous variable was included as the denominator, β_m.

Analyses were conducted using Stata (Release 17, StataCorp LLC, College Station, Texas, 2019).

Ethics

This study was approved by the University of Adelaide Low Risk Human Research Ethics Review Group, approval number H-2018-136.

Results

Study population

155 healthcare practitioners participated in either one or both of the DCEs, completing 4576 choice tasks. Participation flow of ID/clinical microbiology specialists/registrars and hospital pharmacists is shown in Figure 9.2. 131 respondents completed both DCEs, 51 ID/clinical microbiology medical specialists/registrars and 80 hospital pharmacists. 77.9% of all respondents worked solely in the public hospital setting; other respondents worked in private practice, university/research roles or a combination of settings (Table 9.3). Of the 80

pharmacists who completed both DCEs, 73 (91.3%) either worked in an AMS role and/or belonged to the SHPA ID Interest or Practice groups. Respondents were typically experienced clinicians, with 61.1% of respondents having more than ten years' experience in clinical practice and 35.1% having equal to, or greater than, 20 years' experience.

Results of the dominant choice task

All participants were allocated one fixed task in the block of questions they were randomised to in the first DCE. The fixed, dominant choice task was designed to test for task non-attendance. Of participants who completed both DCEs, 81.7% answered the fixed task with the expected answer (84.3% for ID/micro specialists, 80.0% for pharmacists). When excluding all participants who answered the fixed task incorrectly, a total of 121 participants remained in the dataset who participated in either one or both of the DCEs, completing a combined total of 3632 choice tasks.

Conditional logit model results

The results of the conditional logit models, including only those participants who answered the dominant fixed task correctly, are provided in Table 9.4, with the magnitude of the coefficients, the log odds of selection, reflecting the impact on participants' choice. (Note: The output including all participants is provided as supplementary material, Table A8-1).

The conditional logit results show that all attributes (both economic and non-economic attributes) included in this study significantly influenced the participants' antimicrobial preference, except the novelty of the antimicrobial. For all participants combined, price and spectrum of activity were the attributes with the main influence on antimicrobial choice. As the price increased, participants preferred the cheaper of the two options offered, irrespective of the levels of the other attributes.

Sensitivity analysis

The results of the conditional logit model including all participants (including those who answered the fixed question incorrectly) are provided in Appendix 8, Table A8-1. The estimates were similar to the model without those participants who failed the fixed question (Table 9.4). All attributes significantly affected the choice of participants, except for whether the antimicrobial was from a novel class or had a novel mechanism of action.

The results of the mixed logit model (Appendix 8, Table A8-4) were very similar to the conditional logit estimates, indicating that the fixed-effect assumptions of the conditional logit model are consistent without the fixed-effect assumption.

Table 9.3: Demographic characteristics of participants who completed both Discrete Choice Experiments

Infectious diseases / Clinical Microbiology specialists (n=51)	Number (%)	Pharmacists (n=80)		Number (%)
Qualification:		Workplace:		
Infectious Diseases/ Clinical microbiology specialist	44 (86.3)	Public hospital only		63 (78.8)
ID/Clinical microbiology advanced trainee / registrar	6 (11.8)	Private hospital only		7 (8.8)
Did not specify	1 (1.9)	University / Teaching / Research		2 (2.5)
Workplace:		Public hospital + University / Research		2 (2.5)
Public hospital/laboratory only	39 (76.5)	Public hospital + Community pharmacy		1 (1.3)
Private hospital / laboratory only	2 (3.9)	Other (e.g. policy)		4 (5)
Public and Private hospital / laboratory	4 (7.8)	AMS role or SHPA Infectious Diseases Interest/Practice Group:		
Public hospital / laboratory + University / Research	1 (1.9)	Yes		73 (91.3)
Private hospital / laboratory + University / Research	2 (3.9)	No		6 (7.5)
Public and Private hospital / lab + University / Research	1 (1.9)	Did not specify		1 (1.3)
Other	2 (3.9)	SHPA Leadership/Management Interest/Practice Group:		
State / Location of practice:		Yes		23 (28.8)
NSW	15 (29.4)	No		57 (71.2)
Queensland	7 (13.7)	State / Location of practice:		
SA	7 (13.7)	ACT	10 (12.5)	SA	14 (17.5)
Tasmania	3 (5.9)	NSW	17 (21.2)	Tasmania	2 (2.5)
Victoria	12 (23.5)	NT	6 (7.5)	Victoria	14 (17.5)
WA	4 (7.8)	Queensland	9 (11.3)	WA	5 (6.3)
NZ or did not specify	3 (5.9)			NZ or did not specify	3 (3.8)
Years of clinical practice (at current level):		Years of clinical practice		
< 1 year	1 (1.9)	< 1 year		1 (1.3)
≥ 1 year, < 5 years	10 (19.6)	≥ 1 year, < 5 years		4 (5)
≥ 5 years, < 10 years	15 (29.4)	≥ 5 years, < 10 years		19 (23.8)
≥ 10 years, < 20 years	7 (13.7)	≥ 10 years, < 20 years		27 (33.8)
≥ 20 years	18 (35.3)	≥ 20 years		28 (35.0)

Table 9.4: Conditional logit estimates on health provider's preferences for each antimicrobial attribute

(Note: includes only those participants who answered dominant task correctly)

| | POOLED DATA BROTH SCENARIOS[#] | | |
| | All participants | | |
	Coeff.	95% CI		p
Spectrum of activity				
Broad (ref.)				
Narrow	0.886	0.739	0.972	<0.001
Price of antimicrobial per treatment course				
Price*	-0.000993	-0.00112	-0.000868	<0.001
New class of antibiotic				
No (ref.)				
Yes	0.037	-0.077	0.151	0.523
Route of administration				
Parenteral (ref.)				
Oral	0.588	0.464	0.713	<0.001
PBS or hospital-funded				
Hospital (ref.)				
PBS	0.567	0.436	0.697	<0.001
Patient to pay co-payment				
Yes (ref.)				
No	-0.410	-0.528	-0.291	<0.001
Number of participants (N)	121			
Observations	3632			

[#] 100-patient and 1000-patient scenarios combined
*Coefficient corresponds to a $1 increase in price

Subgroup analysis

Figure 9.3 compares the probabilities of pharmacists and ID/micro specialists choosing narrow versus broad-spectrum, with all attributes being equal except the specified attribute varied for the narrow-spectrum option. At baseline both narrow and broad-spectrum drugs were set to oral administration, novel class of antimicrobial, priced at $100 and funded on the PBS, with no patient co-payment required.

Figure 9.3: Probability of selecting narrow spectrum antimicrobial compared to baseline
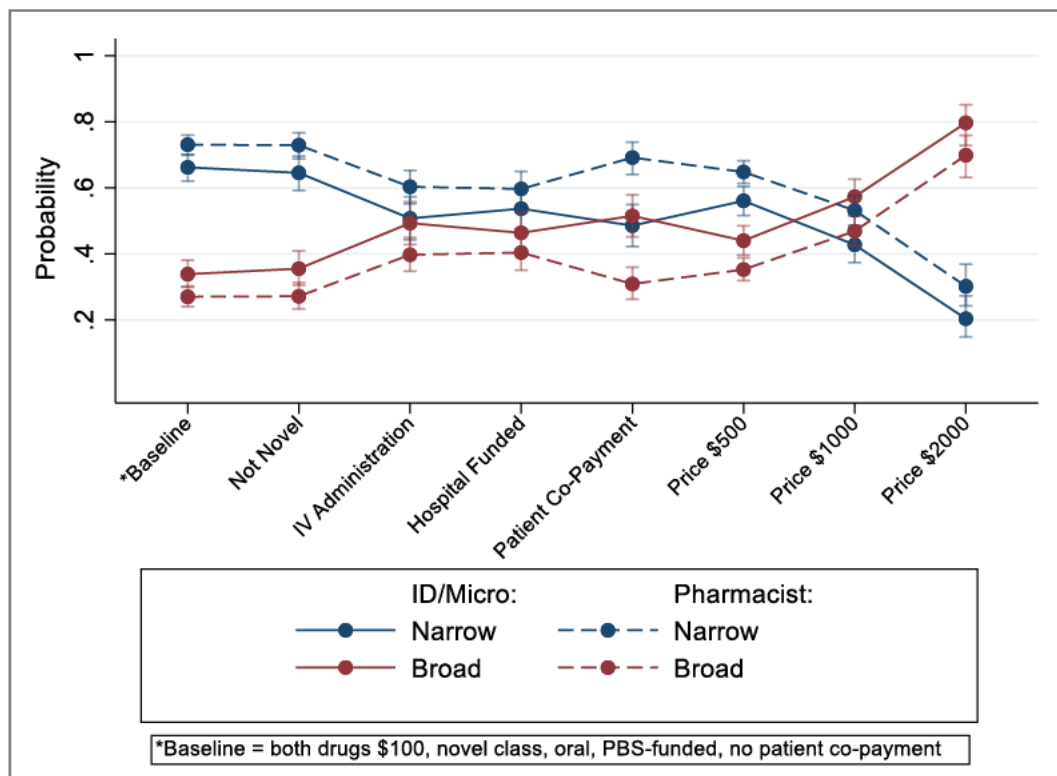
At baseline, with everything else equal, the probability of selecting the narrow-spectrum agent was 0.73 (95% CI: 0.70 – 0.76) for pharmacists and 0.66 (95% CI: 0.62 – 0.70) for ID physicians/clinical microbiologists. If the narrow-spectrum drug was not from a novel class or mechanism of action, there was no significant change in the probabilities of selecting the antimicrobial. If the narrow-spectrum drug was IV administered, the probability of selecting it fell to 0.60 (95% CI: 0.55 – 0.65) for pharmacists and 0.51 (95% CI: 0.44 – 0.57) for clinicians. Patient co-payment and increasing price had the greatest impact on the probability of selecting narrow-spectrum. Holding all other attributes the same, increasing the price of the narrow-spectrum drug to $2000 reduced the probability of selecting narrow-spectrum to 0.30 (95% CI: 0.24 – 0.37) for pharmacists and 0.20 (95% CI: 0.15 – 0.27) for clinicians. For clinicians, if the narrow-spectrum drug had a patient co-payment, there was less chance they would prefer it (Pr = 0.49 (95% CI: 0.42-0.55)). Patient co-payment had little impact on the probability pharmacists would select narrow-spectrum (Pr=0.69 (95% CI: 0.64 – 0.74). The conditional logit estimates for both groups are provided as supplementary material (Appendix 8, Tables A8-2 and A8-3 for pharmacists and ID/micro specialists respectively).

Willingness-to-pay for narrow spectrum

For all pharmacists and clinicians who answered the dominant task correctly, participants were willing to pay $862.06 (95% CI: $725.62 - $998.50) for narrow-spectrum in preference to broad-spectrum. They were also willing to pay $592.70 (95% CI: $476.41 - $708.99) for an orally administered treatment in preference to an intravenous treatment. PBS listing was also strongly preferred; respondents were willing to pay an estimated $570.90 ($454.34 - $687.46) for a PBS-listed drug in preference to one that was hospital funded. Patient co-payment negatively impacted willingness to pay for an antimicrobial; participants were willing to pay $412.61 (95% CI: $291.50 - $533.72) for an antimicrobial treatment that did not require the patient to contribute a co-payment.

Results of non-DCE, multiple-choice questions

The results of the two multiple-choice questions included in the survey (Appendix 8, Table A8-5) reflect the results shown in the analysis of the DCE data. The majority of participants (83.2%) agreed that if two new antimicrobials were equivalent in every respect (efficacy, safety, spectrum of activity, price, route of administration and length of treatment required) that they would choose a PBS-listed drug over a non-PBS listed drug. When asked to select the most important cost-related factor when selecting to use a new antibiotic, 56.5% felt the total cost to the health system would be the most important factor. PBS-funding was more important for pharmacists than for ID/micro specialists, with 25.0% of pharmacists considering it the most important cost-related factor (compared to 11.8% for ID/micro specialists). In contrast ID/micro specialists were more influenced by whether there was a cost to the patient than pharmacists, a result that was mirrored in the output of the DCE. Only 9.2% of all respondents indicated in the multiple-choice question that cost does not impact their choice of preferred antimicrobial.

Limitations

There are a number of limitations to acknowledge. Firstly, the random utility framework assumes that participants pay attention to all attributes; however, there is some published evidence that participants may ignore some attributes entirely when making their discrete

choices.[320, 321] Here we have assumed that all attributes were considered by the participants.

Secondly, the included attributes and their levels were based on both expert opinion, the pre-survey pilot, as well as the findings of qualitative interviews. There may well be other attributes or factors of importance that were not included in the final design and consequently not in the final model. It was also not possible to extrapolate beyond the levels of the attributes.

Discussion

To the best of our knowledge this is the first DCE study to investigate the impact of price and funding source on the antimicrobial preference of health professionals with expertise in AMS. The aim of AMS is to optimise antimicrobial use, employing an underlying principle that antimicrobials with a narrower spectrum of activity are less likely to drive resistance than those with a broad-spectrum. This study provides explicit evidence that the price, the method of funding and patient co-payment all affected the choice of antimicrobial made by ID/micro specialists and AMS pharmacists.

The targeted participant groups of health care practitioners who are typically key individuals responsible for antimicrobial stewardship in the hospital setting is a strength of this study. These findings provide evidence that even individuals with in-depth knowledge of antimicrobial resistance and stewardship are influenced by economic factors when selecting an antimicrobial. This is particularly relevant as ID/micro specialists and AMS pharmacists are key individuals involved in formulary decision-making, including restriction policies on usage of antimicrobials.

18.3% of participants failed the fixed task, and therefore were excluded from the conditional logit models. It is assumed this was due to inattention or fatigue given the relatively high number of tasks (17 choice sets) assigned to each respondent. Increasing the number of choice sets increases the statistical efficiency but this must be balanced with a reduction in response efficiency due to participant inattention or fatigue increasing as the number of choice sets increases. A known challenge of DCE design is predicting the sample size required in order to determine the number of choice sets to offer participants to increase statistical efficiency (minimising the confidence intervals around parameter

estimates).[206] The relatively high failure rate for the fixed task may indicate that 17 tasks was too many. The sensitivity analysis was conducted to determine the possible impact of including or excluding those who failed the fixed task, where the models were re-fitted including participants who failed the fixed question and the output and conclusions are mostly comparable to the results reported above (Appendix 8, Table A8-1).

Everything else being equal, our results show that as the price of the narrow-spectrum antimicrobial increases (compared to the broad-spectrum one), the probability of participants selecting the narrow-spectrum agent decreases. The results of the marginal rates of substitution also showed that if the broad-spectrum agent was PBS-funded, but the narrower one was not, participants were more likely to select the PBS-listed one even though it had a broader spectrum and therefore assumed to be more likely to drive resistance. Patient co-payment was also a strong determinant of drug choice; if the broad-spectrum agent was assumed to have no cost to the patient, but the narrow-spectrum agent required a patient co-payment, participants were inclined to prefer the antimicrobial with no cost to the patient.

Internationally, particularly in the UK, alternative methods of evaluating new antibiotics are being explored. It has been suggested that antibiotics that are of a novel class or have a novel mechanism of action are more 'valuable' to society as it removes or decreases the selection pressure from existing antibiotics that are currently in use.[322] This study however, found that being of a novel class or novel mechanism of action was the attribute least likely to impact the choice of health practitioners.

It is acknowledged that the stated preferences for this group of pharmacists and infectious diseases specialists may not necessarily reflect those of all Australian healthcare providers. However, given the AMS expertise in the study participants it is possible that the impact of cost on the choice of antimicrobial may be even more pervasive in general clinicians. Extrapolation of the results beyond the study population should be done with caution. Investigating antimicrobial preferences of healthcare providers who do not have expertise in antimicrobial resistance or stewardship would provide further insight into the influence of cost (both to the patient and the healthcare system) in decision-making.

Conclusion

The results of this study suggest that the antimicrobial choice of health practitioners with expertise in antimicrobial stewardship is influenced by the price of an antimicrobial, whether it is federally funded and if the patient must make a co-payment for treatment. Despite having a preference for narrow-spectrum antimicrobials when all other factors are equal, as the price differential increases between drug options, health practitioners in this study were less likely to prefer the narrow-spectrum agent as the price increased. Other attributes, such as the route of administration or whether a drug is a new antibacterial class or mechanism of action were of lesser importance in the decision-making. Policymakers considering the reform of funding models for antimicrobials should be aware of economic drivers influencing antimicrobial choice at the point of care. In order to effectively steward appropriate antimicrobial use, the economic factors that drive healthcare providers to select less appropriate antimicrobial choices must be addressed.

*****End of manuscript*****

Synopsis of chapter

This final study in this research provides empirical evidence that antimicrobial choice is influenced by economic factors. The price of the drug, whether it is federally funded on the PBS, and whether the patient is required to make a co-payment were all shown in this study to significantly affect the probability that a clinician would select a narrower spectrum antimicrobial in preference to a broader spectrum one. These findings suggest that these factors could potentially be leveraged by policymakers to optimise antimicrobial use, and should be considered if a new funding framework was introduced for antimicrobials in Australia.

CHAPTER TEN
Discussion and conclusion

Overview

Alternative models of reimbursing pharmaceutical companies based on the volume of sales is acknowledged as not sustainable for antimicrobials due to the economic risks for the manufacturers and the incentive for overuse which is not in the interests of public health. Despite global concern regarding the disinvestment of pharmaceutical companies in the development of new antimicrobials since the 1990's, very few countries have implemented a new framework of reimbursement to ensure sustainable investment into the future. The majority of public investment globally continues to be in the research and pre-clinical phase of antimicrobial development, rather than reform of post-marketing reimbursement models.

This research explored the current regulatory pathway and funding mechanisms for antimicrobials in Australia, and examined the feasibility and challenges to supporting a sustainable antimicrobial market while ensuring appropriate use of these medicines. In focusing on Australia, this research aimed to provide the context of a high-income country with a relatively small economic market globally, and an extremely complex, multi-tiered funding structure. Different services of the universally funded public healthcare system are funded federally or by individual states, with the public system functioning in parallel to a privately funded health sector.

This concluding chapter reviews the key findings to the overarching research objectives and details the theoretical and policy implications of these findings. The chapter concludes with recommendations for further research.

Research answers

The overall aim of this thesis was to explore the feasibility and sustainability of an alternative regulatory and funding model for antimicrobials in Australia, and contextualise that alternative framework within the broader global and national objective of antimicrobial stewardship. The research aims, the key findings and the implications of these findings are summarised in Table 10.1.

Table 10.1: Summary of key findings and policy implications

Research Objectives	Key Findings	Contribution & Implication
To determine the unmet need for registered antimicrobials by: · **quantifying the utilisation of unregistered antimicrobials in Australian clinical practice; and** · **Identifying the clinical indications most commonly treated with unregistered antimicrobials;**	· Across three data sources, 59 unregistered antimicrobials (unique drug and route of administration) were identified as being used in Australian clinical practice. · Usage of unregistered antimicrobials trended upwards in two of the three data sources. · A high proportion (87.7%) of hospital-dispensed unregistered antimicrobials was for outpatient use. 1.1% of the total volume of antimicrobials used in SA public hospitals were unregistered products. · Usage of unregistered antimicrobials in public and private hospitals trended upwards between 2013 and 2018 in Australian public and private hospitals. · The most common clinical indications for unregistered antimicrobials include *Mycobacterium tuberculosis*, refractory *Helicobacter pylori*, chronic bone or prosthesis or graft infection, multi-drug resistant urinary tract infections and fungal eye infections. · 77.1% of applications to use unregistered drugs in the study were for life-threatening indications. · Where clinical justification was required to access an unregistered antimicrobial, the most common reason was that the pathogen was resistant to registered antimicrobials or failed registered options.	· Unregistered antimicrobial use in Australia is widespread and appears to be increasing. · In the tertiary hospital setting, most unregistered antimicrobial use is for life-threatening infections. · Illustrates the increasing unmet need due to no registered alternative antimicrobial being effective or appropriate. · Provides evidence of the heavy reliance on unregistered antimicrobials for treatment of infections with relatively low incidence rate. · Highlights that the usual quality and safety standards that are required for registered medicines may be lacking for a substantial proportion of antimicrobials in clinical practice, in addition to lacking security of supply.

To explore the perspective of stakeholders regarding: · **the feasibility of a de-linked reimbursement model in Australia; and**	· Funding silos for medicines and healthcare are a barrier to de-linking reimbursement · Level of evidence for federal funding (on the PBS) is much higher than required for the hospital setting (where most new antimicrobials are used) · Funding status and/or cost can be a useful tool for stewardship (if expensive, less usage) · Policymakers concerned about overall cost (and increased costs) of delinked model of reimbursement · Inequity of access in the private sector to new antimicrobials, and lack of governance of use.	· Fragmented silos of funding and split responsibility for the future consequences of AMR. Currently not one single 'funder' responsible for both the patient outcome, and the impact on AMR in the future. Potential to consider nationally co-ordinated governance and funding. · Funding status impacts prescribing and could be a potential tool for stewardship.
· **alternative methods of value assessment for regulatory and funding purposes;**	· Consideration of antibiotic spectrum in the assessment of antibiotic value · Price reductions contribute to shortages. · Comparators are cheap and procurement processes (tendering) devalue them further. · Unclear how antimicrobials are incorporated into the economic evaluation of other medicines	· Reliability of supply is worth paying more for, to avoid the consequences of shortages. · The current frameworks for value assessment of new antimicrobials do not reward narrow-spectrum drugs. · Policies aimed at decreasing antimicrobial prices may be contributing to shortages.
To estimate the willingness of health care practitioners to pay for particular attributes of new antimicrobial drugs	· The following economic and non-economic attributes included in this study significantly influenced the participants' preference for antimicrobials: price, spectrum of activity, PBS-funding, patient co-payment and route of administration (IV, oral). Whether the drug was a novel class of antibiotic did not significantly impact antimicrobial choice.	· Economic factors impact the antimicrobial choice of health practitioners with expertise in antimicrobial stewardship. As the price of a narrow-spectrum, targeted drug increased, the preference for a broader spectrum, cheaper option increases. · Potentially price could be utilised as a tool to guide therapy or incentivise stewardship.

Utilisation of unregistered antimicrobials to fill an unmet need

The evaluation of three data sources to estimate the utilisation of unregistered antimicrobials in Australia is the first study that has attempted to quantify the reliance on these medicines in clinical practice. Cheng et al has previously highlighted the barriers to registration for low volume antimicrobials and highlighted the need for a reliable supply of older, generic antimicrobials, to treat infections where there are few therapeutic options available. [93] They emphasised that barriers to the availability and registration of antibiotics needed for otherwise untreatable infections needs to be minimised. Despite those warnings highlighted in Cheng's paper in 2014, the findings in this research indicate that a substantial number of unregistered antimicrobials (59 unique drug and route of administration) are used in Australian clinical practice (and recommended in clinical guidelines), and the usage is increasing. In addition, a high proportion of unregistered antimicrobials dispensed from public hospitals are used in the outpatient setting. Essentially hospitals are funding the supply of these antimicrobials for patients in the community as they are not funded on the PBS like most other medicines in the community sector in Australia. The review of clinical indications for the use of unregistered antimicrobials at two large tertiary hospitals found that the most common clinical justification for utilising an unregistered antimicrobial was that the infection was resistant to registered antimicrobial agents or the patient had failed or was unable to tolerate therapy with an available registered option. Although this review was limited to two South Australian hospitals, these results do provide insight into the typical clinical scenarios where these agents are being utilised. The access to unregistered antimicrobials is not assured, as no company is responsible for supply. With increasing AMR globally but also in Australia, there is an increasing risk that the inability to access to these unregistered antimicrobials when required may result in increasing fatalities.

Challenges with forecasting resistance into the future

The literature review examining the methodologies and uncertainties around existing models of the clinical or economic burden of AMR, provides additional context to this thesis, as without accurate estimates of future resistance it is difficult to illustrate the benefits of interventions which aim to reduce that resistance. The review contributes to the literature, providing a summary of methods used to estimate future resistance in published burden of

disease models, highlighting the sources of uncertainty which could potentially mislead policy decision-making. The challenges associated with forecasting resistance across all sectors highlighted the need to incorporate the impact of antimicrobial use in non-human sectors when estimating the cost-effectiveness of an intervention to reduce AMR or an antimicrobial to treat MDR-infections. The paper concluded with the recommendation that existing reporting standards for best practice in modelling should be adapted to guide the reporting of AMR economic models, to ensure model transparency and validation to accurately inform resource allocation by policymakers.

Analysis of stakeholder interviews

Representatives from the pharmaceutical industry were considered key stakeholders for this study, as the exploration of alternative funding frameworks to stimulate antimicrobial research and development can only be effective if the needs of both the manufacturer and the health system are met. In addition to individuals representing key pharmaceutical companies that have current and ongoing interests in the manufacture of either new or generic antimicrobials, other stakeholders included a representative from Medicines Australia, federal government employees working in AMR policy, state government employees involved with state-wide formulary decision-making and members or ex-members of the PBAC or advisory committees the TGA.

Exploration of the stakeholder perspective found two overarching challenges when considering an alternative funding model for antimicrobials in Australia: the feasibility of introducing a reimbursement model that is independent to the quantity of product sold, and secondly, how to determine how much Australia should pay for the supply of a particular antimicrobial based on the value to clinical practice and public health.

With regard to de-linking reimbursement from sales of antimicrobials, a dominant theme from interviews with policymakers and representatives from the pharmaceutical industry was that the silos of healthcare funding in Australia would be a substantial barrier, and unless there was governance nationwide over antimicrobials, it would likely be difficult to co-ordinate funding and supply across the country without the risk of some states stock-piling. Furthermore, some policymakers felt that removing the link between usage and the

reimbursement to the company, would also remove the disincentive not to use expensive antimicrobials.

Determining the 'value' or amount the drug is worth paying for was a major theme, with policymakers in particular being concerned about a de-linked model costing more in upfront costs. Drug procurement costs are immediately visible however future AMR is largely invisible. There was general agreement across all stakeholders that ensuring a reliable supply without shortages was worth an additional level of reimbursement or conveyed additional 'value' to an antimicrobial, particularly given that if an appropriate drug is not available, an inappropriate, or broader spectrum one is likely to be only other option.

Clinicians' preferences for antimicrobial attributes

Although antimicrobials with wider spectrum are known generally to pose a greater risk to the development of AMR, there is uncertainty regarding the magnitude of the risk. Future rates of AMR are influenced by many factors, of which spectrum of activity is just one. Discrete choice experiments force respondents to indicate their preference for a narrower spectrum agent, given other varying economic or non-economic attributes based on the perceived risk. Given the findings from the stakeholder interviews, where a common theme emerged that the cost of an antimicrobial influenced the choice of both prescribers and policymakers involved with hospital formulary decisions, the purpose of the discrete choice experiment was to provide empiric evidence that this was the case. Results of the discrete choice experiment showed that price and spectrum of activity were the attributes with the main influence on the antimicrobial choice of health practitioners with expertise in antimicrobial stewardship. As the price of the narrow-spectrum agent increased, the probability of selecting a cheaper, broader spectrum alternative also increased. Patient co-payment, whether an antimicrobial was federally funded on the Pharmaceutical Benefits Scheme, and the route of antimicrobial administration also significantly impacted antimicrobial choice in the study.

Implications for policy

Since the commencement of this thesis, the Australian government has published an updated national approach to the management of antimicrobial resistance, *Australia's*

National Antimicrobial Resistance Strategy – 2020 and beyond [60]. The national strategy has identified as a priority that "Innovative ways will be needed to fund, or stimulate, the discovery and development of new approaches to the prevention, detection and containment of antimicrobial resistance, in both the public and private sectors".[60] This research has important findings to inform any future policy reform aimed at funding antimicrobials sustainably, while ensuring reliable access but not incentivising overuse of these essential medicines.

Theoretical implications

This research has found that many economic factors are contributing to the less than optimal use of antimicrobials in Australia. The discrete choice experiment illustrated that the antimicrobial preferences of health practitioners with expertise in antimicrobial stewardship are influenced by the price of the alternative options. Many broad-spectrum antimicrobials, many of which are available as generic products, are extremely cheap in Australia. This research illustrates that where the broad-spectrum option is cheap, all else being equal, as the narrow-spectrum alternative increases in price, the probability that the narrow-spectrum agent is preferred decreases. This finding was mirrored in the stakeholder interviews, with a dominant theme emerging around using price as a stewardship tool. If the price is high, the likelihood of usage goes down. There is the potential for government to intervene and subsidise narrow-spectrum antimicrobials to a level that makes them a preferable selection based not only on spectrum of activity, but also on price.

Stakeholder interviews also highlighted the problem of PBS price reductions, particularly for antimicrobials that are already very cheap. Low return on antibiotics has resulted in antibiotics being considered a low priority by manufacturers (both in development and maintaining supply chains) compared to other medicines. PBS price reductions are government mandated, statutory reductions in the subsidised price of medicines listed on the PBS. These stepwise, periodic reductions in the amount the government will pay for medicines were implemented in order to reduce the overall cost of publicly-funded medicines on the PBS, as pharmacies could sometimes procure PBS-funded medicines for prices lower than the subsidised price. Stakeholders representing the pharmaceutical industry noted that the subsidy for some antimicrobial products is already below the cost price to manufacture them and is a common reason for products being withdrawn from the

market, resulting in shortages. There is no mechanism for the subsidised price of antimicrobials to ever increase, however the costs involved with manufacturing continue to increase, especially for intravenous products. One simple policy solution could be to make antimicrobials exempt from PBS price reductions, or to set a minimum price beyond which the price will no longer drop.

A significant challenge that has been highlighted internationally, but also emerged as a dominant theme with policymakers interviewed for this research, is how to place a value on a new or an old antimicrobial product. The value of an antimicrobial is dependent upon the appropriateness of its intended use, and is relative to the clinical effectiveness in treating an individual as well as its impact (or lack of impact) on driving resistance. Theoretically a narrow-spectrum drug is of less value than a broad-spectrum drug when the causative organism is not known. When it is unclear which organism is the cause of an infection, a wider spectrum of activity is therefore very valuable for empirical treatment as the likelihood of activity over the causative pathogen is higher. However once the organism is identified, a narrower spectrum drug is more 'valuable' as it is targeted against the identified pathogen and also less likely to drive resistance. Therefore the 'value' of an antimicrobial is dependent upon when it is used in the course of treating an infection.

Another dominant theme from the qualitative study was that spectrum of activity needs to be incorporated in the assessment of value of new antimicrobials. This theme expands on the aforementioned one, regarding spectrum of activity. Without an economic incentive to develop narrow-spectrum drugs, manufacturers are likely to only focus on broad-spectrum drugs which have more potential indications for use than a narrow-spectrum drug which may have a single indication. The lesser economic risk associated with the development of broad-spectrum antimicrobials, then leads into a cycle of developing broader and broader spectrum agents, which further increases the risk of resistance (Figure 10.1). Although this is counter-balanced by manufacturers' awareness that the increased risk of resistance also potentially shortens the market life of a broad-spectrum agent. Stakeholders in the qualitative study voiced their concerns regarding the methodological challenges of evaluating the cost-effectiveness of antimicrobials, particularly as currently available comparators are generally low cost, broad-spectrum agents, and the difficulties in quantifying the reduced risk they pose to resistance rates.

At a policy level, the incorporation of spectrum of activity as a parameter in economic models could be explored as a potential method to incorporate the benefits of targeted therapy over blanket broad-spectrum therapy. For example, the use of a spectrum index [323] which has been developed for stewardship purposes could be investigated as a method to leverage the benefits of narrow-spectrum agents in economic models. In this way, spectrum of activity could be incorporated into economic analyses in a systematic manner, and the level of reimbursement could be linked to the spectrum of activity, depending on where in the clinical course an antibiotic is used. In this way, the additional societal 'value' of targeted, narrow-spectrum therapy could be incorporated systematically and transparently based on the theoretical reduction in risk of AMR.

Figure 10.1 : Cycle of developing broader spectrum antimicrobials
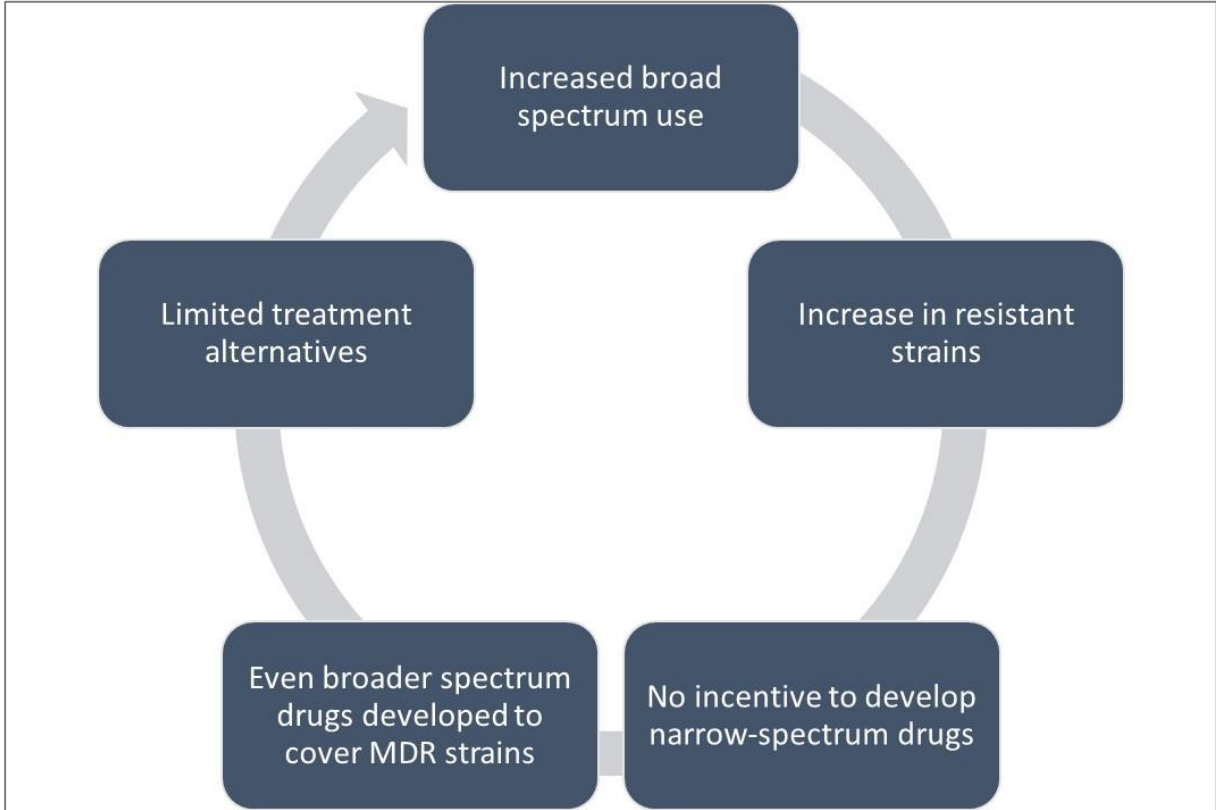
MDR = Multi-drug resistant

The findings of the discrete choice experiment demonstrated that even clinicians with expertise in stewardship are reluctant to pay more for narrow-spectrum drugs, and are

conscious of the cost to the hospital budget. Hospitals in Australia have fixed budgets and therefore formulary decisions, particularly for generic drugs, are frequently decided based on the cheapest tender price. The implication, and the potential for policy intervention, is that efforts should be made by governments to remove the price from the decision-making by prescribers as much as possible, or utilise price as a tool to guide choice. In order to do this, greater governance over antimicrobial use in Australia would be required. The much tighter regulations governing the use of opiate medicines which are aimed at preventing inappropriate use could be emulated for antimicrobials. The Australian government, recognising the risk that opiate medicines pose with regard to increased deaths and hospitalisations, have enforced tighter policies to ensure appropriate and safe access is maintained.[324] Smaller pack sizes and increased consumer targeted information on the risks, in addition to the strict legal requirements governing documentation of usage, are enforced for all opiates as they are recognised as having the potential to cause harm or overuse. Increased governance would also enable improved surveillance of use to more accurately quantify usage. The pharmacoepidemiological study we undertook highlighted that there is no single data set that accurately quantifies the usage of unregistered antimicrobials in Australia. The triangulation of three data sets did illustrate increasing usage, however determination of an accurate consumption rate was not possible. In order to move forward with modelling methodology, a greater understanding of actual consumption in all sectors is required which can only be achieved with tighter governance.

Governance over antimicrobial use in the private sector has been highlighted as particularly challenging in the AURA 2021 report, in particular the inability to accurately estimate total antimicrobial use in the community sector due to non-PBS prescribing or dispensing of 'private scripts'.[15] In the private hospital setting, results of point-prevalence surveillance of appropriate use show that the appropriateness of prescribing in the private sector is lower than rates in public hospitals, with the percentage of prescriptions deemed 'inadequate' being almost double in private hospitals compared to public.[10] In the private hospital setting, if a PBS-listed antimicrobial is prescribed there is less cost to the hospital. This was reflected in the preferences in the discrete choice experiment of participants working in the private sector. One participant in the discrete choice experiment, a pharmacist working in a private hospital, contacted me directly following participation in the survey, and stated

outright in his communication that "Short term priorities of hospital budgets sometimes outweigh social altruism of antimicrobial resistance (even if you Chair your local AMS committee!)". The results of the studies contained in this mixed-methods research imply that until governance in all sectors is increased, there will continue to be economic drivers influencing prescribing behaviour. For policymakers, one first step could be to mandate the documentation of the clinical indication or reason for use on all antimicrobial prescriptions as a legal requirement. This would be beneficial from a stewardship perspective and enable auditing of appropriateness of use. There potentially would then be a mechanism to link funding to appropriateness of use, based on the proportion of appropriate prescriptions rather than volume of supply. This could be used as an economic incentive for both the private sector and also pharmaceutical suppliers, with increased return based on increasing the proportion of appropriate prescriptions.

For the above method of reimbursement to be successful, there would have to be additional policy reform to facilitate the registration with the TGA of antimicrobials with low volume of use. This research has illustrated that in Australia clinicians rely heavily on access to unregistered antimicrobials, with many unregistered products recommended in best-practice clinical guidelines. The pathway to access and the price of unregistered antimicrobials is variable and the supply chain is insecure. Federal funding is unavailable for unregistered antimicrobials and therefore the cost is covered by hospital budgets or by patients. The orphan drug pathway provides a mechanism of entry into the Australian market that is typically used for high cost, low volume drugs that are used for rarer conditions where there is an unmet need.[112] The challenge with AMR is that the unmet need may occur suddenly or unpredictably and a manufacturer cannot predict when resistance may occur to currently available products (to enable their medicine to meet the unmet need and be eligible for orphan status). Theoretically a similar pathway for antimicrobials could be established, to enable manufacturers to register low volume products with the TGA, and eligibility to public funding. The orphan drug pathway waives the application and evaluation fees for registration, as well as the annual fees required to maintain registration, which would then potentially assist companies to maintain registration and in-date stock of older low-priced generic antimicrobials with relatively low utilisation.

The silos of healthcare funding in Australia were cited by stakeholders as a barrier to potential reform of antimicrobial reimbursement framework. This issue has been cited previously with regard to medicines and healthcare access and funding.[115] With antimicrobials however, the cost-shifting incentives could potentially encourage poor stewardship and inappropriate use. For example, if PBS-funded broad-spectrum drugs are used as a "quick fix" to keep people out of hospital, there is an immediate cost-reduction to the hospital budget. This practice does not consider the long-term clinical and economic impact on AMR. From a policy perspective, this highlights again the need for increased governance to enable tighter oversight of usage. Comprehensive data on the appropriateness of use in all settings could provide a mechanism to reward hospitals financially for appropriate usage. A move to centralised funding of all antimicrobials, irrespective of setting, could be explored, potentially with a framework comparable to the National Blood Authority (NBA) funding of blood products. In 2002, the Australian Government and all the state and territory governments signed an agreement to implement a coordinated national approach to policy setting, governance, and management of the blood sector, including financial arrangements. The proven success of the NBA model, illustrates the feasibility of federal oversight of a resource that is precious and where there can be an unpredictable urgency for supply.[325]

Ensuring appropriate use of antimicrobials requires a guaranteed supply when needed, which can oftentimes be the urgent access for time-critical life-saving treatment. A predominant theme that emerged from stakeholder interviews was that guaranteed supply holds additional value, and policymakers agreed it was worth paying more for a generic antimicrobial if assuredness of supply was guaranteed; however, the fixed budgets of hospitals meant that tendering for lower prices was the reality. Industry stakeholders also attributed shortages and the withdrawal of generic products to policies that deflate the price of generic medicines below the "break-even" point. Theoretically if a federal model of funding antimicrobials was introduced, there would be leverage at a national level to pay generic manufacturers at a sufficient level to ensure they do not withdraw generic products from the market, and with more generic manufacturers remaining there would likely be a reduction in the risk of shortages. Economic tools such as financial penalties for non-supply,

or financial rewards for continuous supply, could then be implemented at a national level, which is beyond the capability of hospitals operating on static budgets.

Estimating the 'appropriate' level of reimbursement for antimicrobials has been the subject of much debate internationally, particularly as countries begin to explore alternative funding frameworks independent of the quantity used. Manufacturers argue that new antibiotics should be reimbursed for the additional societal and public health benefits but introducing premiums to incorporate these benefits for new antimicrobials must also consider the affordability for all countries, including lower-income countries. The roll out of COVID-19 vaccines disproportionately favoured high income countries due to their ability to pay, resulting in high-income countries receiving proportionately more doses and enabling them to more comprehensively and quickly vaccinate their populations.[326] This illustrates that even if theoretically there is global co-operation, political interference can result in inequity of access to health technologies. Arguably, the 'value' of a new antimicrobial could be considered greater in locations where MDR infections are more common, and less valuable in locations where MDR pathogens are less prevalent or more susceptible to currently available options. Similar to COVID-19 vaccinations, if the wealthier nations do not support other nations to manage the issue, it will continue to pose an ongoing threat to all societies.

The COVID-19 pandemic has also highlighted that predictive models of infectious diseases that exclude human behaviour associated with risk can result in over-or under-estimation of clinical and economic impact and fail to adequately inform government regarding the optimal policy-based public health response.[327] From a policy perspective, policymakers involved in medicine reimbursement both nationally or at a state level, should consider the long-term impact on resistance rates in the decision making process. In order to do so though, there needs to be a transparent and systematic method to illustrate these additional benefits to policymakers.

HTA processes require a framework to capture the public health value of antibiotics, both the benefits with regards to reducing the risk of spread of MDR pathogens to other individuals, but also the risks associated with resistance. Not only should risks of AMR in the particular organism be considered, but also the impact on other pathogens due to the increased risk of transfer of genetic elements conferring AMR. This research has illustrated,

both from themes that emerged from stakeholder interviews and the DCE, that hospitals and health practitioners with expertise in stewardship grapple with how to estimate the additional benefit of paying for narrow-spectrum drugs. Hospital managers aim to minimise expenditure per patient treated, however a transparent and systematic method to communicate the long-term impacts of AMR resultant from patient treatment is required. Budget holders need information on AMR clearly communicated in HTA reports that extend beyond the evaluation of cost-effectiveness in individual patients and include clear information on the AMR risks to all sectors (humans, animals and the environment) to balance against the benefits gained for individual patients. In this way, reimbursement decisions will be informed by the long-term impact on AMR to ensure cost-effective use of public resources from a 'One Health' perspective.

In addition to including the benefits and AMR risks to society in the evaluation of antimicrobials, there is a clear need both in Australia and internationally to adapt the evidence requirements for reimbursement of antimicrobials (antibiotics in particular). Stakeholders from both industry and government noted that new antibiotics enter the Australian market via the hospital setting, as currently the only new antimicrobials reaching market are broad-spectrum agents which are used to treat life-threatening MDR-infections. A strong theme that emerged from the qualitative study was that the level of evidence required for reimbursement is variable between the PBS and the hospital settings, and that also between hospitals there is variation in formulary listings. For generic antimicrobials the decisions are driven, or influenced, by tender prices and whether the medicine is PBS-listed. For new antimicrobials, pharmaceutical companies do not even consider PBS-listing given the target population are usually hospitalised and the evidence required to list on the PBS is generally phase III randomised trials. Difficulties in obtaining sufficient evidence for registration and funding were referred to by stakeholders in the semi-structured interviews, but have also been cited elsewhere.[131] There are ethical barriers for companies to conduct clinical trials to treat multi-drug resistant infections which limits the patient recruitment process. If the standard of care is the last effective product for that indication (due to resistance to all other drugs), as seen in multi-drug resistant infections where there may only be one or two possible treatment alternatives, conducting a superiority trial with a potential new drug is rarely possible. When resistance to the drug that is currently the standard of

care in clinical practice increases to a level where there is a high risk of treatment failure, the use of that drug as a comparator in clinical trials may become unethical. From a policy standpoint, other methods of prospectively gathering outcome data should be explored and implemented.

Currently there is little capacity across Australia to capture consistent and reliable data on clinical outcomes across all hospital settings. The ACSQHC has advocated for the development of national clinical registries for some health technologies as a cost-effective way of addressing these gaps.[125] A mandatory reporting system for clinical outcomes following the use of new (or 'off label' use of old) antimicrobials would be a way to collect evidence to inform clinical practice, and provide real world data to estimate clinical and cost-effectiveness.

In addition to difficulties designing trials to collect evidence for reimbursement, another issue is that most comparator drugs are very cheap. Because there have been a lack of new antibiotics entering the market in the last two decades, the patent has expired on most currently marketed antibiotics and they are relatively cheap compared to other medicines. Where the best available evidence achievable is non-inferiority to an already cheap comparator, the price a company can ask for their medicine (and still be considered cost-effective within currently used methodology) is very low and not economically viable for manufacturers. This provides additional impetus for government leveraged prices for older antimicrobials, if the purpose is to incentivise new innovative antimicrobials into the marketplace.

Overall these findings provide empirical evidence that many economic factors impact appropriate antimicrobial use in Australia. The price, the source of public or private funding and the cost to the patient all impact the selection of antimicrobials at the point of care. Federal funding of all antimicrobials, delinked from usage, could improve security of access and better facilitate efforts to ensure effective stewardship of antimicrobials. This thesis highlights a number of challenges including the substantial legislative reform that would be required to support a centralised framework that de-links funding from sales and subsidises the cost of antimicrobials based on the appropriateness of use. The concept of de-linking antimicrobial funding from usage would be a process change in a complex system that is

constantly evolving, with many interdependent sectors, and where accurate economic forecasting cannot be based on extrapolations from the past, nor on the analysis of antimicrobial utilisation behaviour in a single sector. Antimicrobial treatment is a function of availability, accessibility, affordability, acceptability, and appropriateness. Reform of the regulation and funding of antimicrobials in Australia, and in other countries, needs to concurrently satisfy all these requirements.

Recommendations for future research

This research has contributed to a greater understanding of the reliance on unregistered antimicrobials in clinical practice in Australia, has explored the economic drivers of antimicrobial access and use, and scoped the perspective of policymakers and the pharmaceutical industry regarding possible reform to support a sustainable supply of effective antimicrobials into the future. Based on the findings in this thesis, several avenues for future research are discussed.

First, further investigation into methods of incorporating the spectrum of antimicrobial activity into economic models should be explored in the future. In general, antimicrobials with a wider spectrum of activity have a greater risk of driving AMR, however there are clinical situations where their use is appropriate and potentially life-saving where they convey considerable 'value' if measured in terms of quality-adjusted life years (QALYs). The optimal method to estimate the additional benefits of narrow-spectrum agents in targeted therapy is currently unclear, and methods should be explored to quantify the comparative reduction in impact on AMR as a method of informing reimbursement.

Second, further exploration on the impact of price on the antimicrobial prescribing decisions of health practitioners could be explored. The DCE in this research targeted participants who were healthcare workers with expertise in AMS, namely specialists in infectious disease and/or clinical microbiology and hospital pharmacists. The hypothetical situation of the DCE was the treatment of a sexually transmitted infection, in the outpatient setting, with a single dose treatment. This research could be expanded to investigate the impact of price and funding source on decisions by other health practitioners who are not experts in antimicrobial stewardship. Researching the impact of price on antimicrobial choice in other clinical settings would further inform government policy regarding antimicrobial funding.

Third, as noted in the review of AMR models and their feasibility and utility to inform policy decisions, to investigate the cost-effectiveness of interventions to address AMR, modelling techniques should take a One Health perspective and incorporate not only the costs and benefits to the human health sector, but also consider the impact on the animal healthcare sector, the food production sector and the health of the environment. As the availability of data on usage and resistance improves across all settings, dynamic models of AMR will be able to be explored, in an attempt to provide more accurate predictions of AMR into the future.

Finally, best practice guidance for modelling should be adapted to guide the reporting of AMR economic models. Without the transparent and consistent reporting of methods and assumptions used to model future resistance rates, policymakers will continue to have difficulty interpreting whether the models are credible and clinically relevant to inform policy or funding decisions.

The COVID-19 pandemic has shown that as the health and economic costs of no solutions increases (rising unmet need), the public acceptance of risk increases. The race to develop vaccines and treatments for COVID-19 globally illustrated that when Governments acknowledge the urgency of a public health risk, mechanisms to fast-track registration and access can be implemented. However unlike COVID-19 where there is only one causative pathogen (albeit many strains of the virus), AMR is a multi-pathogen problem requiring multiple novel approaches to reduce the risk to clinical care and public health. Legislative reform or policy changes which incentivise ongoing private sector investment into novel antimicrobial development will need to be sustainable, not compromise the ongoing supply and access to currently available antibiotics and have tight governance to ensure appropriate use.

Conclusion

Dwight Eisenhower, former president of the United States, once said "*Pull the string, and it will follow wherever you wish. Push it, and it will go nowhere at all*". Eisenhower used this analogy to describe change management, explaining that leaders must lead by example not

push from behind. Eisenhower's quote captures the problem of the antibiotic pipeline succinctly. Disproportionate focus on the premarketing phase by governments, with no reform of the marketing and supply barriers, will result in the conduit becoming congested prior to marketing and will not ensure a sustainable flow of new antimicrobials into the marketplace. The solution instead requires focus on the regulatory and financial incentives and, if tackled appropriately, the innovation of new products will follow.

This thesis provides some initial steps required to reform the pathway by which antimicrobials are registered with the TGA in Australia and the framework by which they are publicly funded. The focus cannot be only on the funding of new antimicrobials; policy reform must include both new and current products under the same overarching governance structure to ensure the focus on stimulating the supply of novel products does not compromise access to current products, and also incorporates a level of governance to prevent excess or inappropriate use in both the public and private sectors.

While this thesis provides further insight into the challenges regarding the antimicrobial supply chain from the Australian context, the solution must be a global one. Australia is a relatively small market globally, and larger countries internationally, such as the US, have other challenges such as a user-pays, insurance-based healthcare system which may be a substantial barrier to the global implementation of pull incentives. Re-designing reimbursement models for antimicrobials globally as well as in Australia will not be without substantial challenges including the costs involved with reform, however inaction will likely prove to be more detrimental economically in the long term.

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Appendix 1: Ethics Approval Notifications

Government of South Australia
SA Health

Central Adelaide Local Health Network
Royal Adelaide Hospital Human Research Ethics Committee
Level 4, Women's Health Centre
Royal Adelaide Hospital
North Terrace
Adelaide, South Australia, 5000
Telephone: +61 8 8222 4139
Email: Health.CALHNResearchEthics@sa.gov.au

Approval Date: 16 December 2017

HREC Reference number: HREC/17/RAH/570

CALHN Reference number: R20171210
please quote this number in all future correspondence

Ms Nadine Hillock
School of Public Health
The University of Adelaide

Dear Ms Hillock,

Project Title: Retrospective review of clinical indications for which unregistered antimicrobial drugs are prescribed.

RE: Audit APPROVAL

Thank you for submitting the above project for ethical review. This project was considered under the expedited approval process of the Royal Adelaide Hospital Research Ethics Committee and deemed to be an audit according to the requirements of the National Statement on Ethical Conduct in Human Research.

The documents reviewed and approved include:
- **Protocol, dated 14 December 2017**
- **SA Health Ethics Application Form, dated 14 December 2017**
- **Data Collection Spreadsheet, dated 14 December 2017**
- **Master Log – study code and MNR Spreadsheet, dated 14 December 2017**

GENERAL TERMS AND CONDITIONS OF APPROVAL FOR AUDITS:

- Adequate record-keeping and data security is important. The duration of record retention for all clinical research data is 15 years.
- Confidentiality is important. The data collected should as much as possible protect the identity of individuals. Where this is not possible, a separate file of subject identifiers should be maintained such that clinical information is kept separately from subject identifiers.
- You must notify the Research Ethics Committee of any changes which might warrant review of the approval.
- Approval is ongoing. Annual or final reports are *not* required.
- The REC must be advised within 30 days of completion so that the file can be closed.

Should you have any queries about the HREC's consideration of your project, please contact Ms Heather O'Dea on 08 8222 6841, or Health.CALHNResearchEthics@sa.gov.au.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a SA Health site until governance authorisation at that site has been obtained. Please contact the CALHN Research Office Health.CALHNResearchLNR@sa.gov.au

This Committee is constituted in accordance with the NHMRC *National Statement on the Ethical Conduct of Human Research (2007) and incorporating all updates.*

The HREC wishes you every success in your research.

Yours sincerely,

A/Prof A Thornton
CHAIRMAN
RESEARCH ETHICS COMMITTEE

THE UNIVERSITY
of ADELAIDE

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CRICOS Provider Number 00123M

Our reference 32905

02 July 2018

Professor Tracy Merlin
Public Health

Dear Professor Merlin

ETHICS APPROVAL No: H-2018-136
PROJECT TITLE: Regulatory framework for medicines in Australia and the implications for development, manufacture, access and funding of antimicrobials: stakeholder perspective

The ethics application for the above project has been reviewed by the Low Risk Human Research Ethics Review Group (Faculty of Health and Medical Sciences) and is deemed to meet the requirements of the *National Statement on Ethical Conduct in Human Research (2007)* involving no more than low risk for research participants.

You are authorised to commence your research on: 02/07/2018
The ethics expiry date for this project is: 31/07/2020

NAMED INVESTIGATORS:

Chief Investigator:	Professor Tracy Merlin
Student - Postgraduate Doctorate by Research (PhD):	Ms Nadine Therese Hillock
Associate Investigator:	Professor Jonathan Karnon
Associate Investigator:	Professor John Turnidge

CONDITIONS OF APPROVAL: Thank you for the response and revised ethics application dated 26 June 2018 outlining the changes to the methodology.

Ethics approval is granted for three years and is subject to satisfactory annual reporting. The form titled Annual Report on Project Status is to be used when reporting annual progress and project completion and can be downloaded at http://www.adelaide.edu.au/research-services/oreci/human/reporting/. Prior to expiry, ethics approval may be extended for a further period.

Participants in the study are to be given a copy of the information sheet and the signed consent form to retain. It is also a condition of approval that you immediately report anything which might warrant review of ethical approval including:

- serious or unexpected adverse effects on participants,
- previously unforeseen events which might affect continued ethical acceptability of the project,
- proposed changes to the protocol or project investigators; and
- the project is discontinued before the expected date of completion.

Yours sincerely,

Ms Sabine Schreiber
Secretary

Appendix 2: Participant Information Sheet – Interviews

PROJECT TITLE: Exploration of an alternative regulatory and funding framework for antimicrobials in Australia: Stakeholder perspective
HUMAN RESEARCH ETHICS COMMITTEE APPROVAL NUMBER: H-2018-136
PRINCIPAL INVESTIGATOR: Professor Tracy Merlin
STUDENT RESEARCHER: Ms Nadine Hillock
STUDENT'S DEGREE: PhD

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?
Due to increasing antimicrobial resistance and the threat to public health, governments worldwide are focusing on strategies to preserve the effectiveness of currently available antimicrobial drugs, to improve access to older antimicrobial drugs and to support the development of new antimicrobials. In this study we are interested in understanding the challenges faced with the current Australian regulatory and funding framework for antimicrobial drugs.

Who is undertaking the project?
This project is being conducted by Nadine Hillock, as part of the degree of Doctor of Philosophy at the University of Adelaide under the supervision of Professor Tracy Merlin, Professor Jon Karnon and Professor John Turnidge. Nadine is supported financially through an Australian Government Research Training Program Scholarship.

Why am I being invited to participate?
You have been invited to participate in this study as part of a larger representative sample of various stakeholders. Invited participants include employees of pharmaceutical companies (who work in either management, medical advisory or regulatory affairs roles), policy makers (who work in policy roles related to drug regulation or funding) infectious diseases / clinical microbiology specialists and hospital pharmacists. If you have any questions or concerns regarding participating in the research, you may contact the principal investigator whose contact details are provided below.

What will I be asked to do?
This study will involve you being interviewed by a PhD researcher, either over the telephone, online, or in person. The aim of the interview is to gain greater insight into your perspective on the topic.

How much time will the project take?
It is anticipated that interviews will take 30-45 minutes.

Are there any risks associated with participating in this project?
There are no foreseeable risks with participating in this study. Anonymity of responses will be ensured in any analyses or reports that are disseminated publicly.

What are the benefits of the research project?
There has been a substantial decline in the number of new antibiotics marketed globally over the last few decades. The World Health Organization is driving global efforts to preserve currently available antimicrobials and to facilitate the development and marketing of new antimicrobials. The purpose of this study is to gather the perspectives of relevant stakeholders, including pharmaceutical

manufacturers and prescribers, regarding possible reform to the regulation and funding of antimicrobial drugs in Australia that would facilitate a sustainable market into the future and would be in accordance with approaches made in other countries.

Can I withdraw from the project?

Participation in this project is completely voluntary. If you agree to participate, you can withdraw from the study at any time. Should you choose to withdraw from the study you may do so without any obligation to give a reason. If you do not want the answers you have provided up to that point to be included in the study, you may email nadine.hillock@adelaide.edu.au and your data will be deleted.

What will happen to my information?

The interview transcripts will be stored securely in electronic form and will only be accessible to the study researchers. All information will remain confidential and no information that would lead to the identification of any individual will be released. The data will be stored electronically following the study to assist our research and will remain anonymous, confidential and password-protected. Summarised results may be used in journal articles, conference presentations or as part of the PhD thesis. All information collected as part of the study will be retained by the University for 5 years following the completion of the PhD, after which it will be destroyed.

Who do I contact if I have questions about the project?

If you would like to hear about the results of the study or have questions about the research, please contact either:

- Professor Tracy Merlin, School of Public Health, University of Adelaide
  Tel: (08) 83133575   Email: tracy.merlin@adelaide.edu.au
- Ms Nadine Hillock, School of Public Health, University of Adelaide
  Tel: (08) 83136580   Email: nadine.hillock@adelaide.edu.au

What if I have a complaint or any concerns?

The study has been approved by the Human Research Ethics Committee at the University of Adelaide (approval number H-2018-136). If you have questions associated with the practical aspects of your participation in the project, or wish to raise a concern about the project, please consult the Principal Investigator. If you wish to speak with an independent person regarding a concern or complaint, the University's policy on research involving human participants, or your rights as a participant, please contact the Human Research Ethics Committee's Secretariat at hrec@adelaide.edu.au. Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

If I want to participate, what do I do?

If you are happy to participate, you can email nadine.hillock@adelaide.edu.au and an interview will be scheduled at a time that is suitable for you. Prior to the interview, you will be asked to indicate whether you consent to participate, by signing and returning a consent form that will be emailed to you.

Thank you in advance for your participation in this research study.

Appendix 3: Consent form – Interview participants

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CONSENT FORM

1. I have read the Participant Information Sheet and agree to take part in the following research project:

Title:	Regulatory framework for medicines in Australia and the implications for development, manufacture, access and funding of antimicrobial drugs: Stakeholder perspective
Ethics Approval Number:	H-2018-136

2. I have had the project, so far as it affects me, and the potential risks and burdens fully explained to my satisfaction by the research worker. I have had the opportunity to ask any questions I may have about the project and my participation. My consent is given freely.

3. Although I understand the purpose of the research project, it has also been explained that my involvement may not be of any benefit to me.

4. I agree to the interview being audio / video recorded

5. I understand that I am free to withdraw from the project at any time.

6. I have been informed that, while information gained during the study may be published, I will not be identified and all responses will remain anonymous.

7. I agree to non-identifiable transcripts of the interview being stored in an online digital repository.

8. I am aware that I should keep a copy of this Consent Form, when completed, and the attached Information Sheet.

Participant to complete:

Name: _____ Signature: _____ Date: _____

Version: 01   Date: May 2018

Appendix 4: Interview guide – stakeholder interviews

Sub-topic	Indicative phrasing of questions
Alternative business models for antibiotics/antimicrobials	Internationally alternative models of reimbursement (including delinking reimbursement from sales volumes) have been proposed for antimicrobial drugs. What are your thoughts on the idea that payment for antimicrobial drugs is independent to sales?
	Do you think a lump-sum reimbursement model for antimicrobials would be possible in Australia? Globally? Do you think a lump sum model could work for both high and low-middle income countries?
	What other incentives do you think may encourage companies to invest in the development of new antimicrobial drugs?
	Australia has two main funding pathways for medicines in the public sector (Federal funding of medicines on the PBS, and state-funding of drugs used in public hospitals). How do you think that impacts the supply of antimicrobial drugs in Australia? What is your opinion on states/hospitals tendering for contract prices for antimicrobial drugs? (Price/supply/access)
	What do you think is the best solution to the challenge of having access to low usage antimicrobials but ensuring companies are appropriately reimbursed?
	What is your opinion regarding a not-for-profit (or government managed) model for antimicrobial supply?
Australia's current regulatory process	A number of antimicrobial drugs are registered overseas but not in Australia. What do you think are the main reasons for this? What changes (if any) to the regulatory process in Australia do you think would encourage companies to market their products here? Does your company supply any antimicrobials through the Special Access Scheme? (*for Pharma participants only*)
	What are your thoughts on a possible fast-track approval process for antimicrobial drugs in Australia? Framework? (similar to EMA PRIME act) Barriers? Main concerns (if any)?
	What are your thoughts on regulating antimicrobial drugs differently to other drugs, by possibly establishing a separate schedule of their own? (of the Therapeutic Goods Act)

	What is your opinion on the use of an outcomes registry to gather evidence for new antimicrobials (or to repurpose older drugs)?
	Do you think the TGA consider pathogen-specific registration instead of indication-specific registration?
	Has your company withdrawn any antimicrobial products from the Australian market in the last 2-3 years? If so, what was the main reason for the withdrawal? (*for Pharma participants only*)
HTA / medicine evaluation / valuing an antimicrobial	How do you think the societal 'value' of a new antimicrobial should be determined? What factors do you think should be considered when assessing the value of a new antimicrobial?
	Antimicrobial resistance to an individual drug is difficult to estimate into the future and is a financial risk for companies investing in antimicrobials drugs. How do you think this risk should be managed or accounted for from a reimbursement perspective?
Antimicrobial stewardship	What role, if any, do you believe pharma companies should have with regard to antimicrobial stewardship?
	Have you heard of the Davos declaration on antibiotic resistance, signed in 2016? (signed by many pharmaceutical companies) - Do you know if your company is a signatory of the declaration? (*Pharma participants only*) - How binding do you think the declaration is? Do you think there is a risk that companies who haven't (or even who have) signed, may undermine the efforts of others in conserving antimicrobials? - Why do you think companies may or may not comply with the agreement?
	Do you think reimbursement should be linked in some way to stewardship? Have you any ideas on how that could work? (i.e. how governments could reward good stewardship)?
Sustainable supply	Low usage products have a unique set of challenges in maintaining a supply chain. How do you think the government could assist companies in sustaining supply of antimicrobials?
	Shortages - Do you think the government could help with continuity of supply in any way? E.g. assist manufacturing capacity in the case of increased demand

Appendix 5: Participant Information Sheet – Surveys

PROJECT TITLE: Willingness to pay for narrow spectrum and other attributes of new antimicrobials
HUMAN RESEARCH ETHICS COMMITTEE APPROVAL NUMBER: H-2018-136
PRINCIPAL INVESTIGATOR: Ms Nadine Hillock

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?
Due to increasing antimicrobial resistance and the threat to public health, there is an increasing focus on the need to develop new antimicrobial drugs. There is uncertainty however, regarding the value to society of the new antimicrobials, and how governments should determine how much to pay for new drugs. This study is investigating which attributes of new antibiotics are considered most important or valuable by health professionals, based on their willingness to pay for those attributes.

Who is undertaking the project?
This project is being conducted by Nadine Hillock, as part of the degree of Doctor of Philosophy at the University of Adelaide under the supervision of Professor Tracy Merlin, Professor Jon Karnon and Professor John Turnidge.

Why am I being invited to participate?
You have been invited to participate in this study as part of a larger representative sample of various stakeholders. Invited participants include infectious diseases / clinical microbiology specialists and hospital pharmacists with an interest in either Infectious Diseases or Leadership/Management.

What will I be asked to do?
This study will involve you completing an online survey. The survey will include a clinical scenario and a series of hypothetical new antimicrobial drugs. You will be asked to select which of the hypothetical antimicrobials who would prefer for a patient, given the attributes of the antimicrobials as well as the price, and whether the patient must pay a co-payment or not.

How much time will the project take?
The survey will take approximately 10 – 15 minutes to complete.

Are there any risks associated with participating in this project?
There are no foreseeable risks with participating in this study. Anonymity of responses will be ensured in any analyses or reports that are disseminated publicly.

What are the benefits of the research project?
There has been a substantial decline in the number of new antibiotics marketed globally over the last few decades. The World Health Organization is driving global efforts to preserve currently available antimicrobials and to facilitate the development and marketing of new antimicrobials. While it is agreed that new antibiotics are needed, there is uncertainty regarding the value of new antimicrobials and how governments should determine what to pay for them. The purpose of this study is to understand the perspective of healthcare professionals, including pharmacists and Infectious Disease Specialists / Clinical Microbiologists, regarding which attributes of a new drug are important based on the willingness to pay for those attributes.

Can I withdraw from the project?

Participation in this project is completely voluntary. If you agree to participate, you can withdraw from the study at any time.

What will happen to my information?

All survey data will be gathered anonymously. No identifiable information will be collected.

Who do I contact if I have questions about the project?

If you would like to hear about the results of the study or have questions about the research, please contact either:

- Professor Tracy Merlin, School of Public Health, University of Adelaide
  Email: tracy.merlin@adelaide.edu.au
- Ms Nadine Hillock, School of Public Health, University of Adelaide
  Email: nadine.hillock@adelaide.edu.au

What if I have a complaint or any concerns?

If you have questions associated with the practical aspects of your participation in the project, or wish to raise a concern about the project, please consult the Principal Investigator. If you wish to speak with an independent person regarding a concern or complaint, the University's policy on research involving human participants, or your rights as a participant, please contact the Human Research Ethics Committee's Secretariat at hrec@adelaide.edu.au.

If I want to participate, what do I do?

If you are happy to participate, you can access the survey via the online link provided. You will be asked to indicate whether you consent to participate, prior to accessing the survey questions.

Thank you in advance for your participation in this research study.

Appendix 6: Online survey (Discrete Choice Experiment)

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Preferences for attributes of new antibiotics

While it is generally agreed we need new antibiotics to managing the increasing number of antimicrobial resistant infections, there is uncertainty regarding the *value* of new antibiotics and how much governments should pay for them.

You are invited to participate in our survey, which aims to understand what **features** of a **new** hypothetical antimicrobial (e.g. spectrum of activity, route of administration, etc) you think **are most valuable.**
The survey will take approximately 15 minutes to complete.

One clinical scenario will be described. You will be given a series of combinations of **TWO hypothetical new drugs**. You will be asked to select which of the two drugs would be your preferred choice based on:
- the features or attributes of the drug
- the price per treatment course
- whether it is listed on the PBS or if the drug is hospital-funded
- if there is a cost to the patient (co-payment)
- the hypothetical number of patients (and the impact on the Australian health budget)

Your participation in this study is completely voluntary. If you agree to participate, you may withdraw from the survey at any point.

Preference of antibiotic attributes - Pharmacists

QuestionPro

This study has been approved by the Human Research Ethics Committee at the University of Adelaide (Approval number H-2018-136). If you have questions at any time about the survey, you may contact Nadine Hillock at nadine.hillock@adelaide.edu.au.
Thank you very much for your time and support.

I agree to participate in this survey. I understand the purpose of the study and am participating voluntarily. I understand I can withdraw from the survey at any time.

○ Yes, I agree to participate

○ No, I do not wish to participate at this time

Preference of antibiotic attributes - Pharmacists

QuestionPro

Hypothetical scenario:

You are a pharmacist working in a large 500-bed tertiary hospital.

Imagine there are *two* **new antibiotics** available in Australia to treat **multi-drug resistant gonorrhoea** (gonorrhoea resistant to *both* ceftriaxone and azithromycin).

You have been asked by a doctor which new drug you personally would recommend for patients presenting with multi-drug resistant gonorrhoea.

When choosing your preferred hypothetical drug, make the following assumptions:
- Both drugs have 100% susceptibility for *Neisseria gonorrhoeae*
- A course of either hypothetical drug is a single dose only
- The patient is to be treated as an outpatient (not admitted to hospital)
- **Assume resistance to all other available antimicrobials**
- Except for potential injection site pain or redness, assume both drugs have similarly low risk of side effects
- The definition of "broad spectrum" refers to a *similar spectrum* to that of a 3rd-generation cephalosporin
- If the antibiotic is a new class of drug with a novel mechanism of action, it may help existing antibiotics to remain effective against other pathogens by reducing selection pressure
- Patient co-payment on prescriptions would be a maximum of $41.30 (or $6.60 for concession card holders)
- The choice of drug is for treatment of a non-pregnant patient, with normal renal and hepatic function

Preference of antibiotic attributes - Pharmacists

P QuestionPro

If **100** patients were expected to require treatment for multi-drug resistant gonorrhoea per year at the tertiary hospital at which you are assumed to work:

Which of these two hypothetical drugs would you recommend to prescribers for treating patients with multi-drug resistant gonorrhoea?

(?)

Step 1 of 9

Spectrum of activity	Narrow	Broad
Price	AU$ 100	AU$ 2000
New class of antibiotic/ novel mechanism of action	Yes	Yes
Route of administration	Oral	Oral
PBS *or* hospital-funded	Funded on the PBS	Funded on the PBS
Cost to the patient (co-payment)	No	Yes
	○	○

• Do you agree or disagree with the following statement?

If two new antimicrobials **were equivalent in every respect** (i.e. *equally effective* for a particular infection, *equally safe*, same spectrum of activity, same price, same route of administration and length of treatment required), I would recommend a PBS-listed antimicrobial over an antimicrobial that was not listed on the PBS.

○ Agree   ○ Disagree   ○ Not sure

Preference of antibiotic attributes - Pharmacists

P QuestionPro

If **1000** patients were expected to require treatment for multi-drug resistant gonorrhoea per year at the tertiary hospital at which you are assumed to work:

Which of these two hypothetical drugs would you recommend to prescribers for treating patients with multi-drug resistant gonorrhoea?

(?)

Spectrum of activity	Narrow	Broad
Price	AU$ 100	AU$ 2000
New class of antibiotic/ novel mechanism of action	Yes	Yes
Route of administration	Oral	Oral
PBS *or* hospital-funded	Funded on the PBS	Funded on the PBS
Cost to the patient (co-payment)	No	Yes
	○	○

• *Thinking about costs*, which of the following would you consider most important in your decision-making regarding a new antibiotic:

○ Total cost to the health system

○ Cost to the patient

○ If it is funded on the PBS

○ None of the above. Cost does not impact my decision-making

Preference of antibiotic attributes - Pharmacists

P QuestionPro

• And finally, some quick questions about you:

Please indicate which SHPA Specialty Interest Groups or Specialty Practice Groups you belong to (select all that are applicable):

☐ Infectious Diseases Interest Group

☐ Infectious Diseases Practice Group

☐ Leadership & Management Interest Group

☐ Leadership & Management Practice Group

☐ None of the above

• I am currently working in an Antimicrobial Stewardship role

○ No   ○ Yes

• I am currently working:

☐ In a public hospital

☐ In a private hospital

☐ In a community pharmacy

☐ In a university/research/teaching role

☐ I am not currently working in paid employment

☐ Other role, e.g. government, policy

Preference of antibiotic attributes - Pharmacists

P QuestionPro

* How long have you been practicing as a pharmacist?

○ Less than 1 year

○ More than 1 year, but less than 5 years

○ More than 5 years but less than 10 years

○ More than 10 years but less than 20 years

○ 20 years or more

* I currently live:

○ In Australia

○ In NZ

○ Country other than Australia or NZ

In which State or Territory do you live?

○ Australian Capital Territory

○ New South Wales

○ Northern Territory

○ Queensland

○ South Australia

○ Tasmania

○ Victoria

○ Western Australia

Preference of antibiotic attributes - Pharmacists

QuestionPro

Appendix 7: Supplementary material – Study two

Table A7-1: Indications for category A applications for access to unregistered antimicrobials

Unregistered antimicrobial	Number of requests
amoxicillin/clavulanate (IV)	
Perforated diverticulitis	1
amphotericin B (IV)	
Aspergillus fumigatus infection of surgical wound - IV product used topically	1
Fungal infection of eye (endophthalmitis or keratitis) - IV product used to prepare eye drops	9
Invasive fungal sinusitis - IV product used intranasally	1
artesunate	
Malaria	3
aztreonam	
Cystic Fibrosis - infective exacerbation	3
bedaquiline	
Multi-drug resistant tuberculosis (TB) - pulmonary & central nervous system (CNS)	1
chloramphenicol (oral)	
Infected EVAR (Endovascular aneurysm repair) graft with Extended-spectrum beta-lactamase (ESBL) *E.coli*	1
cidofovir	
Adenovirus in immunocompromised patient	1
BK virus nephropathy	2
BK virus ulcerative cystitis	1
Laryngeal papillomatosis	8
Indication not provided	1
clofazimine	
Leprosy	2
Multi-drug resistant TB	2
Mycobacterium abscessus infection causing cavitating lung lesions	1
Mycobacterium avium complex (MAC) abscesses (in Cystic Fibrosis)	4
Mycobacterium chelonae cutaneous infection	2
Spinal osteomyelitis secondary to MAC	1
cycloserine	
Multi-drug resistant TB	5
flucytosine (oral)	
Cryptococcal pneumonia	3
Cryptococcal meningitis	8
Cryptococcus - disseminated	2
fosfomycin	
ESBL bacteraemia / septicaemia or urosepsis	4
ESBL Urinary tract infection (UTI)	37
Infected aortic graft	1
UTI prophylaxis (ureteric stent / metastatic colorectal cancer/ history of VRE UTIs)	1

isavuconazole (oral)

Invasive fungal infection - *Zygomycetes rhizopus*	1

ketoconazole

Cushing syndrome	4

moxifloxacin (eyedrops)

Mycobacterial keratitis	1

natamycin (eyedrops)

Fungal (*Fusarium* spp.) corneal ulcer	1
Fungal keratitis	13

nitazoxanide

Clostridium difficile	1
Cryptosporidium diarrhoea	15
Recurrent *Giardia* spp. infection	1

paromomycin

Entamoeba histolytica infection	1

primaquine

Malaria	6
Malarial prophylaxis	1
Pneumocystis pneumonia	1

pristinamycin

Chronic intra-abdominal infection	3
Chronic septic joint infection	2
Deep wound infection (Vancomycin-resistant enterococci (VRE) / Methicillin-susceptible *Staphylococcus aureus* (MSSA) / Coagulase-negative staphylococci)	2
ESBL UTI	1
Prosthetic joint infection	12
Osteomyelitis	4
Bacteraemia (Methycillin-resistant *Staphylococcus aureus* (MRSA) &/or VRE)	3

prothionamide

TB - miliary or multi-drug resistant	7

pyrazinamide

TB - pulmonary and / or extra-pulmonary, including multi-drug resistant TB	176

ribavirin

Respiratory syncytial virus (RSV)	1
RSV (on background of bilateral lung transplant)	1

sulfadiazine

Toxoplasmosis	3

triclabendazole

Fascioliasis	1
Total:	368

Table A7-2: Indications for category B applications for access to unregistered antimicrobials

Unregistered antimicrobial	Number of requests
bismuth subcitrate	
Refractory *Helicobacter pylori* infection	24
chloroquine	
Uncharacterised connective tissue disease	1
clofazimine	
Chronic drug-resistant *Mycobacterium avium* lung disease	2
Miliary tuberculosis, CNS involvement	1
Multi-drug resistant TB	1
Mycobacterium chelonae cutaneous infection	1
fosfomycin	
ESBL Urosepsis	1
ESBL UTI (recurrent)	1
Multi-drug resistant Gram-negative prostatitis	1
ketoconazole	
Cushing syndrome / disease	6
levofloxacin	
Refractory *Helicobacter pylori* infection	1
miltefosine	
Cutaneous leishmaniasis (New World leishmaniasis)	1
nitazoxanide	
Cryptosporidium gastroenteritis	1
Giardiasis	2
paromomycin	
Blastocystis hominis	1
Dientamoeba fragilis infection	6
Entamoeba histolytica	2
pristinamycin	
Abdominal infection, following percutaneous drainage	1
Chronic osteomyelitis	6
Chronic prosthetic infection	9
Mycoplasma genitalium infection	6
Pacemaker infection (drug-resistant *Staphylococcal* infection)	3
VRE bacteraemia with aortic root abscess (palliation)	2
prothionamide	
Multi-drug resistant TB	1
pyrazinamide	
TB	1
sulfadiazine	
Cerebral toxoplasmosis	1
tetracycline	
Refractory *Helicobacter pylori* infection	23
Total:	106

S3: Antimicrobial drugs included in Category C of the Special Access Scheme as at 01 June 2018

Ingredient & dosage form	Indication(s)
Bismuth subcitrate tablet	Resistant *Helicobacter pylori* infection
Clofazimine capsule	Leprosy
Clofazimine capsule	Granulomatous cheilitis
Clofazimine capsule	Melkersson Rosenthal Syndrome
Clofazimine capsule	*Mycobacterium avium* paratuberculosis in immunocompromised patients, recommended by an infectious disease specialist
Clofazimine capsule	Erythema nodosum leprosum
Furazolidone tablet	Resistant *Helicobacter pylori* infection
Levofloxacin tablet	Resistant *Helicobacter pylori* infection
Moxifloxacin 0.5% eye drops	Refractory bacterial conjunctivitis
Natamycin 5% eye drops	Refractory fungal blepharitis, conjunctivitis or keratitis
Nitazoxanide oral suspension	Giardiasis
Nitazoxanide oral suspension	Cryptosporidiosis
Nitazoxanide oral suspension	Blastocystis
Nitazoxanide tablet	Giardiasis
Nitazoxanide tablet	Cryptosporidiosis
Nitazoxanide tablet	Blastocystis
Paromomycin capsule	*Blastocystis hominis*
Paromomycin capsule	*Dientamoeba fragilis*
Paromomycin capsule	*Entamoeba histolytica*
Paromomycin capsule	Parasite infection
Pristinamycin tablet	MRSA and VRE infection where there is history of failed therapy with the other available antibiotics, at sites in relation to bone / joint / prosthesis
Pristinamycin tablet	Refractory or resistant *Mycoplasma genitalium* infections
Pristinamycin tablet	Other infections as prescribed by an ID specialist
Pyrazinamide tablet	Tuberculosis
Tetracycline capsule	Resistant *Helicobacter pylori* infection
Tetracycline tablet	Resistant *Helicobacter pylori* infection

Appendix 8: Supplementary material – DCE study

Table A8 - 1: Conditional logit estimates on health provider's preferences for each antimicrobial attribute – all participants (sensitivity analysis)

(Note: includes participants who answered dominant task *incorrectly*)

	POOLED DATA BROTH SCENARIOS[#]		
	All participants		
	Coeff.	95% CI	p
Spectrum of activity			
Broad (ref.)			
Narrow	0.575	0.480　　0.671	<0.001
Price of antimicrobial per treatment course			
Price*	-0.000822	-0.000927　-0.000717	<0.001
New class of antibiotic			
No (ref.)			
Yes	0.013	-0.083　　0.108	0.796
Route of administration			
Parenteral (ref.)			
Oral	0.467	0.362　　0.571	<0.001
PBS or hospital-funded			
Hospital (ref.)			
PBS	0.505	0.397　　0.614	<0.001
Patient to pay co-payment			
Yes (ref.)			
No	-0.417	-0.513　-0.320	<0.001
Number of participants (N)	155		
Observations	4576		

[#] 100-patient and 1000-patient scenarios combined
*Coefficient corresponds to a $1 increase in price

Table A8 - 2: Conditional logit estimates on pharmacists' preferences

(Note: includes only those participants who answered dominant task correctly)

| | POOLED DATA BOTH SCENARIOS[#] | | |
| | Pharmacists | | |
	Coeff.	95% CI	p
Spectrum of activity			
Broad (ref.)			
Narrow	0.995	0.840 1.150	<0.001
Price of antimicrobial per treatment course			
Price*	-0.000966	-0.00113 -0.000805	<0.001
New class of antibiotic			
No (ref.)			
Yes	0.007	-0.144 0.159	0.924
Route of administration			
Parenteral (ref.)			
Oral	0.577	0.415 0.739	<0.001
PBS or hospital-funded			
Hospital (ref.)			
PBS	0.605	0.432 0.778	<0.001
Patient to pay co-payment			
Yes (ref.)			
No	-0.189	-0.348 -0.031	<0.001
Number of participants (N)	69		
Observations	2112		

[#] 100-patient and 1000-patient scenarios combined

*Coefficient corresponds to a $1 increase in price

Table A8 - 3: Conditional logit estimates on ID/micro specialists' preferences

(Note: includes only those participants who answered dominant task correctly)

	POOLED DATA BROTH SCENARIOS[#]		
	ID/micro specialists		
	Coeff.	95% CI	p
Spectrum of activity			
Broad (ref.)			
Narrow	0.671	0.489 0.853	<0.001
Price of antimicrobial per treatment course			
Price*	-0.00107	-0.00127 -0.000869	<0.001
New class of antibiotic			
No (ref.)			
Yes	0.074	-0.106 0.254	0.422
Route of administration			
Parenteral (ref.)			
Oral	0.642	0.440 0.844	<0.001
PBS or hospital-funded			
Hospital (ref.)			
PBS	0.524	0.324 0.724	<0.001
Patient to pay co-payment			
Yes (ref.)			
No	-0.730	-0.915 -0.544	<0.001
Number of participants (N)	52		
Observations	1520		

[#] 100-patient and 1000-patient scenarios combined
*Coefficient corresponds to a $1 increase in price

Table A8 -4: Sensitivity analysis: Mixed logit estimates

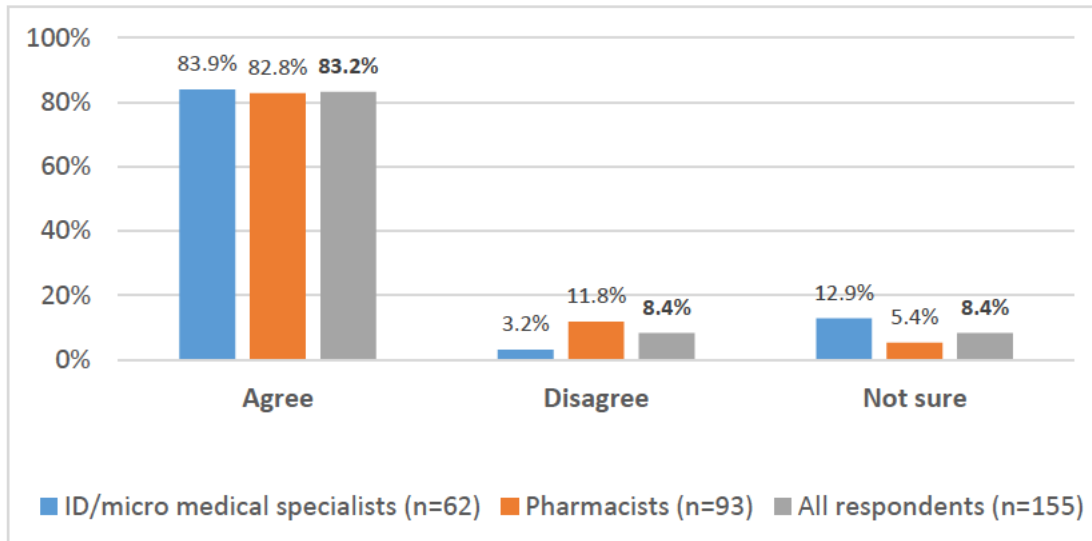(Note: includes participants who answered dominant task correctly)

	POOLED DATA BROAD SCENARIOS[#]		
	All participants		
	Mean Coeff.	Standard error	p
Spectrum of activity			
Broad (ref.)			
Narrow	1.043	0.075	<0.001
Price of antimicrobial per treatment course			
Price*	-0.00127	0.000102	<0.001
New class of antibiotic			
No (ref.)			
Yes	0.059	0.067	0.579
Route of administration			
Parenteral (ref.)			
Oral	0.685	0.099	<0.001
PBS or hospital-funded			
Hospital (ref.)			
PBS	0.723	0.100	<0.001
Patient to pay co-payment			
Yes (ref.)			
No	-0.489	0.084	<0.001
Number of participants (N)	121		
Observations	3632		

[#] 100-patient and 1000-patient scenarios combined

*Coefficient corresponds to a $1 increase in price

A8 - 5: Results of non-DCE, multi-choice questions

If two new antimicrobials were equivalent in every respect (i.e. equally effective for a particular infection, equally safe, same spectrum of activity, same price, same route of administration and length of treatment required), I would recommend a PBS-listed antimicrobial over an antimicrobial that was not listed on the PBS.

Thinking about costs, which of the following would you consider most important in your decision-making regarding a new antibiotic: