Exploring the Role of Community Pharmacists in Antimicrobial Stewardship

by

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Statements

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3. Rizvi T. 'Literature Review- Antimicrobial Stewardship in the Community Setting'. University of Tasmania Graduate Research Conference 2016, Hobart, TAS.

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Abstract

Judicious use of the currently available antimicrobials is crucial as the rate of antimicrobial resistance (AMR) continues to exceed the rate of new drug development. Globally 700,000 people die annually due to infections caused by antimicrobial resistant organisms and this is expected to reach 10 million per year by 2050, causing a loss of up to USD100 trillion to the global economy. A significant force driving the development of AMR is the use and, in particular, the inappropriate use of antimicrobials. It is estimated that almost 50% of all antimicrobials given to humans are inappropriate.

Antimicrobial stewardship (AMS) is defined as a set of coordinated strategies to improve antimicrobial use with the goal of enhancing patient health outcomes, reducing resistance to antimicrobials and decreasing unnecessary costs. There are two main approaches to AMS and these are usually applied in combination. One of the approaches is the front-end or prescription method, which restricts the use of certain antimicrobials by employing an approval process. This approach is usually applied broadly in national, regional and institutionalised settings. The second is the back end or post prescription approach, involving audit and feedback to guide appropriate prescribing and dispensing of antimicrobials. Other approaches or techniques include delayed antimicrobial prescribing, point-of-care testing, providing education and awareness to the public, patients and prescribers, as well as decision support systems integrated into clinical software.

Recently, resistant organisms have been increasingly detected in the community and community prescribers are responsible for about 90% of all antimicrobial prescriptions globally, with respiratory tract infections (RTIs) being the most common indication for prescribing antimicrobials in the community. In Australia, AMS programs are mandatory in hospitals; however, they are not currently present in the community, despite the widespread use of antimicrobials in this setting.

Within primary care, community pharmacists are the most accessible healthcare professionals and consequently, have the potential to play a major role in AMS. The overall aim of the thesis is to investigate the current role of community pharmacists in AMS. The methodology is an explanatory, sequential, mixed

method for the overall project, comprising a literature review, two quantitative studies and one qualitative study (Table 1).

The first chapter of the thesis provides background information related to the overall project. The second chapter is a narrative literature review which describes various AMS interventional studies in community settings. This review evolved and was updated regularly until December 2020. Studies that measured an outcome to optimise antimicrobial use through prescribing or dispensing, compared with usual care or other interventions in the community sector, were included in the review. Most AMS interventions in the community setting were successful in optimising antimicrobials use, although infections other than RTIs were less well studied. The studies that employed multi-faceted interventions showed marginal superiority over studies involving a single intervention. Educational interventions, which were supported with either computerised decision support, delayed prescribing, point-of-care diagnostics or prescriber feedback, were found to be successful in improving appropriate antimicrobial use. Most studies were conducted in GP practices or aged care facilities; only few studies involved community pharmacists.

The first quantitative study, which constitutes the third chapter of the thesis, was the development and validation of a survey questionnaire to explore the knowledge and perceptions of community pharmacists regarding AMS. The questionnaire was piloted amongst Tasmanian community pharmacists and the study has been published in the International Journal of Clinical Pharmacy. The resulting questionnaire to measure pharmacists' perceptions of the enablers and barriers to AMS in community settings demonstrated acceptable reliability and validity. The pilot study found that Tasmanian pharmacists are willing to participate in AMS initiatives, if facilitated with proper training and access to standard antimicrobial guidelines and patient records.

The fourth chapter of the thesis describes the next study in which the newly developed, tested and revised survey questionnaire was deployed nationwide. The objective of the study was to gain more insights into the perceptions and practices of community pharmacists regarding AMS. The additional data from across Australia adds further to the questionnaire's reliability and validity. The study has been published in the Journal of Global Antimicrobial Resistance. The majority of participants reported that they frequently contacted prescribers if they thought antimicrobial prescriptions needed to be changed with regard to allergies, drug interactions and dosage. However, less than half of participants said they frequently contacted prescribers when, in their opinion, the chosen antimicrobial was not appropriate. Major barriers to AMS identified by the participants were lack of access to patient data and lack of access to a standard antimicrobial guideline for all healthcare professionals. These results were consistent with the results of the earlier Tasmanian study presented in the third chapter.

The result of the literature review found there were few qualitative studies regarding community pharmacists' involvement in AMS; therefore, a qualitative telephone study was conducted and this constitutes the fifth chapter of this thesis. The manuscript arising from this study is currently being prepared and will be submitted to a relevant journal. The qualitative study explores the in-depth experiences and views of Australian community pharmacists on AMS in primary care. One-on-one semi-structured telephone interviews were conducted with community pharmacists across Australia. Interviews were transcribed verbatim and analysed using the framework analysis method. Our findings discovered some system-wide and profession-specific issues that are currently limiting community pharmacists' participation in AMS. Pharmacists identified that the clinical needs of patients and policies regarding prescribing and dispensing of antimicrobials are not consistent; these issues were considered to be major barriers to AMS. Respondents also reported that fragmentation of the primary health care system in Australia is limiting information exchange between community pharmacists and general practitioners and, at times, encouraging inappropriate and potentially unsanctioned use of antimicrobials. The existing community pharmacy funding model was also reported as discouraging community pharmacists from participating in AMS, as refusal to dispense an inappropriate antimicrobial agent result in a financial loss for the pharmacy. Pharmacists suggested restricting default antimicrobial repeat supplies, reducing the legal period of antimicrobial prescription validity to less than 12 months and adopting a treatment duration-based approach to antimicrobial prescription, instead of the current quantity-based approach, in which the quantity prescribed is linked to the standard pack size of the antimicrobials.

Overall, my PhD project has advanced our knowledge regarding the current role and potential barriers to the contribution of community pharmacists to AMS. Based on the available literature and the quantitative and qualitative studies undertaken, it is clear that community pharmacy is currently underutilised in the area of AMS. The findings of our studies might help inform changes to the healthcare landscape to facilitate more optimal use of antimicrobials. Use of antimicrobials can be optimised by utilising the skills and services of community pharmacists through development and implementation of community AMS frameworks.

Table 1 - Project design

Study	Approach	Worldview	Research Design	Methods	Participants
Overall project	**Explanatory sequential mixed method**	**Pragmatic**	**Quantitative and qualitative data collection and analysis**	**Online surveys and telephone interviews**	**Community pharmacists**
Study 1	Development of survey and pilot testing	Post positivism	Quantitative	Exploratory survey research	Tasmanian community pharmacists
Study 2	Exploratory	Post positivism	Quantitative	Exploratory survey research	Australian community pharmacists
Study 3	In-depth understanding	Naturalistic	Qualitative	Telephone interviews	Australian community pharmacists

Lists of abbreviations

1. A&F-Audit and Feedback
2. ACF-Aged Care Facility
3. AOM-Acute Otitis Media
4. ASHP-American Society of Health-System Pharmacists
5. AMR/AR-Antimicrobial Resistance
6. AMS-Antimicrobial Stewardship
7. ARI-Acute Respiratory Infection
8. ARS-Acute Rhino Sinusitis
9. CDC-Centers for Disease Control and Prevention
10. CDSS-Clinical Decision Support System
11. CRCT-Cluster Randomised Controlled Trials, CS-Cohort Study
12. EHR-Electronic Health Record
13. GPs-General Practitioners
14. ID-Infectious Disease
15. NH-Nursing Homes
16. NPS-National Prescribing Service
17. OECD-Organisation for Economic Co-operation and Development
18. OM-Otitis Media
19. QES-Quasi Experimental Studies
20. RADT-Rapid Antigen Diagnostic Testing
21. RTI-Respiratory Tract Infections
22. PCT-Procalcitonin testing
23. RCT-Randomised Controlled Trials
24. LRTI-Lower Respiratory Tract Infections
25. LUTI-Lower Urinary Tract Infections

26. SSTI-Skin and Soft Tissue Infections
27. PBS-Pharmaceutical Benefit Scheme
28. PBSAC-Pharmaceutical Benefit Scheme Advisory Committee
29. PCR-Polymerase Chain Reaction
30. POCT-Point of Care Testing
31. TG-Therapeutic Guidelines
32. UK-United Kingdom
33. URTI-Upper Respiratory Tract Infections
34. US-United States
35. UTI-Urinary Tract Infections

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Chapter 1: Context

1.1 Introduction

This chapter of the thesis summarises the context in which the research was carried out, including its purpose and background. A global view of the research problem of antimicrobial resistance (AMR), followed by the overall significance of the topic under research "antimicrobial stewardship (AMS)", will be presented. A description of the guide to the thesis is at the end of this chapter. The guide encompasses the research question, followed by sub-questions of the broader research question and a thesis table to lay out and summarise the following chapters. A literature review following this chapter provides a literature guided background to the research being undertaken and Table 1 will provide a reference glossary of the terms and abbreviations used in the thesis.

1.2 Research problem

Antimicrobials are the most successful group of drugs developed for use in human healthcare and their discovery was amongst the most important advances of the 20th century [1]. Since the discovery of penicillin in 1928, many other antimicrobials have been developed but, with the introduction of each new antimicrobial class, resistant bacterial strains were soon identified and, as such, treatment of some infections has now become a major challenge [2]. For instance, the first penicillin-resistant Staphylococcus aureus emerged less than a year after the introduction of penicillin in 1945 and nearly every antimicrobial agent that has been developed since then has faced substantial resistance problems. AMR is the ability of a microorganism (for example, bacteria, fungi, viruses and some parasites) to stop an antimicrobial (such as antibiotics, antifungals, antivirals and antimalarials) from working against it [3]. Resistance has been reported for every major class of antimicrobials prescribed and used in both community and hospital settings [4]. The resistance of a microorganism to a particular antimicrobial may drive a prescriber's decision to use a different antimicrobial, which then increases the risk of other antimicrobials developing resistance [5]. Though AMR occurs naturally over time through genetic changes, the misuse and overuse of antimicrobials is accelerating the process, resulting in once standard treatments becoming ineffective, with infections persisting in affected patients and thereby increasing the possibility of transmission in the community [6]. An increased risk of adverse effects, more frequent attendance to general practitioners (GPs) and increased medicalisation of self-limiting conditions has resulted in increased morbidity, mortality and cost of health care due to AMR [7]. This also causes a loss of trust in healthcare services. The World Health Organization (WHO) has named AMR as one of the three most important public health threats of the 21st century [8].

1.3 Antimicrobial resistance

Judicious use of the currently available antimicrobial agents is crucial as the rate of growth in resistance continues to exceed the rate of new drug development. AMR has been rated as having a potential impact on humans similar to that of global climate change [5]. Globally, there are already 700,000 deaths annually due to infections caused by antibiotic resistant organisms and this is expected to reach 10 million per annum by 2050 [9]. Moreover, according to a recent report, AMR is estimated to cause around 300 million premature deaths by 2050, with a loss of up to $100 trillion to the global economy [9]. The cost associated with AMR is likely to increase further as resistance to second- and third-line antimicrobial develops [9].

1.3.1 Mechanism

Along with the knowledge of the drivers of AMR in society and the natural environment, it is essential to understand the mechanisms of resistance in order to develop effective therapeutic and diagnostic strategies against multi-resistant organisms. Molecular biology provides a means of understanding the origins and spread of genes responsible for AMR. Most antimicrobials are produced naturally by microorganisms or are synthetic modifications of these substances, with only a few being solely synthetic [10]. Resistance mechanisms are inherent in naturally occurring antimicrobials, for example:

1) In Beta lactam antibiotics and quinolones, resistance is by upregulation of microbial adaptive evolution or efflux pumps of the bacteria.
2) In broad spectrum antibiotics, such as carbapenems, it is by altering the role of quorum sensing apparatus, formation of biofilms or gene amplifications.

In general, bacteria demonstrate one of the five mechanisms of antimicrobial resistance. These are:

- lack of entry or decreased cell permeability;
- greater exit or active efflux;
- enzymatic inactivation of the antibiotic;
- altered target or modification of drug receptor site, and/or
- synthesis of a resistant metabolic pathway.

[11, 12].

One of the most successful AMR mechanisms is inactivation of the antibiotic by adding specific chemical moieties to the compound or the destruction of the molecule itself, rendering the antibiotic unable to interact with its target [11]. The so-called ESKAPE group of pathogens are of particular concern with regard to AMR.

This group comprises both Gram-positive and Gram-negative pathogenic bacteria and the following species: ***E****nterococcus faecium*, ***S****taphylococcus aureus*, ***K****lebsiella pneumoniae*, ***A****cinetobacter baumannii*, ***P****seudomonas aeruginosa* and **E**nterobacter species (ESKAPE). These pathogens are the leading cause of life-threatening nosocomial infections and most of them are multidrug resistant [13]. Although the mechanisms of resistance are not the same for all ESKAPE pathogens, they share one major similarity which is a growing prevalence of antimicrobial use due to selective pressure [14]. Selective pressure from antibiotic use is defined as a force on antibiotic resistant genes by antibiotics which causes a particular bacterium with high fitness (called resistant mutants) to survive, multiply and evolve in a certain direction.

1.3.2 Drivers

The emergence of AMR is a natural evolutionary response to antimicrobial exposure; however, the currently complex and interlinking forces are making it a global threat. Predominantly, this serious global AMR threat is arising from antimicrobial use in agriculture, food production, veterinary medicine, human health and environmental pollution.

1.3.2.1 Agriculture, food production and veterinary medicine

Antimicrobials are used in animals for the prevention and treatment of disease and as growth-promoters. It has been reported that around half of the world's antimicrobial supply is used in animal and fish farming, and this has contributed to the development of AMR [15]. Approximately 80% of antimicrobials in the United States are consumed in agriculture and food production [16]. Infections in animals may also spread to humans through either direct infection with resistant bacteria, followed by sustained transmission of resistant strains arising in livestock to humans, or by transfer of resistant genes from agricultural to human pathogens [15]. Global consumption of antimicrobials in food animals was estimated at 63151 tons in 2010, of which the largest share, 23%, was in China, 13% in the United States of America, 9% in Brazil and 3% in India [17]. The authors predict a 67% increase in the global consumption of antimicrobials by 2030, given the "shifting production practices in middle-income countries in which extensive farming systems will be replaced by large-scale intensive farming operations". The use of antibiotics as animal growth promoters was banned in the European Union (EU) in 2006, although these are commonly used for mass prophylaxis in some countries [17].

1.3.2.2 Environmental waste and contamination

The environment has a major role in the global spread of antimicrobial resistance [18]. Antimicrobials that have been discharged into the environment can promote the occurrence of antibiotic resistant genes (ARGs). ARGs are not degradable pollutants but auto-replicative elements, which is more concerning [19]. These environmental ARGs could serve as a reservoir and can be horizontally transferred to humans, thus contributing to AMR [20]. There are several sources that contribute significantly to the burden of AMR organisms which develop in the environment, for example, hospital waste, water treatment plants, sewage treatment plants or inappropriate disposal of unused drugs. WHO, the European Commission and other environmental regulators have surveillance mechanisms to control and monitor various passages from where the ARGs enter the environment [18]. AMR action plans are incomplete without considering the need to reduce environmental pollution with antibiotic waste from animals, humans and manufacturing [21].

1.3.2.3 Travel, tourism, and migration

Several studies have suggested that the modern and easy travel routes for human, livestock and consumables have substantially contributed to the dissemination of AMR across the globe. Travel, tourism and migration specifically increase resistance for third generation cephalosporins, fluoroquinolones and aminoglycosides to Gram-negative bacteria including *E coli* and *K pneumoniae [22]*. These changes result in increased reliance on carbapenems which are considered to be antibiotics of last resort, subsequently leading to rising rates of carbapenem resistant bacteria worldwide [4]. By being exposed to resistant pathogens, human travellers are highly likely to return, colonised and infected, to their own countries. Several studies have shown that travellers returning from tropical or sub-tropical countries are generally colonised and often infected with extended spectrum beta lactamase (ESBL)-producing Enterobacteriaceae [23].

Globalisation and human migration led to the emergence of carbapenem resistant gram negative bacteria called Enterobacteriaceae (CREs) which are now a serious global threat [24]. Similarly, Colistin resistant gram negative MCR-1 (mobilised colistin resistance-1) gene, a plasmid-borne gene conferring colistin resistance which was first identified in pigs in China in 2014 [25], subsequently spread to dozens of other countries and is another major concern [26]. A group of gut dwelling bacteria called *Klebsiella pneumoniae* are becoming a common cause of untreatable infections in intensive care units as well. New Delhi metallo-β-lactamase (NDM), another enzyme that confers resistance to a wide range of antibiotics after first being detected in 2008, has emerged in the Indian subcontinent and has spread to the UK as a result of medical tourism. The travel pattern for *Klebsiella pneumoniae*, carbapenemase (KPC) and New Delhi metallo-β-lactamase (NDM) positive bacteria has emerged rapidly across the continents [27, 28].

1.3.2.4 Lack of development of new antimicrobials

The adaptive nature of the pathogens necessitates the discovery of new and effective compounds or the re-engineering of existing molecules to combat the resistant organisms. The development of fourteen new classes of antibiotics between 1935-2003 provided humanity with a temporary advantage in the struggle against microorganisms and infectious disease [29]. The resistance to these antibiotics continued to increase over time and the pharmaceutical companies did not invest much in antibiotic research and thereby, fewer new antibiotics were approved until recent times. The justification for this lack of investment is that antimicrobials are generally used only for short courses; hence they provide only a poor return on investment for the manufacturers. Only two new antimicrobials, linezolid and daptomycin, with new targets of action, have been introduced in the last 20 years [30]. According to Dr Tedros Adhanom Ghebreyesus, Director-General of WHO:

"Never has the threat of antimicrobial resistance been more immediate and the need for solutions more urgent. Numerous initiatives are underway to reduce resistance, but we also need countries and the pharmaceutical industry to step up and contribute with sustainable funding and innovative new medicines" [31].

Given the paucity of new antimicrobials, the challenge of managing resistant infections has increased. In the context of limited new antibiotics in the development pipeline, the WHO describes a future post-antibiotic world and warns that less development in antibiotics will eliminate the advances in healthcare of the past 100 years [32]. It is extremely important to invest in extending the evolution of new antibiotics [33, 34]. In 2016, it was estimated that over 40 billion USD is required over the coming decade, in order to take global action on AMR. Almost half of this (16 billion USD) is needed to promote the development of new antibiotics to treat patients in urgent need [9]. In May 2016, the WHO, in partnership with the Drugs for Neglected Diseases initiative (DNDi), acquired seed funding to launch the Global Antibiotic Research & Development Partnership (GARDP), which is an organisation that aims to apply the principles learned from the DNDi's work in developing tools to combat neglected diseases and developing new antibiotics [35].

1.3.2.5 Humans

A significant force driving the spread of AMR is the inappropriate use of antimicrobials in humans. The over prescription of antimicrobials, particularly antibiotics, is mostly due to diagnostic uncertainty, lack of knowledge and patient pressure. It is estimated that 50% of all antimicrobials prescribed to humans are considered unnecessary and the majority of antimicrobial prescribing takes place in the community, rather than in a hospital or acute care setting [10]. The true threat of AMR was revealed to all in the WHO 2014 global report on AMR surveillance [36]. Prevention of AMR needs rigorous actions at the patient level, institution level, national level and supra-national levels. Countries can learn from each other and possibly transplant best practices across borders to prevent AR [37].

1.3.3 Global burden

Estimating the global burden of disease from infections caused by pathogens that have acquired AMR is essential for resource allocation and to inform AMR action plans at national and global levels. According to the European Centre for Disease Prevention and Control, 25,000 people in Europe die each year as a direct result of resistant infection [38]. AMR leads to an increase in healthcare costs, with the complications associated with antimicrobial resistance estimated to cost €9 billion annually in Europe [39]. A recent review demonstrated that the additional cost of AMR could be £20,000 (€23,139.27) per patient episode in hospital [40].

According to the United States AMR Threats Report 2019 from the Centers for Disease Control and Prevention (CDC), antibiotic-resistant bacteria and fungi cause more than 2.8 million infections and 35,000 deaths in the United States each year [41]. When *Clostridioides difficile* is added to these, the toll of all the threats reported in the United States exceeds three million infections and 48,000 deaths. Overall, in the United States, there has been significant progress preventing infections and deaths from resistant bacteria typically associated with hospitals. Deaths from antibiotic-resistant infections in hospitals went down by 28 percent from 2012 to 2017. However, gonorrhoea has developed progressively in the community and has caused drug-resistant Neisseria gonorrhoeae, which is resistant to all classes of antibiotics except for one. Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are one of the leading causes of death because they destroy routinely prescribed antibiotics, such as penicillins and cephalosporins. They make urinary tract infections harder to treat, especially in women, and could undo progress made in hospitals if allowed to spread there. The estimate of the economic burden of AMR on the US economy is $20 billion (2008 currency rates) in direct health care costs, with additional indirect costs as high as $25 billion per year. But the impact is greatest in developing countries because the people who are living there are more exposed to infectious diseases and may be more susceptible due to malnutrition or immunodeficiency and, therefore, have a greater need for antibiotics. Secondly, impoverished individuals may be more at risk to being exposed to sub-inhibitory dosages, antibiotic sharing or the use of lower quality or expired medications. Thirdly, access to appropriate medical care may be more limited in developing countries, thus encouraging individuals to self-medicate or to seek care from less tightly regulated, for-profit providers [42].

A study conducted in a developing country reported excess deaths caused by multidrug resistant bacterial hospital acquired infections in Thailand. It was estimated to be 19,122 deaths per year in a country with a population of about 66 million in 2010; this is a large number of deaths compared with those estimated in the United States (23,000 death per year in a country with a population of 316 million in 2013) (Center for Disease Controls and Prevention and United States Department of Health and Human Services, 2013) and the European Union (25,000 deaths per year in the European Union with a population of about 500 million in 2007) (European Centre for Disease Prevention and Control and European Medicines Agency, 2009). This study is just one example highlighting the need for public health officials and international health organisations to improve systems to track and reduce the burden of AMR in low- and middle-income countries [43].

1.3.4 Response

With the problem of AMR now being found throughout the world, the WHO clearly states that AMR is not a phenomenon occurring in just poor or developing countries. WHO's Global Action Plan (GAP) on AMR was adopted by their member countries at the World Health Assembly in 2015. The overall aim of the GAP is to ensure continuity of successful infection prevention by increasing awareness and understanding of AMR amongst government departments and other stakeholders. This can be achieved by strengthening surveillance and research to reduce the burden of infection, to encourage the rational use of medicines in clinical, veterinary and farming practices, and to re-direct investment in developing new antibiotics, diagnostics and immunisation. [44].

WHO's Global Action Plan is implemented globally through a broad, integrated One Health approach that reflects the links between human health, animal health and the environment, and requires many different sectors to collaborate to address the problem. WHO's Global Antimicrobial Resistance Surveillance System (GLASS), established in 2015, is helping countries strengthen national surveillance systems and provides more comprehensive standardised AMR surveillance data [45].

Recently, AMR has been the focus of several multi-sectoral meetings and conferences, including an AMR workshop at the recent Prince Mahidol Annual Conference in Bangkok, Thailand, a Forum on Microbial Threats of the U.S. National Academies of Sciences, Engineering and Medicine workshop, and the International One Health Congress in Saskatoon, Canada [46].

One Health is the collaborative effort to utilise expertise and resources in a coordinated and collaborative manner to act locally, nationally and globally for the optimal health of humans, animals and the environment. With regard to antimicrobial stewardship, the One Health approach aims for the regulation and registration of antibiotics, the use of guidelines for infection prevention and control, and the optimal use of antibiotics, thus ultimately reducing AMR in all sectors [47].

1.4 Antimicrobial stewardship

It is essential to address the emergence of AMR by conserving the currently available antibiotics. Cost effective antimicrobial optimisation strategies are required in parallel with the giving of effective treatment for infections through antimicrobial stewardship (AMS) initiatives [48]. AMS has evolved in recent years and it is one strategy, intervention or complex multi-component intervention that aims to optimise antimicrobial prescribing, dispensing and use [49].

Now the term AMS is not only applied within human healthcare but it is also referred to and utilised in broader contexts, including plants and animal health, and with other strategies such as One Health, as previously discussed.

1.4.1 The emergence of the term 'antimicrobial stewardship'

Results for the search term '(antimicrobial OR antibiotic) AND stewardship' first appear on PubMed in 1996, reaching over ten hits per year in 2005, over 50 hits per year in 2008 and over 100 per year in 2011

[49]. The total number of citations identified by this search term is now over 2500 and is added in the database as a subject heading (MESH term), due to its exponential use in the last five years.

Antimicrobial stewardship (AMS) is defined as a set of coordinated strategies to improve the use of antimicrobial medications, with the goal of enhancing patient health outcomes, reducing resistance to antibiotics and decreasing unnecessary costs [50]. Important principles of AMS are preventing resistance selection pressure in the patient by avoiding unnecessary antibiotic use, choosing the least broad spectrum antibiotic appropriate for the infection and using adequate doses for the shortest possible duration. Along with infection prevention and control, hand hygiene and surveillance, AMS is considered a key strategy in local and national programs to prevent the emergence of AMR and to avert adverse effects. Effective AMS programs to improve patient care, also known as antimicrobial management programs, should be financially self-supporting. AMS interventions can be broadly divided into two categories, the first being a front end or a prescription approach which uses restrictive methods to optimise antibiotic use. This is usually applied at a national, regional or institutional level. The other category is called back-end or post-prescription strategy, that is the audit and feedback of prescribing patterns by generating and sharing performance reports. Other strategies reported in the studies include diagnostic testing, computer assisted decision support, clinical guidelines, behavioural change interventions and education. These interventions, approaches or techniques are applied differently in different settings but it is unclear which interventions are most effective in improving antimicrobial management. This will be discussed more in the following chapter, in which different interventional studies will be reviewed.

1.4.2 Hospital

It is estimated that up to 38% of the antibiotic usage in European hospitals was not compliant with the guidelines and requires optimisation through the AMS framework [51]. A survey of hospital-acquired infections in the US in 2011 reported that approximately 722,000 cases and 75,000 deaths were associated with nosocomial infections and approximately 70% of such infections were resistant to at least one clinically relevant antibiotic [52]. Numerous professional, clinical and public health organisations recommend AMS programs for hospitals, in order to optimise antibiotic prescribing by promoting guideline concordant treatments. For example, the National Action Plan to Combat Antibiotic Resistant Bacteria calls for all US hospitals to have AMS programs. The goal of the Core Elements of Hospital Antibiotic Stewardship Programs is to provide a framework for AMS implementation in hospitals, regardless of the facility's size or resources [53].

An international cross-sectional survey conducted in 2015 reported the extent and components of global efforts for AMS in hospitals. It revealed that 52% of 660 hospitals from 67 participating countries have national AMS standards, 4% of them are in the planning stage, while 58% had an AMS program [17]. Similarly, in North America, Europe and Australia, collaborative groups, through a consensual approach, identified and implemented essential core elements for hospital AMS programs. Core elements of AMS are leadership commitment, accountability, drug expertise, action, tracking, reporting and education. This is in addition to identifying champions and leadership commitments and putting into place routine protocols that address the decision to start, continue or stop an antibiotic. The AMS frameworks programs are generally developed and implemented by a team representing infectious diseases, pharmacy, microbiology, nursing and other hospital practitioners. Various AMS strategies to implement the core elements of a hospital AMS framework include antibiotic substitution of the same class for cost-saving purposes, intravenous-to-oral switching programs for highly bioavailable drugs, computerised decision support, antimicrobial cycling and pharmacokinetic consultation services.

Teaching hospitals are significantly more likely to have an AMS program but the best hospital AMS strategies are not definitively established and can over- or under-estimate the effect of interventions on outcomes [54]. Often multiple interventions are made simultaneously, making it difficult to determine whether the benefit is attributable to any one specific intervention [55]. Despite all the challenges, massive progress has been made in the last two and a half decades in hospital AMS [55]. Pulcini *et al* have recently proposed the core elements and a checklist of items for global hospital AMS programs, which may be useful for those countries where such programs are not yet implemented [56].

1.4.3 Aged care facilities

Antimicrobials are amongst the most frequently prescribed medications in aged care facilities, skilled nursing facilities and assisted living facilities, which are collectively known as aged care facilities (ACFs) or long-term care facilities (LTCFs). ACFs represent a reservoir of multi-drug resistant bacteria because of overuse of antimicrobials which can have direct adverse consequences for ACF residents [57]. In a controlled clinical trial with placebo, undertaken in 12 European countries and including more than 3000 older-aged adults with an acute cough, it was found that the use of ampicillin causes harm in non-pneumonia patients (67). Up to 70% of residents receive one or more courses of systemic antibiotics annually [58, 59]. Almost 12% of ACF patients have an infection at any given time and it is estimated that up to 75% of antibiotic prescriptions are inappropriate in terms of their indication, dose or the duration of therapy in such facilities [59].

Antibiotic overuse in aged care facilities not only promotes the emergence and persistence of AMR but may lead to adverse effects such as C. difficile colitis. Guidelines recommend development of AMS programs for these facilities to promote optimal antibiotic use. However, the effectiveness of AMS programs or the contribution of any specific AMS component are not known [60]. Interventions that can be employed include education, guidelines development, feedback to practitioners and infectious disease consultation. The next chapter, a literature review of studies conducted in ACFs, reports that most studies in ACFs focussed on specific aspects of treatment of urinary tract infections, limiting treatment of asymptomatic bacteriuria or prophylaxis of urinary tract infections. There were no reports of cost-effectiveness and the sustainability of most of the AMS interventions was unclear. There is a need for further evaluation to characterise effective AMS studies for ACFs.

As discussed above, suspected urinary tract infections are the most common reason antibiotics are prescribed in ACFs. However, it has been reported that in around 33% of cases, the problem is asymptomatic bacteriuria rather than a true infection [61]. In 2017, based on these findings, the Centers of Disease Control and Prevention of the US introduced the core elements of hospital AMS programs in ACFs. The only difference was pertaining to its implementation in this setting. The subsequent studies found that to implement such AMS frameworks effectively, ACFs should improve drug expertise, that is, the employment of infectious disease (ID) trained pharmacists, overcoming any difficulties in tracking and reporting because, generally, ACFs have fewer staff, limited IT capability, lack of training and no centralised monitoring system [62]. Previous systematic reviews, which have been conducted to report AMS studies in ACFs, found a major gap in the context of the global challenge of AMR and ageing populations. They reported a lack of evidence of AMS interventions to optimise antimicrobial use in ACFs. The paucity of good quality studies and the heterogeneity in outcome measures of antimicrobial use calls for more rigorous methods to be employed. Quality improvement, performance development and process evaluations should be considered important components of future studies [59].

1.4.4 Community Antimicrobial Stewardship

In the past, AMR was predominantly considered a problem in hospitals; therefore the majority of AMS initiatives target the inpatient setting. Multi-drug resistant organisms have emerged and are often identified in community settings, suggesting that reservoirs of antibiotic-resistant bacteria are present outside the hospital [63]. General practitioners write about 90% of all antibiotic prescriptions and respiratory tract infections are the leading reasons for prescribing in the community [64]. Common bacterial pathogens in the community, such as community acquired extended spectrum beta lactamases (ESBL) and *Streptococcus pneumoniae,* have become progressively more resistant to traditional antibiotics and Salmonella strains are beginning to show resistance to crucial fluoroquinolones [65].

Multifaceted interventions to reduce the overuse of antibiotics have been found to be effective and better than single component initiatives. Important community AMS initiatives, strategies and interventions include enforcement of the policy of prohibiting the over-the-counter sale of antibiotics, the use of AMS programs, the active participation of clinicians in audits, the utilisation of valid rapid point-of-care tests, the promotion of delayed antibiotic prescribing strategies, the enhancement of communication skills with patients and the performance of more pragmatic studies.

In Europe, upper respiratory tract infections account for 57% of the antibiotics used, with a further 30% for lower respiratory tract infections, followed by urinary tract infections at 7% [66]. In general, antibiotic prescribing has been shown to be influenced by several factors, including cultural aspects related to the country, socio-economic factors, patient demands and clinical autonomy [67]. Inequalities might also explain the variability of antimicrobial use. Similarly, diagnostic uncertainty plays an important role in antibiotic overprescribing. Misconceptions and uncertainties regarding the role of antibiotics also exist among patients which leads to unnecessary pressure on prescribers to prescribe antibiotics [68, 69]. There also appears to be a dissonance between prescriber and patient expectations during consultations for respiratory tract infections [70]. A recent survey, which included more than 1000 GPs, was carried out in the UK and found that 55% felt under pressure, mainly from patients, to prescribe antibiotics, even if they were not sure that they were necessary, and 44% admitted that they had prescribed antibiotics to get a patient to leave the clinic [71]. Another European study reported that around half of the patients believed that antibiotics were effective in treating viruses, cold and flu, with considerable differences across countries [72]. Other important factors which should be taken into consideration while proposing any AMS framework or program in community settings include care coordination, professional collaboration, communication and teamwork, prescribers' and pharmacists' knowledge about AMS and the doctor-pharmacist–patient relationship.

In 2007, AMS guidelines to inform the development of institutional programs were released by the Infectious Diseases Society of America with the support of the American Academy of Pediatrics, the American Society of Health System Pharmacists, the Infectious Diseases Society of Obstetrics and Gynaecology, the Pediatric Infectious Diseases Society, the Society for Hospital Medicine and the Society of Infectious Diseases Pharmacists [50]. The Centers for Disease Control and Prevention (CDC) identified 18 drug resistant threats. The United States National Action Plan for Combating Antibiotic-Resistant Bacteria, developed in 2015, addresses the AMR problem in the United States [73]. In 2016, the United States' Centers of Disease Control and Prevention rolled out core elements of AMS in outpatient settings. Countries such as Australia, France, Germany, Ireland, Spain, the Netherlands and the United Kingdom have established complementary recommendations guiding antimicrobial stewardship initiatives in their respective communities [74].

The implementation of a successful AMS program is an urgent matter in Asia, due to the high prevalence of multi-drug resistant organisms in the region. National action plans against AMR, with AMS as a core element, are evolving in different Asian countries, following the WHO action plan on AMR [75].

However, in China and Japan, inappropriate antibiotic prescribing is high; 44% and 34.4% of antibiotic prescriptions respectively are considered inappropriate [76]. According to a recent systematic review and meta-analysis evaluating the impact of AMS programs [75], it has been found that Asia also lags behind in matters of public hygiene, patient/prescriber communication and public awareness about the prudent use of antibiotics when compared with western countries. These findings are concerning, given that these are the factors which are important determinants of the effectiveness of AMS programs.

In South East Asia, antibiotic use is high and AMS policies are either absent or poorly implemented [77]. In South Asian communities antibiotic use is high, with up to 67% of all outpatients being given antibiotics [78]. In 2013, India passed the Chennai Declaration, a five-year plan to address AMR by reducing and restricting both inpatient and outpatient antibiotic use. In India, the burden of infectious disease is the highest in the world, resulting in 30% of all deaths [79] and there are no restrictions on dispensing Over the Counter (OTC) antibiotics without a prescription.

1.4.5 Notable global AMS efforts

Other notable global AMS efforts include the implementation and prospective reporting of an AMR strategic framework in South Africa. More robust AMS practices and related structures are present in South Africa, compared with other countries in Africa.

AMS in Australia has evolved significantly over time and from January 2013, AMS programs have been considered mandatory for hospital accreditation by the Australian Commission on Safety and Quality in Healthcare (ACSQH) [80]. The aims of the AMS initiatives in Australia are to improve the safe and appropriate use of antimicrobials, reduce patient harm and decrease the incidence of AMR in Australian hospitals. At the heart, ACSQH criteria of AMS require that all healthcare services:

- have an AMS program in place;
- provide clinicians prescribing antimicrobials access to the currently endorsed Therapeutic Guidelines on antimicrobial usage;
- follow regular surveillance and monitoring of antimicrobial prescribing, dispensing and AMR, and
- take action to improve the effectiveness of AMS.

1.4.6 AMS education

A major cause of antimicrobial misuse is insufficient knowledge regarding antimicrobial prescribing amongst many categories of professionals [81]. In order to produce clinical professionals who are prepared to sustain future AMS programs, the curricula of medical, pharmacy, nursing and veterinary programs must consider how to integrate the concept of AMS in their coursework. To optimise the chances of success, AMS programs require an interdisciplinary team effort. Given the need for stewardship programs, the question arises of how to best prepare healthcare professionals for participating in AMS efforts. Most current efforts are focussed on an institutional level, where a physician and a pharmacist are called upon to design and implement AMS programs. Ideally, AMS programs should be anchored with advanced infectious disease training [50]. Therefore, the use of an outcome-based approach is necessary, considering the heterogeneity of global need and the focus of AMS. This method has been described within various forms of medical education frameworks [82, 83].

The most common AMS intervention is the provision of education and training [84]. Fortunately, several governmental, non-governmental ,professional and academic organisations have developed a multitude of AMS education and training programs [85]. These educational programs cover a diverse range of topics and offer flexible delivery in terms, face-to-face or online options. Many of these programs are available to healthcare professionals free of charge, thanks to the growing interest in Massive Online Open Courses (MOOCs). Weir *et al* recently published an international inventory of AMS training programs across the globe [86]. It is expected that these and similar courses will help address the current gap in AMS education for a range of health care professionals, including medical practitioners who prescribe and pharmacists who dispense antimicrobials [87]. While a detailed account of all such programs is beyond the scope of this thesis, some of the widely known programs are covered below:

One example is the MOOC offered in four languages by the WHO which is aligned with the domains of the WHO AMR competency framework [88]. The WHO course focuses on knowledge improvement and its impact on intention to change antimicrobial prescribing patterns in accordance with the clinical guidelines. This course intends to reduce the time needed to develop learning material by the individual countries. However, it is expected that the people who are interested to participate in such online courses have a higher understanding of AMS and AMR. A similar course is offered by the University of Dundee in collaboration with British Society of Antimicrobial Chemotherapy (BSAC [89]. The course is offered as MOOC and offers learning modules, reference to guidelines, promotional materials and other web-based resources to educate healthcare professionals. The course has attracted participants across the globe with thousands of clinicians completing and rating the quality of instructions and education material [90]. In 2018 a comprehensive e-book was released for free online learning by the British Society of Antimicrobial Chemotherapy and the European Society of Clinical Microbiology and Infectious Diseases (the ESCMID Study Group) jointly developed an eBook on AMS [91]. The two societies also develop and coordinate courses, study groups and are involved in collaborative research projects on AMS [91]. The Australian NPS MedicineWise project regularly produce and disseminate, in collaboration with other government and professional societies, AMS resources and course content for AMS learning [85]. A few notable programs are: the online modules provided by the Stanford University of Medicine under the Stanford Safety and Sustainability Program and Centre for Disease Control and Prevention, National Centre for Antimicrobial Stewardship and American Society of Health Care Pharmacists also launched various multifaceted, interprofessional mentoring initiatives for quality improvement of AMS [92].

1.4.7 AMS Education-prescriber

Educating prescribers is important in overcoming antimicrobial misuse and is seen to be equally effective in inpatient and outpatient care [93]. There is a growing need that prescribers from developed, developing and underdeveloped countries come together to share information. AMS leaders are advocating the need of free/open access to educational resources so that prescribers can interact with experts to learn, share and inquire, regarding recent developments in AMR and AMS.

1.4.8 AMS Education-Undergraduate medical curriculum

It is crucial that academia and ministries of health and education focus jointly on an adapted undergraduate medical curriculum which teaches the necessary principles of microbiology, infectious diseases and clinical pharmacology, with emphasis on the principles of prudent antibiotic prescribing [81]. AMS leaders have stressed that medical students must engage in problem-based learning and interactive discussions in order to update their AMS knowledge [81]. An outcomes-based approach for delivering training for medical undergraduates was also proposed by the British Society of Antimicrobial Therapy in 2005. The Infectious Disease Society of America (IDSA) guidelines also recommend that the fundamental principles of AMS should be integrated into preclinical medical curricula [94]. In March 2012, a Policy Statement on AMS by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS) was published. Key recommendations were:

- SHEA, IDSA, and PIDS believe that significant knowledge deficits in the areas of AMR and AMS are prevalent among healthcare providers in the US;
- educational programs which teach the science behind the principles of and the tools essential for the practice of effective AMS should be developed for those in training programs, as well as for all prescribing clinicians, and
- education about AMR and AMS should be incorporated into curriculum requirements for medical students and post graduate residents and fellows. It is crucial that currently practising clinicians become proficient in these areas.

In the Australian guidelines for AMS, the educational requirements and competency of prescribers are described in more detail [95]. According to that, all healthcare professionals in contact with patients must be educated about AMR, the benefit of antibiotics in different conditions and related beliefs and the use of laboratory tests to guide antibiotic treatment, as well as being given the opportunities to develop their knowledge of symptom management.

1.4.9 AMS Education-Public Awareness

Public awareness campaigns contribute to the prudent use of antibiotics in outpatients in high prescribing countries [96, 97]. In the last decade, numerous notable national and regional campaigns have been conducted to educate the public worldwide, for example:

- in the US, the Centers for Disease Control and prevention (CDC), " Get smart about antibiotics" (www.cdc.gov/getsmart/);
- in Canada, "Do bugs need drugs?", (www.dobugsneeddrugs.org);
- across Europe, the European Centre for Disease Prevention and Control (ECDC) "European Antibiotic Awareness Day" (http://ecdc.europa.eu/en/eaad/Pages/Home.aspx), and
- in Australia, NPS-MedicineWise is an independent, government funded organisation, founded in 2012, which is providing public awareness and education through its "Resistance Fighter Campaign" (https://www.nps.org.au/medical-info/consumer-info/antibiotic-resistance-the-facts).

1.4.10 AMS Education-Medical curricula

The concept of prudent antimicrobial prescribing behaviour was first established during medical study [98]. Increasingly, the focus is on adding AMS education to undergraduate education, rather than postgraduate education. European academics think that time is the most important constraint in learning; therefore instead of class room courses, e-learning is a better option for education on AMS [99]. Education on AMS and/or AMR has an important role in promoting awareness and practical skills across all clinical disciplines. All those involved in patient care must be able to provide safe and effective care for patients across all medical specialties, including AMR/AMS. An Australian survey of final year medical students found students feel less confident and less clinically knowledgeable in their infectious disease knowledge as compared with other conditions [95].

1.4.11 AMS Education-Survey studies

Although there is a widely recognised need to train clinical professionals to participate in AMS programs, there is little literature regarding approaches for AMS education. A recent survey of undergraduate health care and veterinary programs in the UK found that many programs include components of AMS (80.7% of respondents), but few programs (36.3%) addressed all of the key topics as recommended by current UK AMS policies [100]. However, students recognise the need to engage in AMS and they appreciate that their clinical decisions can contribute to the development of resistance [101]. Yet, in another survey of US medical students, more than two-thirds of respondents reported that they did not feel well prepared to streamline or de-escalate antibiotic therapy, which is a key concept in AMS [93].

1.4.12 AMS Education-Pharmacy programs

For Doctor of Pharmacy (PharmD) programs, there is little guidance about incorporating AMS into the standard curriculum. Student performance on AMS-related questions varies widely by school, suggesting that the approaches to AMS education are likely to be disparate across PharmD programs [102]. Reports on elective courses for AMS suggest that student understanding of AMS principles can be improved in smaller settings with active learning components but such offerings are limited to specific programs [103, 104]. In a recently proposed model for AMS education in PharmD curricula in the US, AMS principles were integrated into all stages [105]. A greater emphasis of AMS education was suggested during advanced pharmacy practice experience in which students are introduced to patient care under the guidance of a preceptor, similar to an apprenticeship, in their final year of coursework [106]. Pharmacy programs vary as to whether microbiology is required as a prerequisite for entry into the professional phase of the program. The available literature for AMS education in pharmacy programs demonstrates that senior students perform well with case-based, active-learning approaches in elective settings [81, 103, 104]. Together, these findings suggest that the foundations for AMS can begin in a didactic setting but must ultimately shift to a more problem-based approach, in order for the students to hone their clinical decision-making skills.

1.5 Community Pharmacist and Antimicrobial Stewardship

There are many studies exploring the role of GPs, including a systematic review of prescriber related AMS strategies [107] but little is known about the issues and experiences of community pharmacists in AMS [108]. Pharmacists have the potential to play an important role in AMS [109-111]. They are well positioned to contribute to the development and implementation of AMS initiatives in the community by providing their expert services to the prescribers, patients and their carers [112].

However, there is a lack of evidence regarding AMS understanding of community pharmacists, how they perceive their role and how they can effectively contribute [113-115]. The knowledge, attitude and practice (KAP) surveys conducted in this regard show that the participants' knowledge and attitude regarding AMS were positive but their practices regarding AMS were not up to date [116, 117]. For example, they can play a major role in providing education to patients, as they are involved in direct patient care during their daily practice [118]. Other AMS initiatives in which community pharmacists can be involved include facilitation in delayed supply of antibiotics [108, 119], point of care testing [120, 121], prescribers' education [122-125], public awareness [126] and provision of self-care advice [127, 128] in respiratory tract, urinary tract [129-131] and other infections [132, 133]. Community pharmacists can also help to develop a AMS framework for community pharmacies, through leadership, facilitation and communication initiatives [126, 128, 134].

1.6 Conclusion:

There have been numerous initiatives, action plans and studies addressing or investigating the effects and component initiatives of AMS in hospitals. However, little research has been undertaken to study or implement AMS initiatives in community settings and to investigate the role of community pharmacists in AMS programs. Most antimicrobials are prescribed in the community setting but less attention is given to AMS in this sector [135]. More research is required to establish baseline community antibiotic usage, identify inappropriate antibiotic prescribing and develop benchmarks for comprehensive AMS programs for the community. This thesis reviews the available studies related to antimicrobial stewardship in community settings and investigates the current practices, barriers and facilitators of community pharmacists in AMS.

1.7 Guide to the Thesis

1.7.1 Research Question

What is the role of the community pharmacist in antimicrobial stewardship?

1.7.2 Research Sub-Questions

The research sub questions are interrelated and inform and build on each other in sequence, in order to respond to the overarching research question. (Phases)

Q1. What are the various AMS interventions being applied in community settings internationally?

Q2. What are the 'enablers of' and 'barriers to' community pharmacists' participation in AMS?

Q3. What are the current practices for and perceptions of community pharmacists of AMS?

Q4. What are the various barriers limiting Australian community pharmacists' participation in AMS and what are the possible solutions to overcome such barriers to facilitate greater involvement of community pharmacists in AMS initiatives?

1.7.3 Thesis Layout

<table>
<tr><td colspan="3">What is the role of the community pharmacist in Antimicrobial Stewardship?</td></tr>
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Context</td></tr>
<tr><td>Q1. What are the various AMS interventions being applied in community settings internationally?</td><td>Chapter 2
Literature Review of Various Antimicrobial Stewardship Interventions in the Community Setting</td><td></td></tr>
<tr><td>Q2. What are the enablers of and barriers to community pharmacists' participation in AMS?</td><td>Chapter 3
Development and validation of a questionnaire to explore community pharmacists' knowledge and perceptions</td><td>Embedded Publication
Rizvi T, Thompson A, Williams M, Zaidi STR. Perceptions and current practices of community pharmacists regarding antimicrobial stewardship in Tasmania. Int J Clin Pharm. 2018 Oct;40(5):1380-1387. doi: 10.1007/s11096-018-0701-1. Epub 2018 Aug 2. PMID: 30069668; PMCID: PMC6208572.</td></tr>
<tr><td>Q3. What are the current practices for and perceptions of community pharmacists about AMS?</td><td>Chapter 4</td><td>Embedded Publication
Rizvi T, Thompson A, Williams M, Zaidi STR. Validation and implementation of a national survey to assess antimicrobial stewardship awareness, practices and perceptions amongst community pharmacists in Australia. J Glob Antimicrob Resist. 2020 Jun;21:28-33. doi: 10.1016/j.jgar.2019.08.025. Epub 2019 Sep 7. PMID: 31505297.</td></tr>
<tr><td>Q4. What are the various barriers limiting Australian community pharmacists' participation in AMS and what are the possible solutions to overcome such barriers to facilitate greater involvement of community pharmacists in AMS initiatives?</td><td>Chapter 5</td><td>Undergoing Revision for Publication</td></tr>
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Chapter 2: Antimicrobial stewardship in community settings: a literature review

2.1 Introduction

As a consequence of antimicrobial use over the last 70 years, resistant microbes have emerged and infections are becoming more difficult to treat [136]. The gravity of the problem has been highlighted by the World Health Organization (WHO) through its Global Antimicrobial Surveillance System, which reported in 2019 that antimicrobial resistance (AMR) is responsible for over 23,000 deaths annually and affects around 700,000 people with suspected multi-drug-resistant tuberculosis [137]. If not tackled, the problem of AMR is likely to worsen in the future [138]. Modelling in the report "Antimicrobial resistance: Tackling a Crisis for the Health and Wealth of Nations 2014" predicts that globally AMR will cause 10 million deaths annually by 2050 and will be associated with a financial burden exceeding USD 100 trillion [9].

In order to optimise antimicrobial use and help combat the increasing threat of AMR, there has been a growing interest in the concept of antimicrobial stewardship (AMS) [139]. AMS is defined as a set of coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy and route of administration [140]. In some developed countries, governmental agencies are mandating AMS programs as one of the accreditation requirements for hospitals [141]. As an example, all Australian hospitals are now required to have an AMS program, as per standards developed by the Australian Commission on Safety and Quality in Health Care (ACSQHC) [142].

Whilst it was in hospital settings where AMS programs were originally developed, the majority (90%) of antimicrobials are used in community settings [143]. Furthermore, some of the antimicrobials commonly used in community healthcare settings have been linked to the emergence of community associated multidrug resistant (MDR) bacteria [144]. Hence, there is a recognised and immediate necessity for more widespread implementation of AMS initiatives in the community setting [143, 145]. It is, therefore, important to review and summarise the available evidence regarding AMS initiatives in this sector.

While a considerable number of reviews have been conducted on AMS initiatives in hospital settings [146-148], the relative paucity of AMS activity in community settings has resulted in a comparatively smaller body of associated research in this sector. While previous reviews published by Arnold *et al* [146] in 2005 and Ranji *et al* [149] in 2008, discussed the effectiveness of AMS in community settings, the growing interest in community AMS warrants a contemporary review of the topic. A review was conducted by Drekonja *et al* in 2015 [63]. However, this did not include searches from the databases CINAHL® and Scopus®. These databases cover nursing and broader healthcare-related literature; therefore the scope of the Drekonja review may have been limited, given the multidisciplinary nature of AMS initiatives. In 2017, work by Dobson *et al* highlighted a lack of best practices in AMS in outpatient settings [150]. In the same year, a narrative review by Bishop *et al* and a systematic review by Saha *et al*, pointed to the expanding roles and importance of community pharmacists in AMS [112, 151]. This chapter aims to review the contemporary literature and summarise the current state of evidence to identify and appraise AMS initiatives in community settings.

2.2 Method

This is a narrative review which aims to provide a broad description of various AMS studies conducted in the community sector. The search was conducted using the electronic bibliographic databases MEDLINE®, Embase®, Cochrane's CENTRAL®, CINAHL® and Scopus® covering the period January 2008 to November 2020. The search began in 2015 and was most recently updated in November. Studies published before 2008 were excluded as they pre-date the introduction of the concept of AMS [152]. A combination of 'free-text' and 'subject specific headings' (Medical Subject Headings-MeSH) for MEDLINE and Emtree terms for EMBASE were used. The search was limited to literature published in English.

2.2.1 Eligibility criteria

This review focusses on general practices and aged care facilities (aged care homes). Discussion of antimicrobial stewardship in other outpatient settings is outside the scope of this review. Studies involving any AMS interventions in primary care (community) settings, with an outcome measure of optimising antimicrobial use, were included in the review. Studies were included if the intervention were clearly described and evaluated using an experimental or quasi-experimental design. Descriptive papers, editorials, letters, conference reports, reviews or studies which did not report any AMS related outcomes were excluded, as were studies that lacked an appropriate control. Studies conducted in countries where antimicrobials are available without prescription were also excluded from the review.

2.2.2 Definitions

- For this review, a study was considered successful if it achieved an outcome measure of significant improvement in appropriate antimicrobial prescribing, dispensing or use.
- Appropriate antimicrobial prescribing is defined for this review as antimicrobial prescribing according to the antimicrobial prescribing guidelines.
- Unnecessary or inappropriate prescribing is defined as prescribing antimicrobials in conditions in which antimicrobial use is not indicated in the guidelines.
- Single component studies are defined as studies involving single AMS intervention which may or may not have more than one activity to implement that intervention.
- Complex interventions with multiple component studies are defined as studies involving more than one AMS intervention, with more than one activity to implement the interventions.
- For this literature review aged care facilities (ACFs) are defined as residential structures for the long-term care of elderly people.

2.2.3 Data extraction

I, Tasneem Rizvi (TR) independently screened the titles and abstracts of all studies for the review. Discrepancies were discussed and resolved with mutual discussions amongst the team (Mackenzie Williams-MW, Angus Thompson-AT and Syed Tabish Razi Zaidi-STRZ). Data extracted included authors, year of publication, country, study design, settings, intervention types and study outcomes.

2.3 Results

An initial electronic search retrieved 3298 citations, out of which 290 potentially relevant articles were short-listed. We included 73 studies in our final analysis based on our inclusion criteria. The study selection process is outlined in Figure 1.

2.3.1 Study characteristics

More than half of the studies were conducted in Europe (n=40), with the remainder conducted in North America (n=25) and Australasia (n=8). The majority of studies were either cluster or randomised controlled trials (n =49), with smaller numbers of quasi experimental studies (n=17) or control before and after studies (n=7). In terms of interventions, 25 studies were single faceted and 36 studies were multifaceted; 11 studies were multifaceted studies conducted in aged care facilities (ACF). 51 of all studies included in the review focussed on respiratory tract infections (RTIs). Cost effectiveness of analysis was reported in one study [153]. A description of the study's characteristics is included as Table 1.

2.3.2 Single component studies

Twenty-six studies employed single component AMS intervention. The discussion below will categorise the AMS interventions as per the classifications proposed by King *et alet al* [154]. This classification has been chosen because it has been used by others [155] thus making comparison with the broader relevant literature logical. The intervention categories are:

- education which can be either patient education, clinician education (clinicians also referred to as prescribers, physicians, family physicians, providers or general practitioners-GPs) or communication skills training;
- diagnostic or point-of-care testing (POCT);
- active monitoring, watchful waiting or delayed prescribing;
- clinical decision support systems (CDSS);
- audit and feedback (A&F, including peer comparisons), and

- other behavioural sciences driven interventions which include financial incentives, accountable justification and public commitment posters.

2.3.2.1 Education

Educational interventions included in the review were either clinician related or patient related, with regard to antimicrobial guidelines, communication or behavioural skills. Of the 75 studies included in the review, 55 had educational interventions either alone or as part of a multifaceted intervention. Eight studies employed educational intervention as the sole AMS intervention. Four out of the eight single faceted educational studies focussed on patients or their carers, whereas the other four focussed on prescribers' education or training. Table 1.1 summarises the single component studies which have an educational component.

2.3.2.1.1 Patient education

Francis *et al* [156] used an interactive booklet for children with acute cough during clinical consultations. In the intervention group, GPs were trained to use this booklet during the consultation to provide patient education; after the consultation this was given to patients as a take home resource. GPs in the control group conducted their consultations as usual. The intervention halved the prescribing of antibiotics for acute cough (19.5% vs 40.8% $p<0.001$). Likewise, Dekker *et al* [157] studied the impact of an educational booklet used during the consultation by GPs. It was complemented with web-based training of GPs, to educate parents of children presenting with fever. This study also led to a reduction in antibiotic dispensing (32 courses/1000 children lower than the control group adjusted for baseline prescribing, rate ratio 0.78, 95% CI 0.66-0.92). The study by Lee *et al* [158] investigated the benefits of the GPs imparting awareness through patient information pamphlets, in order to provide knowledge to adult patients with upper RTIs. No significant reduction in antibiotic prescribing (20.6% active vs 17.7% control $p=0.313$) was reported. The study by De Bont *et al* [159] also used an information booklet to educate parents of children with fever, regarding the rational antibiotic use. However, the study resulted in an insignificant reduction in antibiotic prescribing. A closer look at the study revealed that uptake of the booklet was low and, in cases in which the booklet was used, antibiotic prescribing rates were significantly reduced, (that is, 21.9% active vs 25.2% control, odds ratio=0.83, 95% CI 0.74-0.94, intra cluster correlation coefficient=0.002).

2.3.2.1.2 Prescriber related education

Prescriber related educational interventions in the form of promoting guideline adherence and communication skills training were reported in two studies. The study conducted by Butler *et al* [160] comprised five online training seminars related to guidelines and communication skills. This educational program, titled "Stemming the Tide of Antibiotic Resistance (STAR), reported a positive effect in the form of a 4.2% (p=0.02) decrease in total antibiotic dispensing for the year relative to the control group. Magin *et al* [161] investigated the effect of GP training in upper respiratory tract infections (URTIs), acute bronchitis and bronchiolitis. The intervention was influenced by a large-scale European trial called INternet Training for Reducing AntibiOtic use-INTRO [162] which was adapted for the Australian context and applied to GP registrars/trainees. Intervention was in the form of face-to-face education sessions, complemented with online modules covering antibiotic guideline adherence and communications skills. The intervention led to significant reduction in antibiotic prescribing for bronchitis and bronchiolitis, when the adjusted absolute reduction in antibiotic prescribing was 15.8%, 95% CI: 4.2%-27.5%, p=0.040. Except for bronchitis and bronchiolitis, the study reported no significant change in antibiotic prescribing in any other URTIs; this may be due to baseline levels of antibiotic prescribing for URTIs already being modest in the pre-intervention period.

Two studies evaluated educating GPs using presentations, posters, e-mail reminders, handouts and peer education in 'out of hours' settings [163, 164]. Willems *et al* [163] employed key messages through e-mails, presentations and posters for the GPs in the facility, from the national urinary tract infection (UTI) guidelines for the treatment of cystitis in females. The relative proportion of appropriate antibiotic prescriptions increased two-fold during the intervention time (26.9%-69.4%) in the intervention group but decreased afterwards (40.8%), while in the control group it remained unchanged (that is, it remained between 35 to 40%) before and after the intervention time. Levels of significance (p values) were not mentioned in the study. While Dyrkorn *et al* [164] employed specially trained GPs who taught the topic of the use of antibiotics in acute respiratory infections, (ARI) according to the national guidelines, in a peer education program. The study led to a significant decrease (8.8% $p<0.05$) in the use of macrolides and lincosamides. There was also a statistically significant rise in the use of penicillin V (from 2.3% to17.4% $p<0.05$). However, there was no significant change in total antibiotic prescribing. The authors attributed the decreased use of macrolides and the corresponding high use of penicillin V as important and desirable for reducing the development of macrolide resistance in the Nordic region where the study was conducted.

Table 1.1 Single component studies - Education

Author **Year** **Country** **Study design**	**Settings** **Study arms** **Number of sites**	**Indication** **Age group**	**Intervention**	**Outcome measures**	**Findings**
Francis *et al* 2009 UK [156] CRCT	General practices 61 in active and 22 in control Multiple sites	RTI Children	Education (provider and patient)	Decrease in antibiotic prescribing and re-consultation	**Successful** Decrease in antibiotic prescribing in the active group vs control. (19.5% vs 40.8% p<0.001); no significant difference in re-consultation
Dekker *et al* 2018 USA [157] CRCT	General practices 15 in active and 17 in control Multiple sites	Fever Children	Education (provider and patient)	Decrease in antibiotic dispensing	**Successful** In the intervention group antibiotic dispensing was 32 courses/1000 children lower than the control group.
Lee *et al* 2017 Singapore [158] RCT	General practices 35 GPs from 24 clinics	RTI	Education (patient)	Decrease in antibiotic dispensing	**Unsuccessful** No significant decrease in antibiotic dispensing (20.6% active vs 17.7% control p=0.313)
De Bont *et al* 2018 The Netherlands [159] CRCT	Out of hours general practices 10 each in active and control Multiple sites	Fever Children	Education (patient)	Decrease in antibiotic prescribing	**Unsuccessful** Insufficient evidence of reduction in antibiotic prescription rate due to intervention; Use of booklet was low. (21.9% active vs 25.2% control, odds ratio=0.83, 95% CI 0.74-0.94, intra cluster correlation coefficient=0.002).
Butler *et al* 2012 UK [160] RCT	General practices 34 each in active and control Multiple sites	General infections All ages	Education (provider)	Decrease in antibiotic dispensing	**Successful** 4.2% reduction in antibiotic dispensing in the active group vs control (p=0.02)
Magin *et al* 2018 Australia [161] NRCT	General practices 217 GP registrars (trainees) in active group and 311 in control group through GP regional training providers	RTI and acute bronchitis/bronchiolitis	Education (provider)	Decrease in antibiotic prescribing and consultations	**Partially successful** Significant reduction in antibiotic prescribing for bronchitis and bronchiolitis; (The adjusted absolute reduction in antibiotic prescribing was 15.8%, 95% CI: 4.2%-27.5%, p=0.040); no significant

					change in antibiotic prescribing in URTIs
Willems *et al* 2012 Belgium [163] QES	GPs in large scale out-of-hours services 2 regional out-of-hours services (1 active and 1 control) Multiple sites	Lower UTI in females (age 20-80 years)	Education (provider guidelines)	Change in antibiotic prescribing	**Successful** The relative proportion of appropriate antibiotic prescriptions in the active group increased two-fold during the intervention time. (26.9%-69.4%)
Dyrkorn *et al* 2016 Norway [164] RCT	Out of hours services 22 GPs in the active and 31 in the control Single site	RTI Adults	Education (provider)	Decrease in the use of macrolides and lincosamides and total antibiotic prescribing	**Successful** Decrease in the use of macrolides and lincosamides, 8.8% ($p<0.05$) for all diagnoses in the active group; statistically significant rise in the use of penicillin V after the intervention in the active group; no significant change in total antibiotic prescribing in the two groups

2.3.2.2 Point of care or other diagnostic testing

Rapid diagnostic tests can be performed in the clinical setting to assist with the diagnosis of acute RTIs. These point of care tests (POCT) may reduce unnecessary use of antibiotics by GPs. Two types of POCT are generally available to support clinical decision making in infections: 1) tests measuring the level of non-specific inflammatory markers in the blood (for example, C-reactive protein) and 2) tests assessing the presence of a pathogen (for example, Rapid Streptococcal Antigen Detection test). There were three studies in this review which used this method and all were successful. Table 1.2 summarises the single intervention studies describing POCT intervention.

2.3.2.2.1 C-reactive protein tests

C-reactive protein (CRP) is an acute phase protein that shows increased levels in serum during infection and tissue damage. The study by Andreeva *et al* [165] found that antibiotic prescribing rates in adult patients with acute cough/RTI were significantly lower in the group in which CRP testing was conducted, compared with controls (37.6% vs 58.9%, p=0.006). Butler *et al* [166] evaluated the impact of CRP testing amongst general practice patients with acute exacerbations of chronic obstructive pulmonary disease (COPD). Fewer patients in the CRP-guided group reported antibiotic use than in the control group (57.0% vs 77.4%; adjusted odds ratio, 0.31; 95% CI 0.20-0.47).

2.3.2.2.2 Rapid antigen detection tests

Rapid antigen detection test (RADT) to identify group A beta haemolytic streptococcus in acute pharyngitis is another type of POCT. Llor *et al* [167] examined the effects of RADT on the utilisation of antibiotics and the appropriateness of their use in acute pharyngitis in adults. The study found that the GPs in the active group who performed tests were less likely to prescribe antibiotics, compared with those in the control or usual care group with no access to testing (43.8% vs 64.1, p<0.001). Hence the POCT intervention was effective in significantly decreasing the number of antibiotic prescriptions.

2.3.2.2.3 Other rapid diagnostic tests

Multiplex polymerase chain reaction (PCR) assays to test patients with RTIs using nasopharyngeal and throat swabs are an improved and rapid method of diagnostic testing as they have a short turn-around time at the laboratory. Brittain-Long *et al* [168] studied the effectiveness of multiplex real-time PCR testing targeting 13 viruses and two bacteria in ARI adult patients. In the intervention group, diagnostic results were received on the following day and fewer patients received antibiotics at the initial visit, compared with the patients in the delayed result group who received results in eight to twelve days (4.5% vs 12.3%, p=0.005). However, at follow-up, there was no significant difference between the two groups in the percentage of patients who received antibiotics (13.9% vs 17.2%, p=0.359).

Table 1.2 Single intervention studies-Point of care or other diagnostic testing

Author **Year** **Country** **Study design**	**Settings** **Study arms** **Number of sites**	**Indication** **Age group**	**Intervention**	**Outcome measures**	**Findings**
Andreeva *et al* 2014 Russian Federation [165] CRCT	General practices 18 each in active and control Multiple sites	Acute cough/RTI Adults	POCT C-reactive protein testing	Decrease in antibiotic prescribing	**Successful** 37.6% lower in the intervention group than in the control group 58.9% (P = 0.006)
Butler *et al* 2019 UK [166] RCT	General practices 86 practices 325 patients in active and 324 in control	Acute exacerbation of chronic obstructive pulmonary disease (COPD)	POCT C-reactive protein testing	Patient reported antibiotic use	**Successful** Lower rate of patients reported antibiotic use (57.0% vs. 77.4%) in active group
Llor *et al* 2011 Spain [167] CRCT	General practices 10 each in active and control Multiple sites	RTI Adults	POCT Rapid antigen detection testing	Decrease in antibiotic prescribing	**Successful** Decrease in antibiotic prescribing rate in the active group vs control (43.8% vs 64.1% p<0.0001)
Brittain-Long *et al* 2011 Sweden [168] RCT	Outpatient units 12 outpatient units, 406 patients (202 in the rapid result group and 204 in the control group) Multiple sites	RTI Adults	POCT Access to multiplex PCR assay panel; rapid results in active or delayed result in control group	Decrease in antibiotic prescribing	**Successful** Fewer patients received antibiotics at the initial visit, compared with the patients in the delayed result group who received results in eight to twelve days (4.5% vs 12.3%, p=0.005). However, at follow-up, there was no significant difference between the two groups (13.9 vs 17.2%, p=0.359).

2.3.2.3 Clinical decision support

A number of clinical decision support tools (also known as clinical decision support systems-CDSS) have been developed and incorporated into clinical practice to assist prescribers. These tools are either documentation/paper-based or incorporated into electronic prescribing systems, via electronic health records (EHR). Most of these interventions have been developed for the management of RTI with variable effectiveness. Six studies included in our review involved CDSS interventions. Table 1.3 summarises single faceted studies with a CDSS approach.

Linder *et al* [169] conducted a study in which a print based CDSS tool was provided to assist clinicians in prescribing only the recommended antibiotics to the RTI patients. The intervention was not widely used and hence, the study led to neither a reduction of overall antibiotic prescribing, nor a significant improvement in antibiotic prescribing. The main reason for the CDSS not being widely used was its poor uptake; the authors attributed it to adding complexity to the existing workflow of the prescribers. The print-based form was only associated with a lower antibiotic prescribing rate for acute bronchitis (OR, 0.5; 95% CI, 0.3-0.8). Bourgeois *et al* [170] incorporated an interactive template within EHR in paediatric practices. This CDSS intervention was also not widely used and was not associated with a change in antibiotic prescribing rates. The authors concluded that the reason the intervention was not widely used could have been obstruction in the workflow demands and prescribers' CDSS needs. However, when the intervention was used, it was associated with significantly reduced antibiotic prescribing (31.7% vs 39.9%, $p=0.02$), particularly in the use of macrolides (6.2% vs 9.5%, $p=0.02$).

Rattinger *et al* [171] targeted inappropriate antibiotic prescriptions, that is those which were not congruent with the acute RTI guidelines for azithromycin and gatifloxacin. It was a four-year study in which the CDSS intervention was in the form of displayed treatment guidelines at the time of prescribing. The proportion of inappropriate prescriptions of the targeted antibiotics decreased due to the intervention (22% to 3%, $p<0.0001$) for a four-year period.

In another study, McGinn *et al* [172] assessed the influence of clinical prediction rules (CPRs) in EHR as an evidence-based form to facilitate GPs' decision making. The CPR tool appeared on the GPs' screens during clinical encounters with patients having complaints related to pharyngitis or pneumonia. GPs were then invited to complete a CPR risk score calculator and were given management recommendations based on the score. The GPs in the intervention group were significantly less likely to prescribe antibiotics than the control group (age-adjusted relative risk, 0.74; 95% CI 0.60-0.92). The intervention group was significantly less likely to order rapid streptococcal tests (relative risk, 0.75; 95% CI, 0.58-0.97; p=0.03) and had good overall adaption rate (62.8%) compared with the control group.

Gulliford *et al* [173] also examined the impact of an intervention delivered electronically by a CDSS for RTI patients. The CDSS prompt directed the GPs in the intervention group to decide between no antibiotic or delayed antibiotic prescription. The intervention was associated with a 1.85% (p=0.038) reduction in the proportion of consultations in which antibiotics were prescribed and a 9.69% reduction in the rate of antibiotic prescribing for RTIs (p=0.034).

Jenkins *et al* [26] developed and adapted clinical pathways, in the form of a one-page decision support algorithm, to assist GPs in determining whether an antibiotic should be prescribed, the optimal antibiotic when one was indicated and the shortest, most appropriate duration of therapy. One GP from each of the four intervention practices was selected to educate and advocate to the other GPs of the clinic regarding the pathways. The intervention led to a significant decline in antibiotic prescribing for non-pneumonia acute RTIs (42.7% to 37.9%,11.2% relative reduction, p<0.0001 vs 39.8% to 38.7%, 2.8% relative reduction in the control, p=0.25). In addition, the overall use of broad-spectrum antibiotics in the study group decreased (26.4% to 22.6%, 14.4% relative reduction, p<0.0001 and from 20.0% to 19.4%, respectively, in the control group, 3.0% relative reduction, p=0.35).

Table 1.3 Single intervention studies - Clinical decision support

Author Year Country Study design	Settings Study arms Number of sites	Indication Age group	Intervention	Outcome measures	Findings
Linder *et al* 2009 USA [169] CRCT	General practices 14 in active and 13 in control Multiple sites	RTI All ages	**CDSS within EHR** An EHR based feedback system for GPs related to antibiotic prescribing	Decrease in antibiotic prescribing.	**Unsuccessful** No decrease in antibiotic prescribing rate in the active group vs control. (47% vs 47% p=0.87)
Bourgeois *et al* 2010 USA [170] RCT	Ambulatory paediatric practices 7 in active and 7 in control Multiple sites	RTI Children	**CDSS within EHR** Interactive template within EHR as clinical management decision aid and documentation aid for GPs	Decrease in antibiotic prescribing	**Unsuccessful** Decrease in antibiotic prescribing (31.7 vs 39.9 p=0.02) but the low use of intervention lead to ineffective intervention
Rattinger *et al* 2012 USA [171] QES	General practices 1 each in active and control Multiple sites	RTI Adults	**CDSS within EHR** A CDSS for fluoroquinolones and azithromycin	Decrease in antibiotic prescribing	**Successful** Decrease in antibiotic prescribing, in the active group 9.5% (p<0.0001) relative to the control group
McGinn *et al* 2013 USA [172] RCT	GP practices 2 practices (1 active 1 control; 168 GPs-586 patients were seen by the active group and 398 patients were seen by the control group). Multiple sites	Pharyngitis and pneumonia in all age groups	**CDSS within EHR** Clinical prediction rules tool in EHR The active group had access to the tool and the choice to complete risk score calculators, order medication and generate progress notes at the point of care. The control group received only journal articles related to the indication.	Decrease in in antibiotic prescribing	**Successful** Decreased antibiotic prescribing in active group than in control group (Relative Risk=RR, 0.74 p=0.008)
Gulliford *et al* 2014 UK [173] CRCT	General practices 53 in the active and 51 in the control Multiple sites	RTI All ages	**CDSS within EHR** EHR based prescribing support tool to the GPs in the active group	Decrease in antibiotic prescribing per 1000 patient years	**Successful** The rate of antibiotic prescribing per 1000 patient years declined from 116 to 108 per 1,000 in the active group (p=0.034) vs the control group.

Jenkins *et al* 2013 USA [174] RCT	General practices 4 each in active and control Multiple sites	RTI, AOM UTI, SSTI and pneumonia All ages	**Education (provider and patient-clinical pathways)** Clinical pathways, patient education and peer leader advocacy	Decrease in antibiotic prescribing	**Successful** Decreased antibiotic prescribing in active group; 11.2% ($p<0.0001$) vs 2.8% in the control ($p=0.25$)

2.3.2.4 Audit and feedback

Audit and feedback interventions consist of providing data to prescribers regarding their prescribing habits, with comparisons with expected norms (for example, guidelines) or with other prescribers in the same practice area. The strategy of reviewing GPs' prescribing patterns and providing feedback to them has been shown to reduce unnecessary prescribing by changing clinical practice behaviours [175]. Table 1.4 summarises the single- faceted studies related to audit and feedback interventions.

Elouafkaoui *et al* [176] studied the impact of individualised graphical data of antibiotic prescribing in dental care practices across Scotland. As defined in the study, the prescribing volume was the number of antibiotics prescribed and dispensed in a community pharmacy each month. This intervention led to a decrease of 0.4 antibiotic items per 100 treatments, dispensed over a 12 months post intervention period in control practices, and by 1.0 in intervention practices representing a significant reduction (-5.7%, p=0.01) in the intervention group.

Similarly, Hemkens *et al* [177] conducted a study to improve antibiotic prescribing amongst the highest antibiotic prescribing group of physicians through quarterly updated antibiotic prescription feedback, both via mail and online for two years. Prescribers in the intervention group prescribed the same amount of antibiotics to all patients in the first year (p=0.64) and in the second year (p=0.32), compared with the control group. However, antibiotic prescribing in children aged six to 18 years was 8.61% lower in the intervention than in the control group in the first year (p=0.01). This difference diminished in the second year (p=0.25). Moreover, the study reported that the GPs receiving feedback prescribed fewer antibiotics to adults aged 19 to 65 years in the second year (p<0.01).

Table 1.4 Single intervention studies-Audit and feedback

Author **Year** **Country** **Study design**	**Settings** **Study arms** **Number of sites**	**Indication** **Age group**	**Intervention**	**Outcome measures**	**Findings**
Elouafkaoui *et al* 2016 Scotland [176] CRCT	General dental practices 632 in active and 163 in control	Dental infections All ages	Audit and feedback	Decrease in antibiotic prescribing	**Successful** Relative decrease-5.7% (p=0.01) in antibiotic prescribing in the intervention group
Hemkens *et al* 2017 Switzerland [177] RCT	General practices 2900 (1450 each in active group and in control group)	General infections	Audit and feedback	Prescribed defined daily doses (DDD) of any antibiotic	**Unsuccessful** Physicians receiving feedback prescribed the same amount of antibiotics to all patients as did the physicians who did not receive feedback.

2.3.2.5 Delayed prescribing/dispensing

Delayed prescribing or delayed dispensing (also known as watchful waiting) is another AMS strategy that involves delaying commencement of the antibiotic and only commencing it if symptoms persist or deteriorate. This strategy has been advocated as a means of demonstrating to patients that antibiotics are not always necessary [178]. One way of using this strategy involves prescribers giving the patient an antibiotic prescription at the time of the consult but with instructions not to have it dispensed (or with a request to the pharmacist not to dispense) before a certain date or unless symptoms deteriorate. Another way involves the prescription being held by the clinic, only to be picked up and dispensed in the event of deterioration. Table 1.5 summarises the single faceted studies related to delayed prescribing/dispensing.

Worrall *et al* [179] compared two delayed prescribing strategies; in the control arm, the post-dated antibiotic prescription was given to the patient on the consultation day, while in the intervention arm, it was given to the patient after two days. No significant reduction in antibiotic prescribing rate was found in the intervention group for whom 43.2% of the antibiotic prescriptions were filled while 44.0% of the post-dated antibiotic prescriptions were filled in the control group. In both groups, prescriptions were filled earlier than the recommended 48 hours by 21% of the patients. The rates of antibiotic use between the two groups and t tests to compare the mean time to fill the prescription between the two groups indicated that these results were not significant in terms of antibiotic use ($p > 0.05$).

De la Poza Abad *et al* [180] examined four antibiotic prescription strategies to investigate the impact of delayed prescribing. Group One was patient-led delayed prescription, that is, trusting the patient not to fill the antibiotic prescription. Group Two received a post-dated prescription to be collected at a later date. Group Three obtained immediate antibiotic prescribing and Group Four was given no antibiotic. 91% of the patients who were in Group Three (that is, the immediate prescribing group) used antibiotics, while 33% of the patients in Group One (that is, the delayed antibiotic group) used antibiotics, 23% of the patients in Group Two (to be collected at a later date if required) used antibiotics and 12% of the patients who were not prescribed any antibiotics, that is, Group Four ($p<0.001$).

Table 1.5 Single intervention studies-Delayed prescribing/dispensing

Author Year Country Study design	Settings Study arms Number of sites	Indication Age group	Intervention	Outcome measures	Findings
Worrall *et al* 2010 Canada [179] CRCT	General practice 4 in active and 4 in control Multiple sites	RTI Adults	**Delayed prescribing** Post-dated prescription for patients after 2 days in active group and delayed prescriptions dated the same day for controls	Decrease in antibiotic prescribing	**Unsuccessful** No decrease in active group vs control (43.2% vs 33% p>0.05).
De La Poza Abad *et al* 2016 Spain [180] RCT	General practices 398 patients randomised to 4 groups in 23 primary care centres in 4 regions Multiple sites	RTI Adults	**Delayed prescribing** 4 prescription strategies: delayed patient led prescription strategy, delayed prescription collection strategy, immediate prescription strategy and no prescription strategy	Decrease in antibiotic prescribing, duration and severity of symptoms, patient satisfaction and patients' beliefs	**Successful** Decreased antibiotic use in delayed prescribing and no prescribing strategies; decrease in patient belief in antibiotic effectiveness compared with the immediate prescription group. Duration of severe symptoms remained similar in the immediate and in two delayed prescription strategies.

2.3.2.6 Financial incentives

The impact of financial incentives through a policy change has been found to significantly decrease antibiotic use [181]. An incentive program to reward clinical commissioning groups in the United Kingdom was initiated by the National Health Service (NHS) to reduce antibiotic prescribing for RTIs amongst GPs [182]. In a subsequent study, Bou-Antoun [183] undertook a time series analysis of patient consultation and prescribing data to study the impact of this financial incentive. The study reported decreased antibiotic prescribing rates over a period of six years of 3% ($p<0.05$). A concurrent 2% relative reduction in the rate of broad-spectrum antibiotic prescribing was also reported. Table 1.6 Single intervention studies comprising of persuasive strategies, summarises the single intervention study related to financial incentives.

Table 1.6 Single intervention studies-Financial incentive

Author **Year** **Country** **Study design**	**Settings** **Study arms** **Number of sites**	**Indication** **Age group**	**Intervention**	**Outcome measures**	**Findings**
Bou-Anton *et al* 2018 UK [183] ITS	Clinical commissioning groups (responsible for the planning and commission of health care services in their region) 431 GP practices 2 million patients	RTI in all age groups	**National financial incentive** (the Quality Premium)	Decrease in antibiotic prescribing	**Successful** A sustained reduction of 3% coincided with the introduction of the Quality Premium. There was a concurrent 2% relative reduction in rate of broad-spectrum antibiotic prescribing.

2.3.2.7 Persuasive strategies

This review included three studies in which persuasive strategies were directed to change patients' behaviour, or their perception that antibiotics can treat viral infections [184-186]. Table 1.7 summarises the single intervention studies related to persuasive studies.

In a study by Meeker *et al* [184], commitment posters (CP) emphasising physicians' commitment to guidelines for RTI management were displayed in the examination rooms of five clinics. The intervention led to a 19.7% absolute reduction in inappropriate antibiotic prescribing, relative to control ($p=0.02$).

The impact of CPs was also evaluated by Sallis *et al* [185] who conducted a three-armed study in upper RTIs. One intervention arm involved advocating safe antibiotic prescribing (CP group); the second intervention arm had an automated message (AM group) regarding AMS on telephone appointment booking lines, along with the poster (CP&AM group), while the fourth arm was a control group who received usual care. The poster in this study was inspired by that tested by Meeker *et al* [184] and the Antibiotic Guardian poster from the English Primary Care antimicrobial stewardship campaign [187]. The primary outcome measure was the number of antibiotic items dispensed per 100 patients with RTIs. Data were extracted from the national database which cover prescriptions written in England and dispensed in the UK. In the primary analysis, there was no effect on the overall dispensing rates for either intervention compared with usual care per 100 patients (CP 5.673, $p=0.458$; CP&AM −12.575, $p=0.167$). In the secondary analysis, when the effects of the AM were separated from the CP in a single model, a significant reduction in the number of antibiotic items dispensed per 100 patients with RTI in the AM group was reported (−18.444, $p=0.01$). Fewer penicillins and macrolides were dispensed, which was consistent with the local guidelines, per 100 patients with RTI in the CP&AM group, compared with the control arm (−12.996, $p=0.018$). This study did not lead to significant antibiotic reduction (19.7%) as noted in the study of Meeker discussed earlier [184]. The authors reported the results to be as expected, as their aim was to reduce overall antibiotic prescribing and not inappropriate prescribing [184].

The third study was based on two behavioural theory-based interventions and was conducted by Milos *et al* [186]. The questionnaires, based on graded task interventions and persuasive communication, were sent to GPs by mail. In the graded task intervention group, the GPs received questionnaires addressing GPs' beliefs in their capability to manage URTIs without antibiotics. The study failed to report any significant reduction in antibiotic prescribing for patients of all ages. However, a significantly lower prescription rate was reported in the persuasive communication group (p=0.037) for patients 0–6 years of age.

Table 1.7 Single intervention studies-Persuasive strategies

Author **Year** **Country** **Study design**	**Settings** **Study arms** **Number of sites**	**Indication** **Age group**	**Intervention**	**Outcome measures**	**Findings**
Meeker *et al* 2014 USA [184] RCT Single	General practices 7 each in active (449 patients) and control (505 patients) Multiple sites	RTI Adults	Behavioural nudge	Decrease in inappropriate antibiotic prescribing	**Successful** Decrease in inappropriate antibiotic prescribing. 19.7% reduction in the active group relative to control (p=0.02)
Sallis *et al* 2020 UK[185] CRCT	General practices 42 Clinical Commissioning Groups Multiple sites	RTI in all age groups	Commitment poster (CP)	Antibiotic item dispensing rates per 1000 population	**Unsuccessful** There was no effect on the overall dispensing rates for either interventions compared with usual care (CP 5.673, 95%CI −9.768 to 21.113, p = 0.458; CP&AM, −12.575, 95%CI −30.726 to 5.576, p = 0.167). Secondary analysis, which included pooling the data into one model, showed a significant effect of the AM (−18.444, 95%CI −32.596 to −4.292, p = 0.012). Fewer penicillins and macrolides were prescribed in the CP&AM intervention group, compared with usual care (−12.996, 95% CI −34.585 to −4.913, p = 0.018).
Milos *et al* 2013 Sweden [186] RCT	Primary health care centres (PHCC) 19 PHCCs (7 in control 7 in active 1 5 in active 2) Multiple sites	URTI in all age groups	Persuasive communication theory and graded task activities	Decrease in antibiotic prescribing	**Unsuccessful** No decrease in antibiotic prescribing in active groups as compared with the control

2.3.3 Complex intervention studies with multiple components

Thirty-six studies employed two or more components as a complex intervention. Most studies describing complex interventions were difficult to categorise under a particular sub-heading, due to the plurality of the intervention components. As such, the discussion below will present the most dominant components, while mentioning other supplementary components which form a particular complex intervention.

2.3.3.1 Training and education promoting guideline adherence, along with audit and feedback as the most dominant components

There were twelve studies which investigated the effect of providing training, learning or educational activities to promote guideline adherence along with audit and feedback, in order to optimise either overall antibiotic prescribing or a desired class of antibiotic. Table 2.1 summarises the details of the studies having the elements of education along with audit and feedback.

Regev-Yochay *et al* [188] studied the impact of an educational program comprising focus groups, workshops and seminars for primary care paediatricians, supplemented by audit and feedback reports. The researchers took an engaging approach by firstly developing the local guidelines and then educating a group of prescribers and patients. A range of activities, such as learning the local antibiotic guidelines, a campaign targeting parents and children using posters, pamphlets and colouring booklets, diagnostic skills and parent-physician communication skills training, was employed. The study resulted in a significant reduction in antibiotic prescribing rates in the intervention group when compared with the control group (40% vs 22%, RR, 0.89; 95% CI, 0.81–0.98) and this was sustained for four years after the intervention. The study also reported 50% less macrolide antibiotic prescribing when compared with the control group ($p<0.001$). In addition to the aim to reduce unnecessary antibiotic use, this study also focussed on reducing treatments with antibiotic classes that particularly promote antimicrobial resistance, including macrolides.

Similarly, Fernandez-Urrusuno *et al* [189] carried out a multi-faceted intervention to improve adherence to a regional antibiotic guide developed by a multi-disciplinary team. The interventional activities were prescriber education through workshops, conferences and meetings, and supported by financial incentives, audit and feedback reports. The study reported a significant improvement in the percentage of appropriate antibiotic prescribing, from 36% in the pre-intervention period to 57% in the post-intervention period ($p<0.001$).

Vellinga *et al* [130] also conducted a study to improve the quality of antibiotic prescribing by reinforcing guideline adherence. The researchers firstly conducted a workshop to discuss antibiotic prescribing guidelines and to practice audit reports; then the intervention group was divided into two interventions arms. The first intervention arm was given electronic reminders to prescribe first line treatment, whereas the second arm received electronic reminders suggesting delayed prescribing. The proportion of guideline-concordant antibiotic prescribing increased in both intervention arms, relative to the control (adjusted overall odds ratio 2.3, 95% CI, 1.7 to 3.2; arm A adjusted OR 2.7, 95% CI 1.8 to 4.1; arm B adjusted OR 2.0, 95% CI 1.3 to 3.0), and this was sustained for five months.

Cummings *et al* [190] conducted a provider and patient focussed campaign to optimise antibiotic use. Prescribers were engaged in learning activities through presentations, e-mail reminders and web pages related to guideline concordant prescribing and peer comparison of antibiotic prescribing data. Patient education material was distributed during an antibiotic awareness week, along with public awareness, media advisory broadcasts. Public commitment letters to increase patient awareness regarding antibiotics were also placed simultaneously in the waiting rooms during the study period. As a result, fewer inappropriate or non-guideline-concordant antibiotic prescriptions were recorded in the intervention period as compared with the pre-intervention period, leading to a decrease in inappropriate antibiotic prescriptions (14.9%, $p=0.014$). Antibiotic inappropriateness was calculated by comparing the baseline percentage with the number of acute RTI encounters during the intervention period.

A study by Papaevangelou *et al* [191] comprised a number of paediatrician and patient focussed strategies to optimise antibiotic prescribing in children. The campaign included workshops for paediatricians on the topic of antibiotic misuse in children, therapeutic algorithms and weekly feedback reports of antibiotic prescribing. The campaign also included public engagement activities, such as lectures for parents by local paediatricians, instructive pamphlets for parents, informative videos in waiting rooms and a 30-minute discussion in a radio broadcast. The intervention significantly decreased antibiotic prescribing in the intervention district, as compared with the control district. The index of consumption/URTI incidence was used to compare antibiotic use between the two arms, which decreased from 0.929 to 0.707 in the intervention district pre- to post-intervention and increased from 1.341 to 1.557 pre- to post-intervention in the control district (p=0.008).

Gerber *et al* [192] studied the impact of a one-hour on-site paediatrician education session related to guideline adherence for antibiotic prescribing in children. This intervention was complemented by the quarterly audit and feedback reports. Afterwards, the intervention broad-spectrum antibiotic prescribing decreased significantly (6.7%; p=0.01) as well as off-guideline prescribing for children with pneumonia (10.7%; p<0.001).

The study of Wilf-Miron *et al* [122] described and evaluated a peer-to-peer technique of educating GPs. The aim was to influence antibiotic prescribing patterns among prescribers with above average prescribing rates. The intervention was implemented through four meetings each, with a gap of two months. In the meetings, the intervention group was engaged with a group leader in learning activities related to audit and feedback of prescription data, antibiotic overuse (including adherence to clinical guidelines and pressure due to consumer demands), followed by a talk from an infectious disease expert on best patient care practices. The study reported a significant but modest decrease (0.17 to 0.12, p<0.001) in antibiotic prescribing rates in the intervention group. The antibiotic prescribing rate was defined as the number of antibiotic prescriptions divided by the total number of consultations.

Shively *et al* [193] studied the effect of targeted educational sessions by an infectious disease physician on ‘antibiotic overuse and treatment guidelines for common infections’ followed by monthly e-mail-based peer comparisons of overall antibiotic prescribing rates for primary care providers of a health care network. The mean rate of monthly antibiotic prescriptions reduced significantly from a baseline of 76.9 to 49.5 per 1000 office visits in the intervention period (35.6%, p<0.001)

Zhen *et al* [194] studied the impact of a regional program comprising regular educational workshops on levels of antibiotic use, supported by regular monitoring through audit and feedback. The study found significant reduction in the monthly antibiotic use after the implementation of the program (6.15% reduction, p=0.089).

Hurlimann *et al* [195] also examined the impact of implementing a detailed local antibiotic prescription guideline, with sustained, regular and individual prescribing feedback. The study aimed to:

- increase the percentage of penicillin prescriptions for RTIs;
- increase the percentage of trimethoprim/sulfamethoxazole prescriptions for all uncomplicated lower UTIs;
- decrease the percentage of quinolone prescriptions for all cases of exacerbated COPDs, and
- decrease the proportion of sinusitis and other upper RTIs, treated with antibiotics.

The study did not lead to any reduction in the overall antibiotic prescribing rate for sinusitis or other RTIs but successfully increased the use of appropriate antibiotics for URTIs and UTIs. There was a significant increase in the percentage of prescriptions for penicillins for all RTIs treated with antibiotics (57% vs 49% p=0.01), paralleled by a decrease in the cephalosporin prescription rate. The percentage of trimethoprim/sulfamethoxazole prescriptions for all uncomplicated lower UTIs treated with antibiotics also increased (35% vs 19%, p=0.01) in the intervention group, paralleled by a decrease in the quinolone prescription rate.

McNulty *et al* [196] investigated the impact of education along with prescribing feedback. The trial was designed in such a way that the research subjects who were the prescribers were blinded from the actual study. The engagement activities included presentations of prescribing data, clinical scenarios, action planning and promotion of patient and GP resources through workshops. The program, titled ‘Treat Antibiotics Responsibly, Guidance, Education, Tools’ (TARGET) an antibiotics toolkit developed by the professional societies of the UK and hosted on their web site, aims to positively change prescribers’ and patients’ attitudes and perceptions, to optimise antibiotic use. The primary outcome measure was the total oral antibiotic items dispensed/1000 patients for the year after the workshop, obtained from the Centre of Infectious Disease Surveillance and Control, Information Management and Technology Department. In the intention to treat analysis, the absolute number and rate of total antibiotics dispensed in the intervention year was not significantly lower than the year before (2.7% lower in intervention practices, p=0.06) compared with controls. However, the study reported that, according to the complier average causal effect analysis, which estimates impact on those prescribers who comply with the assigned interventions, the total antibiotic dispensing rate was significantly lower (6.1%, p=0.04) and the trimethoprim dispensing rate was also significantly lower (11%, p=0.02) in the intervention practices. Furthermore, in the intervention group, the use of both amoxicillin/ampicillin and trimethoprim was significantly lower (-4.4%, p=0.02, -5.6%, p=0.03 respectively), whereas use of nitrofurantoin was not significantly higher (+7.1%, p=0.06). The data on antibiotic use was collected electronically from pharmacies when each antibiotic prescription was dispensed.

Table 2.1 Complex intervention studies with multiple components - Education

Author **Year** **Country** **Study design**	**Settings** **Study arms** **Number of sites**	**Indication** **Age group**	**Intervention**	**Outcome measures**	**Findings**
Regev-Yochay *et al* 2011 Israel [188] CRCT	Primary care paediatric practices 52 paediatricians (26 each in active and control group) Multiple sites	General infections	Education (provider and patient) + audit and feedback	Annual antibiotic prescribing	**Successful** Decrease of 40% vs 22% active vs control
Fernandez-Urrusuno 2020 Spain [189] QES	General practices	General infection	Education (provider) + audit and feedback	Change in the rates of antibiotics use	**Successful** Overall antibiotic rates dropped by 28% in the intervention area and 22% in the control district (p<0.001).
Vellinga *et al* 2016 Ireland [130] CRCT	General practices 30 general practices (10 in each of the three arms)	Urinary tract infections	Education (provider) + audit and feedback	Appropriateness of antibiotic prescribing	**Successful** The proportion of antibiotic prescribing according to guidelines significantly improved in active arms; adjusted overall odds ratio 2.3, 95% CI, 1.7 to 3.2; arm A adjusted OR 2.7, 95% CI 1.8 to 4.1; arm B adjusted OR 2.0, 95% CI 1.3 to 3.0
Cummings *et al* 2020 USA [190] QES	3 urgent care clinics (UCC)	Acute respiratory tract infections	Education (staff/patient) + audit and feedback	Appropriateness of antibiotic prescribing	**Successful** Absolute decrease of 14.9% (p=0.014)
Papaevanglou *et al* 2012 Cyprus [191] RCT	Paediatric practices 33 paediatricians, two districts (one active-17 practices and one served as control-16 practices) Multiple sites	Upper respiratory tract infections	Education (provider and patient) + audit and feedback	Appropriateness of antibiotic prescribing	**Successful** Decreased antibiotic prescribing in the active district vs control (p=0.008)
Gerber *et al* 2013 USA [192] CRCT Multifaceted	Paediatric practices 18 practices (9 each for active and control groups) Multiple sites	Acute respiratory tract infections in children	Education (provider) + audit and feedback	Overall reduction in antibiotic prescribing and broad-spectrum antibiotic prescribing	**Successful** Decrease in broad spectrum antibiotics 6.7% (p=0.01); decrease in offline guideline prescribing in pneumonia 10.7% (p<0.001)

Wilf-Miron *et al* 2012 Israel [122] RCT Multifaceted	General practices 11 in active 72 in control Multiple sites	All infections	Education (provider) + audit and feedback	Overall reduction in antibiotic prescribing	**Successful** 0.17 to 0.12 (p<0.001)
Shively *et al* 2019 USA [193] Pre post analysis Regression model	General practices 7 in total Multiple sites	All infections	Education (provider) +audit and feedback	Per month reduction in antibiotic	**Successful** 35.6% (p<0.001)
Zhen *et al* 2018 China [194] Interrupted time series Pre-experimental study design	Rural clinics Non-randomised study No controls Multiple sites	All infections	Education (provider) +audit and feedback	Per month reduction in antibiotic prescribing	**Successful** 6.15% (p=0.089)
Hurlimann *et al* 2015 Switzerland[195] CRCT	Primary care physicians 140 general practices (70 each in active and control groups) Multiple sites	Upper RTI and UTI in adults	Educational (provider) + audit and feedback	Decrease in the percentage of penicillin in RTI antibiotics, percentage of trimethoprim/sulfamethoxazole for UTIs, percentage of quinolones for all cases of eCOPD and antibiotics in URTI	**Unsuccessful** There was no decrease of antibiotics and quinolones in control and active groups, in URTI and eCOPD. Penicillins increased in URTI (OR 1.42 p=0.01) and sulphamethoxazole for UTI (OR 2.16 p=0.01) in the active group.
McNulty *et al* 2018 UK RCT	General practices 73 GPs in active and 59 in control	General infections	Education (provider) +audit and feedback	Antibiotic dispensing	**Successful** 2.7% lower in intervention practices (p=0.06) compared with control

2.3.3.2 Academic detailing with audit and feedback as the most dominant components

Seven studies in this section examined the effects of academic detailing along with audit and feedback (A&F). Academic detailing in the included studies attempted to influence antibiotic prescribing with an academic/clinical educator detailing a physician or GP to discuss the choice of antibiotics, encouraging use of a particular protocol or guideline. One of the studies [153] in this section also presented a cost analysis of the interventions, because academic detailing is regarded as being costly as compared with other educational strategies. Table 2.2 summarises the details of the studies having the elements of academic detailing, along with audit and feedback.

Vinnard *et al* [123] reported two studies to improve GPs high antibiotic prescribing rates. In one study, prescribers were given academic detailing by a pharmacist and an opinion leader regarding current evidence on optimal antibiotic use. In this study, patient information material developed by Centers for Disease Control and Prevention [197] in the form of a prescription pad, was also provided to the prescribers to be given to the patients. In the second study, prescriber approved patient education material was mailed directly to the patients. There was significant reduction in antibiotic prescribing in the academic detailing study (43% to 33%, adjusted ROR 2.80 95% CI, 1.32–5.95), while there was no change in the mailing intervention study.

Naughton *et al* [153] also compared the effects of academic detailing with postal prescribing feedback, and postal prescribing feedback only. Both interventions significantly decreased overall antibiotic prescribing which was presented as regression coefficients, defined as proportion change in prescribing per month and 95% confidence intervals (CIs). Regression coefficient β=-0.02, 95% CI -0.04, -0.001 in postal prescribing feedback and β=-0.02, 95% CI -0.03, -0.001 in academic detailing group were reported immediately after the intervention. Second-line antibiotic prescribing also decreased significantly, 2–3% in both groups. However, there were no significant differences in antibiotic prescribing between the randomised groups in the immediate or long-term, post-intervention period. Although prescribing feedback significantly reduced overall and second-line antibiotic prescribing, academic detailing was not significantly more effective than postal bulletin in changing antibiotic prescribing practice. This study also undertook a cost-effectiveness analysis of the interventions. According to the study results, a postal prescribing feedback service would cost €88 per percentage change in prescribing practice, compared with €778 for a prescriber adviser service, indicating that an efficient postal prescribing feedback service would be more cost-effective.

Based on baseline prescribing habits of the GPs, Neels *et al* [198] rolled out an AMS intervention in a large clinic. The intervention comprised academic detailing sessions, along with A&F reports. The academic detailing was related to AMS, AMR, guidelines, microbiological testing and antibiotic prescribing, according to the Australian Therapeutic Guidelines-Antibiotic [199]. The implementation of the intervention led to significant improvements compared with pre-intervention in appropriate antimicrobial selection (73.9% vs 92.8%, RR = 1.26; 95% CI = 1.18–1.34), appropriate duration (53.1% vs 87.7% , RR = 1.65; 95% CI = 1.49–1.83) and compliance with guidelines (42.2% vs 58.5%, RR = 1.39, 95% CI = 1.19–1.61)

Penalva *et al* [200] studied the effects of another multimodal intervention in which five interviews, based on the appropriateness of prescribers' most recent antibiotic prescriptions, were conducted with each GP by a GP academic detailer. The aim of the study was to reduce the incidence of infections caused by extended-spectrum β-lactamase-producing *Escherichia coli* in the community by optimising antibiotic use. Inappropriate antibiotic prescribing, that is, non- compliance with the reference guidelines, was identified in 36·5% versus 26·9% of educational interviews pre- versus post-intervention (p<0·0001). The intervention was also associated with a sustained reduction in the use of ciprofloxacin (−15·9%, 95% CI −23·9% to −8·0%) and cephalosporins (−22·6%, 95% CI from −35·9% to −9·2%) and sustained increase in the use of amoxicillin (22·2%, from 6·4% to 38·0%) and fosfomycin trometamol (6·1%, 2·6% to 9·6%).

The Gjelstad *et al* [201] study comprised two visits from a peer-led academic detailer, presenting national clinical guideline for antibiotic use in ARI, along with discussing individual antibiotic prescribing patterns with the GPs. Non-penicillin V prescribing per 1000 patients decreased from 47.5 to 41.4 in the active group and increased from 47.6 to 54.4 in the control group. In an adjusted, multi-level model, the effect of the intervention was a reduction in antibiotics compared with the controls (OR 0.72, 95% CI: 0.61-0.84).

Smeets *et al* [202] conducted a study which involved re-implementation of an already proven effective multiple intervention study [203] but tested on a larger scale. Number of components, including academic detailing, group education meetings, communication skills training and provision of patient education material were employed. The study failed to show any reduction in antibiotic prescription rates and this was attributed to weak monitoring and implementation.

In the study by Plachouras *et al* [204], GPs in one district were given extensive training in the form of academic detailing regarding judicious use of antimicrobials in RTIs and the benefits of Rapid Antigen Detection Tests; another district was used as a control. The intervention also included education for patients and parents in the form of an education campaign. The intervention was not successful as antibiotic consumption remained unaltered at 26 defined daily doses per 1000 inhabitants, which was similar to other regions. However, the utilisation of amoxicillin and penicillin increased by 34.3%, while the use of other antimicrobial classes, including macrolides, cephalosporins and fluoroquinolones, decreased by 6.4-21.9%. Though a reduction in the total antimicrobial consumption was not achieved, more rational choices of antibiotics were noted in this study.

Table 2.2 Complex intervention studies with multiple components – Academic detailing

Author **Year** **Country** **Study design**	**Settings** **Study arms** **Number of sites**	**Indication** **Age group**	**Intervention**	**Outcome measures**	**Findings**
Vinnard *et al* 2013 USA [123] QES Multifaceted	General practices 28 GPs (7 in intensive active group 1, 7 in mild active group 2 and 14 in control)	URTI in all age groups	Education (Provider and patient) + academic detailing	Decrease in antibiotic prescribing	**Successful** Decreased antibiotic prescribing in one active group (43% to 33% before and after intervention); no change in other groups
Naughton *et al* 2009 Ireland [153] RCT	General practices 48 practices in active group 1and 50 in active group 2 Multiple sites	RTI and OMI in all age groups	Academic detailing + postal prescribing feedback	Decrease in overall and second line antibiotic prescribing	**Unsuccessful** No significant decrease in overall antibiotic prescribing and second line antibiotic prescribing between the groups (p=0.26)
Neels *et al* 2020 Australia [198] Before and after study	General practice Single site	General infections	Academic detailing + postal prescribing feedback	Appropriate antimicrobial (oral antibiotic) selection	**Successful** There was significant reduction in prescriptions without a listed indication for antimicrobial therapy, prescriptions without appropriate accompanying microbiological tests and the provision of unnecessary repeat prescriptions (p< 0.001).
Penalva *et al* 2020 Spain [200] QES	214 primary health centres for primary health care districts	General infections	Academic detailing + postal prescribing feedback	Quarterly antibiotic use; appropriate prescribing, defined as compliance of all checklist items with the reference guidelines	**Successful** The intervention was associated with a sustained reduction in the use of ciprofloxacin (relative effect −15·9%, 95% CI −23·9 to −8·0) and cephalosporins (−22·6%, −35·9 to −9·2), and a sustained increase in the use of amoxicillin (22·2%, 6·4 to 38·0) and fosfomycin trometamol (6·1%, 2·6 to 9·6).
Smeets *et al* 2009 The Netherlands [202] CBA Multifaceted	General practices 264 practices (137 in active and 127 in control group) Multiple sites	RTI in all age groups	Education (Provider communication skills) + academic detailing + audit and feedback	Decrease in antibiotic prescribing and change in second choice antibiotics	**Unsuccessful** No decrease in antibiotic prescribing in the active group; no change in second line antibiotic prescribing
Plachouras *et al*,	Primary care physicians	RTI in all age groups	Education (Provider and patient) +	Decrease in antibiotic	**Unsuccessful**

2014 Greece [204] CBA	and parents in a district 772 parents, 111 physicians and 30 dentists Multiple sites		academic detailing + audit and feedback	consumption as defined daily doses per 1000 inhabitants per day	Antibiotic consumption remained unaltered at 26 defined daily doses per 1000 inhabitants per day.

2.3.3.3 Point of care testing as most dominant component

There were nine studies in the review which employed point of care testing (POCT) to support prescribers' decision making in prescribing an antibiotic only when indicated. The majority of the studies had more than one intervention arm to compare or combine the effect of POCT with other strategies, such as communication skills training for prescribers [162, 205], audit and feedback [206], delayed prescribing [207], patient education [206, 208, 209] or parental advice[210]. Table 2.3 summarises the details of the studies involving POCT, along with other components.

There were two studies by Cals *et al* [211, 212] which investigated the impact of POCT. The first study [211] comprised C reactive protein testing (CRP) and communication skills training (CST) for GPs. The study led to significant reduction in the antibiotic prescribing rate (31% POCT vs 53% control, p=0.02 and 27% CST vs 54% control group). In their second study [212], the effect of CRP assistance was evaluated along with a practice-based seminar for the GPs which included information about delayed antibiotic prescribing. The seminar was in addition to a demonstration to the nurses of the CRP device and the trial procedure. There was a 43.4% reduction in the POCT group, versus 56.6% in the controlled group (p=0.03).

Another three studies were conducted by Llor *et al* [206, 208, 209], involving RADT along with prescriber and patient education, audit and feedback. All three studies led to significant reduction in the antibiotic prescribing rate. In the first study [208], a rapid antigen detection testing (RADT) workshop, GP courses related to guideline adherence, a patient information leaflet and the use of rapid antigen detection tests (RADTs) in consulting offices were offered for one intervention arm. The second intervention group received all except the workshop. The antibiotic prescription rate was significantly lower after intervention in the full intervention group but not in the second, partial intervention group. The odds ratio of antibiotic prescription after the intervention was 0.52 [95% CI 0.23– 1.18] in the partial intervention group and 0.23 (95% CI 0.11–0.47) in the full intervention group.

In the second study [206] which was similar to the researchers' earlier study, two types of interventions were evaluated:

1. The first was full intervention consisting of individual prescribing feedback based on results from the first registry courses in rational antibiotic prescribing, guidelines, patient information leaflets, workshops on rapid tests and the use of the CRP test.

2. GPs in the partial intervention group underwent all the above interventions except for the workshop and they did not have access to CRP. Antibiotics were prescribed in 82.9% patients in the partial intervention group and 86.7% in the control group ($p<0.001$). Antibiotic prescription was significantly reduced in the full intervention group, with an odds ratio of antibiotic prescribing of 0.12 (95% CI 0.01-0.32).

In the third study by Llor *et al* [209], the effect of access to POCT on decreasing antibiotic prescription in patients who explicitly requested an antibiotic prescription was evaluated. Two types of intervention groups were compared: the first intervention group received prescribing feedback, courses for GPs, guidelines, patient information leaflets, workshops and access to POCT (RADT and CRP); while the partial or second intervention group received all except POCT. In the partial intervention group, fewer patients requesting antibiotics received a prescription before, than after the intervention, (53.1% vs 60% without statistical differences being observed). In the group of GPs assigned to the full intervention group, a significant difference in antibiotic prescribing was noted (55.1% vs 36.2%, respectively, with a difference of 18.9%, 95% CI: 6.4%–30.6%, $p<0.05$). All the three studies found that access to POCT reduces antibiotic use in RTI patients.

Lemiengre *et al* [210] examined the effect of CRP testing and parental guidance in the management of non-severe ARIs in children. The first intervention group was exposed to CRP testing; the second intervention group was provided with guidance in the form of parental information leaflets, and the third group had both CRP testing and parental advice. The CRP testing did not significantly influence antibiotic prescribing (AOR 1.01, 95% CI 0.57 to 1.79). Antibiotic prescribing increased in the parental guidance group (AOR 2.04, 95% CI = 1.19 to 3.50) but this disappeared in the combined intervention group. The combined intervention group was not found to be superior to the parental guidance group.

A large study was conducted by Little *et al* [162] across Europe, assessing the effects of CRP testing and communication skills training. The interventions (INternet Training for Reducing AntibiOtic use-INTRO) were aimed at adult RTI patients, at different locations in the UK, the Netherlands, Belgium, Poland and Spain. The three intervention groups involved web-based training of prescribers regarding CRP testing, communication skills alone and the two parts combined. The intervention led to a significant reduction in antibiotic prescribing for RTIs in all the three study arms. The antibiotic prescribing rate was lower with CRP training than without (33% vs 48%, adjusted risk ratio 0·54, 95% CI 0·42–0·69) and also lower with enhanced-communication training than without (36% vs 45%, 0·69, 0·54–0·87). The combined intervention was associated with the greatest reduction in the antibiotic prescribing rate (CRP risk ratio 0·53, 95% CI 0·36–0·74, p<0·0001; enhanced communication 0·68, 0·50–0·89, p=0·003; combined 0·38, 0·25–0·55, p<0·0001).

In another study by Little *et al* [213], the impact of RADT and clinical scores was evaluated to optimise antibiotic prescribing in people with sore throats, aged three years or above. In the control arm, an antibiotic prescription was left to be collected if the symptoms persisted for five days. In the first intervention group, patients were tested on pre-approved clinical scores that predict streptococcal antigen and an antibiotic was prescribed accordingly. In the second intervention group, POCT was completed for patients whose clinical scores required further investigations. There was a significant decrease in the antibiotic prescribing rate in the intervention groups. Use of antibiotics in the clinical score group was 29% lower (adjusted RR 0.71, 95% CI 0.50 to 0.95; p=0.02) and in the POCT group, it was 27% lower (0.73, 0.52 to 0.98; p=0.03) than the comparator group.

Burkhardt *et al* [207] also studied the impact of PCT testing on antibiotic prescribing decisions. Patients in both groups who required an antibiotic received a prescription with the request to redeem the prescription only after they had been advised to do so by telephone. The PCT testing was undertaken in the intervention group and if the levels of PCT were higher than 0.25 $ngml^{-5}$ the antibiotic was prescribed. If the final decision were made against an antibiotic, the patients were asked to return the prescriptions. The study resulted in a 41.6% reduction in the antibiotic prescribing rate in the intervention group during the intervention period, compared with the baseline period. Reduction in the antibiotic prescribing rate was also significant as compared with the control (36.7% control vs 21.5% POCT, p=0.0005).

Table 2.3 Complex intervention studies with multiple components – Point of care testing

Author Year Country Study design	Settings Study arms Number of sites	Indication Age group	Intervention	Outcome measures	Findings
Cals *et al* 2009 The Netherlands [211] CRCT	General practices 3 groups of 5 practices each as active groups, fourth one is control Multiple sites	Lower respiratory tract infections in all age groups	POCT + communication skills training	Decrease in antibiotic prescribing	**Successful** Decrease antibiotic prescribing in the active POCT group vs control (31% vs 53%, p=0.02) and communication skills group vs control (27% vs 54% p<0.01); no significant decrease in the combined group
Cals *et al* 2010 The Netherlands[212] RCT	General practices 258 patients and 32 GPs Multiple sites	LRTI and rhino sinusitis in adults	POCT + practice-based seminar	Decrease in antibiotic prescribing	**Successful** Decreased antibiotic prescribing in active group (43.4% vs 56.6% RR=0.77) and decreased number of prescriptions in delayed prescription choice within active group (23% vs 72%, p<0.001), as compared with control group
Llor *et al* 2011 Spain [208] CBA Multifaceted	General practices 339 GPs (210 in active group 1 70 in activegroup 2 59 in control arm) Multiple sites	Pharyngitis in adults	POCT+ education + A&F .	Decrease in antibiotic prescribing	**Successful** Decrease in antibiotic prescribing in active group one only (OR 0.52)
Llor *et al* 2012 Spain [206] CBA Multifaceted	General practices 340 GPs (210 GP in active group 1and 71 in active group 2and 59 in control) Multiple sites	Rhino sinusitis in all age groups	POCT+ education + A&F	Decrease in antibiotic prescribing	**Successful** Decreased antibiotic prescribing in the active 1 group (46.7 vs 82.0 p<0.001) (OR-0.12)
Llor *et al*, 2014 Spain [209] CBA Multifaceted	General practices 210 in active group 1 and 71 in active group 2 Multiple sites	RTI in all age groups	POCT+ education + A&F	Decrease in antibiotic prescribing	**Successful** Significant reduction in antibiotic prescribing in active group 1 as compared with active group 2 (18.9% p<0.05)
Lemiengre *et al* 2018	General practices	General infections	1) Point of care C-reactive protein	Reduction in antibiotic prescribing	**Unsuccessful** No reduction in antibiotic prescribing in

Belgium [210] CRCT	131 Family physicians	Children	test (CRP) 2) Parental advice 3) Combination of both		POCT and combination arms and an increase in antibiotic prescribing in parental advice group
Little *et al* 2013 Europe [162] CRCT	General practices 62 in active group 1 61 in active group 2 62 in active group 3 61 in control	RTI in people aged 3 years and above	POCT Communication skills training in active group 2 Combination of 2 in active group 3	Decrease in antibiotic prescribing	**Successful** Significant reduction in antibiotic prescribing rates in all three active groups Greatest reduction recorded in active group 3 (p<0.0001)
Little *et al* 2013 UK [213] RCT Multifaceted	General practices 21 practices- patients randomised to three groups. (@ 200 in each group) Multiple sites	Acute sore throat in all age groups	POCT + Education	Decrease in antibiotic prescribing and symptom severity	**Successful** Decreased antibiotic prescribing; 27% lower in the RADT test and 29% less in the clinical score group compared with the control group (p=0.033 and p=0.018 respectively)
Burkhardt *et al* 2010 Germany [207] RCT	General practices 45 GPs-550 patients 275 each in active and control groups) Multiple sites	RTI in adults	POCT PCT-guided antibiotic treatment in the active group along with watchful waiting-delayed prescribing	Decrease in antibiotic prescribing	**Successful** Decrease in antibiotic prescribing in the active group compared with the control group (36.7% control vs 21.5% POCT, p=0.0005)

2.3.3.4 Clinical decision support as the most dominant component

Five studies in this review incorporated a CDSS tool to support prescribers in decision making at the time of diagnosis and prescribing, along with other complementary strategies. Most studies were conducted within a practice group which shared the same EHR. One study employed an academic detailing element in addition to a CDSS tool [214], while the remaining four studies evaluated CDSS, along with an A&F component [215-218]. Table 2.3 summarises the studies.

Sharp *et al* [214] investigated the effect of an electronic CDSS reminder that pops up in the form of an evidence-based recommendation for patients presenting with acute sinusitis. The intervention was supported with a recorded online academic detailing session and two training webinars. This strategy led to a reduction in antibiotic prescribing and an increase in guideline concordant antibiotic use (adjusted odds ratio [AOR], 0.78; 95% CI, 0.71-0.87).

Four trials in this review examined the effects of CDSS along with A&F. In the first study, the effect of different decision support strategies on prescribing for patients with uncomplicated acute bronchitis was investigated by Gonzales *et al* [215]. The study had three arms: the first group had a document-based decision support; the second group had a computer-based decision support, and the third group was the control. The study found the traditional print-based decision support strategy as effective as the computer-based decision support strategy. Compared with the baseline period, the percentage of adolescents and adults prescribed antibiotics during the intervention period decreased at the printed decision support intervention sites from 80.0% to 68.3% (p=0.003) and at the computer-assisted decision support intervention sites from 74.0% to 60.7% (p=0.01). The percentage of antibiotics increased at the control (from 72.5% to 74.3%). However, the differences for the intervention sites were statistically significant from the control (p=0.003) compared with printed decision support intervention sites and when compared with the computer-assisted decision support intervention group (p=0.01) but not significantly between the two interventions (p=0.67).

Mainous *et al* [216] conducted a study in which an electronic CDSS tool based on the recommendations of the Centers for Disease Control and Prevention (CDC) "Get Smart" program [197] was evaluated. The GPs were also engaged in academic detailing, workshops regarding judicious use of antibiotics and performance reviews. In adult patients, inappropriate antibiotic prescribing in acute ARI episodes reported a modest decline among intervention practices compared with the control practices (-0.6% vs + 4.2%, p=0.03). The investigators defined inappropriate antibiotic prescribing according to CDC guidelines, that is, diagnoses for which antibiotics are generally inappropriate comprise nonspecific upper respiratory infections, acute bronchitis, acute pharyngitis (but not streptococcal pharyngitis or group A b-hemolytic streptococcal pharyngitis) and otitis media with effusion. The CDSS intervention reduced broad spectrum antibiotic prescribing in adult patients among intervention practices, versus an increase in control practices (16.6% vs 1.1 %, p<0.0001). A similar effect on broad spectrum antibiotic prescribing was found in paediatric patients with a significant decline among intervention practices, compared with an increase in the control practices (19.7% vs 0.9% p<0.0001).

Meeker *et al* [217] also conducted a study to influence GPs' decision-making behaviour through CDSS; this was called accountable justification and peer comparison. In the first intervention group, prompts within the EHR system were visible to GPs only. In the second intervention, decisions justifying prescription of an antibiotic were visible to the patients in their medical records, while the third group of prescribers received peer compared audit and feedback reports as e-mails. Antibiotic prescribing rates were significantly decreased in all the intervention groups. The absolute difference in the prescribing rate was -11% for control practices during the intervention, -16% for the first intervention group (p=0.66), -18.1% for the second intervention group (p< 0.001) and -16.3% for the third intervention group (p<0.001).

Gulliford *et al* [218] investigated the impact of another CDSS tool supported by a training webinar and monthly antibiotic prescribing feedback reports. The link to the CDSS tool appears on GPs' screen menus at the time of prescribing. The link led to a summary of antibiotic prescribing recommendations, a patient information sheet and guidance for no antibiotic or delayed antibiotic prescribing. In this study called the REDUCE trial, antibiotic prescribing was reduced in adults aged 15-84 years old (adjusted rate ratio 0.84, 95% CI 0.75 to 0.95) and there was no reduction in children younger than 15 years (adjusted rate ratio 0.96, 95% CI 0.82 to 1.12) or people aged 85 years and older (0.97, 0.79 to 1.18).

Table 2.4 Complex intervention studies with multiple components – Clinical decision support systems

Author Year Country Study design	Settings Study arms Number of sites	Indication Age group	Intervention	Outcome measures	Findings
Sharp *et al* 2017 [214] USA CRCT	General practice 6 medical service areas 21,949 encounters	Acute sinusitis	CDSS + academic detailing	Receipt of an antibiotic prescription	**Successful** Decreased use of antibiotics but pre- and post-absolute differences were small (85.9% vs 83.9%)
Gonzales *et al* 2013 USA [215] CRCT Multifaceted	General practices 33 practices (11 in active group 1, 11 in active group 2, 11 in control group) Multiple sites	Acute, uncomplicated bronchitis in all age groups	CDSS + academic detailing + audit and feedback	Decrease in antibiotic prescribing	**Successful** Decrease in antibiotic prescribing (80.0% to 68.3% in active group 1, 74% to 60.7% in active group 2 and 72.5% to 74.3% in control) Decrease was significant as compared with control site in both active 1 and active 2 groups respectively (p<0.003 and p=0.01).
Mainous *et al* 2013 USA [216] QES Multifaceted	General practices 70 practices (9 practices in active and 61 in control) Multiple sites	ARI in all age groups	CDSS + academic detailing + audit and feedback	Change in antibiotic prescribing	**Successful** In adult patients, a moderate decrease in overall antibiotic prescribing (-0.6% vs +4.2%, p=0.3%); significant decline in broad-spectrum antibiotic use in adult patients (-16.7% vs +1.1%, p<0.0001); significant decline in broad-spectrum antibiotic use in paediatric patients (-19.7% vs +0.9%, p<0.0001)
Meeker *et al* 2016 USA [217] CRCT Multifaceted	General practices 42 practices in active group and 6 in control Multiple sites	RTI in adults	CDSS + audit and feedback	Decrease in antibiotic prescribing.	**Successful** Decrease in antibiotic prescribing (-16%)
Gulliford *et al* 2019 UK [218] CRCT Multifaceted	General practices 41 practices in active and 38 in control Multiple sites	RTI in adults	CDSS + audit and feedback	Decrease in antibiotic prescribing	**Successful** Reduced in adults (adjusted rate ratio 0.84, 95% CI 0.75 to 0.95); no reduction in children younger than 15 years (adjusted rate ratio 0.96, 95% CI 0.82 to 1.12) or people aged 85 years

					and older (0.97, 0.79 to 1.18)

2.3.3.5 Delayed prescribing/dispensing as the most dominant component

Two studies in this review evaluated the effect of delayed prescribing and dispensing, the details of which are summarised in Table 2.5.

In a study by Hoye *et al* [219] GPs in the first intervention group were trained to offer delayed antibiotic prescriptions to RTI patients, while in the second intervention group a screen pop-up was installed on GPs' software systems as a prompt to consider whether a delayed prescription might be appropriate or not. The interventions were complemented with two educational outreach visits to present and discuss the national RTI guidelines to the GPs' medical education groups, a one-day regional seminar, collection of antibiotic prescription data and an audit report. The intervention had no effect on the antibiotic prescribing rate. During the intervention, the GPs in both intervention groups prescribed antibiotics to 29.3% of the patients with RTI ($p=0.90$). The first intervention group, which was only educational, led to a small but not statistically significant decrease in the risk of antibiotics being dispensed (RR 0.99). The second intervention, which was combined with a pop-up reminder on delayed prescribing, decreased the approximated risk of antibiotics being dispensed (RR 0.96), without any increase in antibiotic prescribing.

The study by Vervloet *et al* [119] comprised a peer group-based intervention which included communication skills, delayed prescribing/dispensing training, the implementation of antibiotic prescribing agreements in electronic prescribing systems and quarterly feedback. The intervention was effective in reducing the number of RTI-related antibiotic prescriptions for adolescents and adults combined, (−27.8 vs −7.2 per 1,000 patients, $p<0.05$) but not in children.

Table 2.5 Complex intervention studies with multiple components – Delayed Prescribing/Dispensing

Author **Year** **Country** **Study design**	**Settings** **Study arms** **Number of sites**	**Indication** **Age group**	**Intervention**	**Outcome measures**	**Findings**
Hoye *et al* 2013 Norway [219] CRCT Multifaceted	CME groups of general practices 81 CME groups, 40 in active group and 41 in control group (328 GPs- 156 GPs in active group and 172 GPs in the control group. Active group was again divided in 2: 107 GPs in delayed prescribing popup-active 1 and 49 GPs in not delayed prescribing popup active group-2) Multiple sites	RTI in all age groups	Delayed prescribing + CDSS +academic detailing + A&F	Decrease in antibiotic prescribing	**Partially Unsuccessful** The intervention which was combined with a pop-up reminder on delayed prescribing, decreased the approximate risk of antibiotics being dispensed (RR 0.96), without any increase in antibiotic prescribing.
Vervloet *et al* 2016 The Netherlands [119] CRCT Multifaceted	Groups of Family physicians and pharmacists four in active and four in control group. Multiple sites	RTI in all age groups	Delayed prescribing + CDSS + Education (Provider guidelines and communication skills) + audit and feedback	Decrease in antibiotic prescribing	**Successful** 27.8% vs 7.2% ($p<0.05$) reduction in adolescents and adults vs control groups

2.3.3.6 Theory based behaviour intervention as the most dominant component

There were two studies which employed a shared decision-making program with the elements of audit, feedback, education and communication skills training. Table 2.6 summarises the studies.

Legare *et al* [220] implemented a theory based behavioural intervention program comprised of three components:

- interactive workshops for prescribers to promote the concept of shared decision making between prescribers and patients which includes communication skill training and provision of patient education material;
- reminders of expected behaviours through mail to the prescribers, and
- feedback on the agreement between prescriber and patient related conflicts.

The authors reported that this bundled pilot interventional program, known by the name DECISION+, reduced the immediate use of antibiotics and this was sustained for eight months in the intervention group (16%, p=0.08). According to the study, the decisional conflict agreement was stronger in the intervention group between the prescribers' and the patients' decision to use antibiotics (p =0.06). The other outcomes, that is, decisional regret and perceptions of the quality of the decision and of the health status in the two groups, were similar.

Shen *et al* [221] studied the impact of an interactive web-based educational aid comprised of theory and evidence-based ingredients, in order to promote shared decision making, along with a feedback component of performance scores. This study led to a reduction in overall antibiotic prescribing (88.8% to 62.3%, p<0.001) which was consistent for both RTIs (87.1% to 64.3%, p<0.001) and gastrointestinal tract infections (94.7% to 52.4%, p<0.001).

Table 2.6 Complex intervention studies with multiple components – Theory based interventions

Author **Year** **Country** **Study design**	**Settings** **Study arms** **Number of sites**	**Indication** **Age group**	**Intervention**	**Outcome measures**	**Findings**
Legare *et al* 2011 Canada [220] CRCT	General practice four family medicine groups (2 in active group and 2 in control group) Multiple sites	URTI in all age groups	Shared decision making	Decrease in immediate use of antibiotics	**Unsuccessful** 16% (p=0.08) compared with control
Shen *et al* 2018 China [221] RCT	24 village clinics 1048 patients 269 in active and 263 in control	Respiratory or gastrointestinal infections	Shared decision making	Decrease in antibiotic prescribing	**Successful** Overall prescribing reduced from 88.8%-62.3%, p<0.001 in the intervention group; decrease in RTIs was from 87.1% to 64.3%, (p<0.001) and in gastrointestinal tract infections from 94.7% to 52.4%, (p<0.001).

2.3.4 Multifaceted studies conducted in aged care facilities

Eleven studies conducted in aged care facilities (ACFs) are described in this section separately because of the differences between ACF and community dwelling patients and associated prescribing practices. The review also found that aged care residents have different complex health care issues with unique challenges and the studies which were conducted in ACFs were part of quality or performance improvement initiatives under a limited organisational umbrella. Most interventions involved an educational or learning arm, either with an audit and feedback element or with activities to improve guideline adherence or use of POCT. Most of the studies were conducted for urinary tract infections (UTIs) [222-224]. Three trials included pharmacists in addition to prescribers and nursing staff [222, 225, 226]. Table 2.7 summarises the details of the AMS studies.

2.3.4.1 Education

The following three studies focussed their interventions on the optimisation of antibiotic use in UTIs. Nace *et al* [222] studied the impact of a complex intervention with multiple components addressing the diagnosis and treatment of suspected, uncomplicated cystitis. The intervention included a one-hour introductory webinar led by expert physicians and pharmacists, pocket-sized educational cards, tools for system change, audit and feedback, and clinical vignettes. This was a quality improvement initiative for the nursing and prescribing staff, which led to a 17% reduction in overall antibiotic use, compared with the control facilities ($p=0.04$).

The study of Zabarsky *et al* [224] was also a multifaceted intervention that focussed on education and monitoring the rates of asymptomatic bacteriuria (ASB). This study was conducted by the facility's infection control nurse as a quality control initiative. The study aimed to discourage the collection of urine samples in the absence of symptoms suggestive of a UTI and to educate the prescribers not to treat ASB in such cases. This trial resulted in the decrease of inappropriate submission of urine cultures from 2.6 to 0.9 per 1000 patient days ($p<0.0001$) and the reduction of the overall rate of treatment from 167.7 to 117.4 per 100 patient days ($p<0.001$).

Pasay *et al* [223] also studied the impact of staff training and academic detailing, along with the introduction of a clinical decision-making tool on the rates of urine culture testing and antimicrobial prescribing for UTIs. The CDSS tool guided staff through a checklist to identify a UTI, based on clinical symptoms. The study resulted in statistically significant decreases in the rate of urine culture testing (−2.1 tests per 1,000 resident days [RD]; −2.5 to −1.7; p<0.001) and antimicrobial prescribing for UTIs (−0.7 prescriptions per 1,000 RD; p<0.001) in the intervention group.

Linnebur *et al* [226] also evaluated the impact of academic detailing on guideline adherence for management of nursing home acquired pneumonia (NHAP). This intervention included educational sessions for nursing staff and academic detailing for clinicians by pharmacists regarding diagnostic and prescribing practices. The mean adherence score for optimal antibiotic use in intervention ACFs increased from 60% to 66%; whereas the control ACFs increased from 32% to 39% (p=0.3). Mean adherence to guidelines recommending antibiotic use within four hours of NHAP diagnosis increased from 57% to 75% in intervention ACFs but decreased from 38% to 31% in control ACFs (p=0.0003). There was no difference between intervention and control ACFs for guideline adherence regarding optimal duration of antibiotic use.

Pluss-Suard *et al* [227] introduced quality circles comprised of a physician, a pharmacist and a nurse for the implementation of guidelines. Antibacterial use decreased from 45.6 to 35.5 DDD per 1000 beds per day (-22%, p <0.01) over the six-year study period, which was mostly explained by reduced fluoroquinolone use (-59%, p<0.001).

2.3.4.2 Education with audit and feedback

The study of Pettersson *et al* [225] comprised small educational group sessions with nurses and prescribers to improve quinolone prescribing in lower UTIs in women. The engagement activities included feedback on prescribing, presentation of guidelines and written materials concerning the treatment of infections in ACFs. The proportion of quinolones decreased significantly in the intervention and control groups by -0.196 and -0.224, respectively (95% CI -0.338, -0.054 and -0.394, -0.054). The difference between intervention and control groups was not significant, with an absolute risk reduction of 0.028 (95% CI -0.193, -0.249) and hence, the reduction in quinolone prescribing could not be definitively attributed to the intervention.

2.3.4.3 Miscellaneous quality control initiatives

Fleet *et al* [228] evaluated the impact of an AMS toolkit titled the Resident Antimicrobial Management Plan. The plan expected documentation of antimicrobial prescribing, administration and monitoring, on a pre-printed form. The intervention required the nursing staff to record initiation and review of systemic antibiotic treatment, using tick boxes for ease of completion. The corresponding pre- and post-intervention point prevalence of systemic antibiotic prescribing for treatment of infection was 6.46% and 6.52% in the intervention group (p=0.94), compared with 5.27% and 5.83%, respectively, in the control group. There was a significant decrease of 4.9% in the intervention group (p=0.02), compared with a significant increase of 5.1% in the control group (p=0.04).

Van Buul *et al* [229] studied decisions to prescribe or withhold antibiotics for each type of infection within ACFs through a participatory action research approach. In this initiative, tailored interventions were developed for each of the ten participating ACFs by conducting group meetings and focus group discussions in order to improve prescribing. More appropriate prescribing decisions at the start of data collection and before receiving feedback on prescribing behaviour were observed. The appropriateness of prescribing decisions based on infections was measured by the prescribers with an algorithm. However, no changes in antibiotic use or guideline-adherent antibiotic selection were noted in the intervention ACFs. (The proportion of appropriate prescribing decisions was 82% in the intervention and 70% in the control group ACFs). There was no significant difference in the appropriateness of prescribing decisions between the intervention and control ACFs (crude: p=0.26; adjusted for covariates: p=0.35).

As a part of quality improvement program, Sloane *et al* [230] studied the impact of a multi-component stewardship intervention on antibiotic use in ACFs. The nursing staff and prescribers of the ACF were provided training modules, posters, algorithms, communication guidelines, quarterly information briefs, an annual quality improvement report, an informational brochure for residents and families, and free continuing education credits. Antibiotic prescription rates decreased from the baseline by 18% at 12 months and 23% at 24 months. A 10% increase in the proportion of residents with the medical director as primary physician was associated with a 4% reduction in prescribing (IRR=0.96; 95% CI = 0.92-0.99).

March-Lopez *et al* [231] conducted a study based on the CDC's Core Elements of Outpatient Antibiotic Stewardship [232]. The study comprised 30-minute face-to-face sessions with the prescribers along with the provision of educational leaflets, posters and local guidelines on antibiotic usage. A 60-minute workshop in all the participating centres was also provided for tracking and feedback. Antibiotic consumption was measured in defined daily doses per 1,000 inhabitants per day (DID) and compared pre- and post-intervention. Overall antibiotic consumption decreased from 16.01 to 13.31 DID (-16.85%). The study also reported decreases in the prescribing of amoxicillin/clavulanic acid and quinolones from 6.04 to 4.72 DID (−21.88%) and 1.64 to 1.23 DID (−25.06%), respectively. The percentage of patients treated with antibiotics decreased from 26.99 to 22.41%.

2.3.4.4 Diagnostic testing

Dowson *et al* [233] conducted a study involving nurse-initiated polymerase chain testing (PCR) in three ACFs. The number of PCR tests of respiratory specimens (over 12 months) increased from five to 67 when nurses could initiate the tests. Although more viral pathogens were identified by the PCR testing, there was no change in the rates of antibiotic therapy (Incidence rate ratio 0.94, 95% CI, 0.25-3.35, p=0.92).

Table 2.7 Multiple component studies-Aged care facilities

Author Country Year	Subjects	Design	Setting	Indication	Intervention	Outcome	Results
Nace *et al* USA [222] 2020 CRCT	Nursing staff	Cluster randomised controlled trial	25 nursing homes	Urinary tract infections	One hour introductory webinar and other educational tools + A&F	• Antimicrobial use	**Successful** Fewer unlikely cystitis cases were treated with antibiotics in the intervention group.
Zabarsky *et al* USA [224] 2008 CBA	Nursing staff and primary care practitioners	Before and after study	One long-term care facility of Veteran Affairs	Asymptomatic bacteriuria	Education of nursing staff to discourage collection of urine samples in the absence of symptoms and primary care practitioners not to treat	• Inappropriate submission of urine cultures • Rate of treatment • Antimicrobial days of therapy	**Successful** Sustained reduction in: • inappropriate submission of urine cultures • rate of treatment total antimicrobial days of therapy
Pasay *et al* Canada [223] 2019 CRCT	Onsite staff and physician, families and caregivers	Cluster randomised controlled trial	42 nursing homes	Urinary tract infections	Education-onsite staff, academic detailing to physicians and an integrated clinical decision-making tool	Rate of • urine culture • antimicrobial use • hospital admissions	**Successful** Statistically significant decrease in the rate of: • urine culture testing • antimicrobial prescribing No difference in hospital admissions
Linnebur *et al* USA [226] 2011 QES	Nurses and practitioners	Quasi experimental study	8 nursing homes	Nursing home acquired pneumonia	Education-multidisciplinary, academic detailing on adherence to guidelines by pharmacist to practitioners	• Timely antibiotic administration according to guidelines	**Unsuccessful** No significant difference in guideline adherence for optimal antibiotic use
Pluss-Suard Switzerland [227] 2019 Quality improvement study	Physician, pharmacist and nurse	Quality improvement study	23 long term care facilities	Not specific	Education-physician pharmacist nurse quality circle and publication of local guidelines	• Facility-level antibacterial use	**Successful** Antibacterial use decreased from 45.6 to 35.5 DDD per 1000 beds per day (-22%, P <.01) over the 6-year study period, which was mostly explained by reduced fluoroquinolone use (-59%, P <.001).
Pettersson *et al* Sweden [225] 2011 CRCT	Nurses and physicians	Cluster randomised controlled trial	58 nursing homes	Lower urinary tract infections	Education-group sessions, feedback, presentation and written materials on guidelines	• Proportion of quinolone prescribing	**Unsuccessful** No significant reduction in the proportion of quinolone prescribing
Fleet *et al* UK [228] 2014	Nurses	Cluster randomised controlled trial	30 nursing homes	Not specific	Education-Resident Antimicrobial Management Plan (RAMP)	• Systemic antibiotic use	**Successful?** Total antibiotic decreased 4.9% (CI95% 1.0%, 8.6%)

CRCT					pre-printed form "initiation of treatment" and "review of treatment" (48h-72h) completed by nurses + support pack (signs and symptoms in the elderly, collecting clinical specimens and information on antimicrobial resistance)		(p=0.02); no significant difference between systematic antibiotic prescribing
Van Buul *et al* Netherlands [229] 2015 QES	Physicians	Quasi experimental study	10 nursing homes	Not specific	Appropriateness of prescribing decisions	• Antibiotic use reduction through **participatory action** research approach	**Unsuccessful** Participatory action research approach was not effective to decrease antibiotic use.
Sloane USA [230] 2020 Pragmatic implementation trial	Nursing staff and medical care providers	Pragmatic implementation trial	27 nursing homes	Not specific	Education training modules, posters, algorithms, communication guidelines	• Systematic antibiotic prescription rates	**Successful** Systematic antibiotic prescription rates decreased by 18% from baseline.
March-Lopez Spain [231] 2020 QES	Physicians and paediatricians	Quasi experimental study	18 nursing homes and one acute care teaching hospital and 8 primary health care centres	Pharyngotonsillitis, acute otitis media, acute sinusitis, acute bronchitis and urinary tract infections	Based on 2016 Core Elements of Outpatient Antibiotic Stewardship	• Overall antibiotic consumption • Percentage of patients treated with antibiotics. • Dispensing cost	**Successful** • Overall antibiotic consumption decreased (16.85%) • Percentage of patients treated with antibiotics decreased (5%) Cost saving of 72,673 Euros.
Dowson *et al* Australia [233] 2019 Pragmatic historically controlled study	General practitioners and nurses	Pragmatic, historically controlled study	3 nursing homes	Respiratory tract infections	Education- sessions on therapeutic guidelines-antibiotic related to diagnostic testing using polymerase chain reaction (PCR)	• Antibiotic days of therapy	**Unsuccessful** No change, incidence rate ratio=0.94, 95% Cl, 0.25-3.35, p= 0.92

2.4 Discussion

The literature review described in this chapter was chronologically carried out at the commencement of the PhD candidature and presents a summary of the different AMS interventions that have been studied in the community setting to optimise antimicrobial use. This review provided the foundation for the quantitative and qualitative studies of the research project. Prior to the initiation of this review, there had been no Medline term for Antimicrobial Stewardship. In fact, little had been published in the international infectious diseases, pharmacy and microbiology journals on community based AMS prior to 2016. The findings from the review served several important functions:

1) They provide a useful background and foundation for the current AMS developments in community settings.
2) They identified a need for further research to explore the role of the community pharmacist in AMS, due to an identified gap in the literature.
3) They informed the methodology and design of the subsequent studies which undertook a deeper investigation of the barriers to and enablers of AMS in the community pharmacy.

2.4.1 Review of the main findings and comparison with existing literature

The review identified 73 studies evaluating the effectiveness of a range of AMS interventions in optimising antimicrobial use in community settings, from educational strategies to point of care testing. The majority (64%) of the studies involved multifaceted, complex AMS interventions and were successful in reducing antimicrobial prescribing rates, confirming previous reviews that a multifaceted approach is necessary to optimise antimicrobial use [63]. However, in many of the complex multi-faceted studies, the success of each element could not be individually determined. In terms of the types of infection, the majority of included studies, which were conducted in general practice sites, involved respiratory tract infections. This reflects the high prevalence of these infections in the community and their significant contribution to overall antibiotic use. Previous studies have reported that up to half of outpatient antimicrobial use is in self-limiting respiratory tract infections (RTIs), when either the antimicrobials are not indicated or broad spectrum instead of narrow spectrum antimicrobials are prescribed [234]. This review found that the most successful interventions were educational and aimed to modify the behaviour of prescribers and/or patients regarding antimicrobial use. It searched for studies which employed interventions to optimise antimicrobial use, and which were directed at prescribers, nursing staff, pharmacists, patients and the wider public. Prescriber-focussed interventions included educational materials (for example, guidelines, lectures, workshops, webinars, conferences), audit and feedback on antibiotic prescribing practices, electronic or paper reminders, computer-aided clinical decision support systems, point-of-care testing, and behavioural theories-based interventions. This finding is similar to a 2005 Cochrane review which examined the effectiveness of professional interventions in improving the prescription of antibiotics in ambulatory care, concluding that the most effective multi-faceted interventions were those in which educational interventions occur on multiple levels, that is, prescriber, patient and pharmacy staff [146]. A more recent review assessed the effectiveness of interventions to reduce community antimicrobial prescribing, concluding that interventions using active clinician education may lead to larger reductions in antibiotic prescribing [149].

2.4.1.1 Educational and learning interventions

Overall, this review found that most studies were intended to benefit the whole general practice through an established AMS educational program. The interventions included practice-based activities reflecting on the practices' own prescribing data, along with elements to reinforce guideline adherence and communication skills training for shared decision making. Examples of such programs employed in the reviewed studies include England's Public Health Royal College of General Practitioners TARGET toolkit-(Treat Antibiotics Responsibly, Guidance and Education Tool) [196], the blended learning program STAR (Stemming the Tide of Antibiotic Resistance) [160], the Nudging Guideline-Concordant Antibiotic Prescribing program [184] and CDCs by (Centers of Disease Control and Prevention) Get Smart Program [197, 216]. These programs resulted in a reduction of inappropriate antibiotic prescribing by 2.7% when the TARGET toolkit was used in one of the included studies, during the educational intervention [196], by 4.2% when the STAR learning program was employed [160], by 19.7% when Meeker *et al* employed Nudging Guidelines in their study [184] and by 16.7% in adults and 19.7% in children in broad spectrum antibiotic use when CDC's Get Smart Program was utilised [216].

There were 12 multi-faceted studies in this review in which learning elements related to guideline adherence were considered, along with auditing and feedback. Most studies promoting guideline adherence recommended accessible, short, easy-to-understand guidance to reach both GPs and community pharmacists. Studies combining the dissemination of user-friendly guidelines with an active promotional and educational campaign demonstrated sound success in reducing overall antibiotic prescribing rates, as well as a decrease in broad spectrum prescribing [119, 122, 163, 164, 171, 188, 193, 198, 200, 206, 209, 216, 225, 227, 230], except for one study [195]. Amongst the various AMS strategies employed, guideline promotion was found to be a very effective and easy approach to the education of prescribers. It represents the best available, practice-based evidence and expert opinion to support GPs in antibiotic prescribing. This finding is consistent with the systematic review by Drekonja *et al* [63], which identified that development, promotion and adherence to antibiotic prescribing guidelines were associated with improved antibiotic outcomes (for example, reduced overall use or improved agent selection by the prescriber) in the community setting [63].

2.4.1.2 Audit and feedback

An audit and feedback (A&F) strategy, when employed in a non-judgemental trusting environment, was found to be a powerful strategy. The studies which employed audit and feedback strategies alone, or in combination with an educational intervention, led to decreases in overall antibiotic prescribing, ranging from 5% to 14%. This review found the A&F activities employed in the studies comprised the following elements:

1) group peer review meetings to discuss performance reports in practice sites, networks or locality;
2) online, faxed, or postal quarterly feedback reports, and
3) sharing graphical data of the prescribing patterns by a regulatory authority.

In one of the included studies, quarterly feedback to prescribers, along with education on guideline adherence, nearly halved the prescribing rate of broad-spectrum antibiotics for bacterial infections [192]. However, the sustainability of the intervention was not evaluated in most of the included studies and this requires further investigation.

2.4.1.3 Persuasive strategies

While education, audit and feedback-based multi-faceted interventions help to optimise antimicrobial prescribing and dispensing, new and enhanced multifaceted interventions with the concept of shared decision making and behaviour change theories, targeting both prescribers and patients, were also included in the review. These emerging interventions are mostly grounded in behavioural science and based on the emotional, social and cognitive behaviours behind a prescriber writing an antibiotic prescription and a patient wanting an antibiotic [235]. The review found that studies based on behavioural change and utilising communication skills training of prescribers, lead to larger reductions in antibiotic prescribing (4.2%, 16%, 18%, 26.5%) [160, 188, 202, 220, 221] respectively. It was also found that behavioural change theory-based interventional studies, which involved a public commitment letter or posters led to a significant decrease of 16% to 19.5% [184, 190]. Our findings are in line with the overview of systematic review by Tonkin-Crine *et al* [107] which reports that any strategy which encourages a prescriber to discuss, management options with the patient, including GP-delivered patient education material, communication skills training and shared decision making, is useful. The WHO report to the Secretary General of the United Nations by the Interagency Coordination Group on Antimicrobial Resistance, recommends that countries optimise antibiotic use and advises the use of behaviour change interventions aimed at both the public and professionals [236].

2.4.1.4 Point of care testing

Point of care testing (POCT), with good specificity and sensitivity in the community setting, was another strategy that has been evaluated as a guide to optimise the use of antibiotics. Sore throat or pharyngitis is a common but often viral condition which can often be managed without antimicrobials [140]. However, diagnosis or identification of Group A streptococcal (GAS) infection, which affects only a small proportion of patients complaining of a sore throat, can be difficult. POCT can distinguish patients with GAS versus viral infection and can swiftly identify bacterial pathogens [112]. The included studies in the review reported the most significant reductions in antibiotic prescribing, ranging from 18.9% to 37.6% in this segment. Therefore, it appears that POCT to assist with diagnosis of bacterial infections in the community setting may be a particularly useful strategy in optimising antibiotic use. These interventions were studied in various diseases such as influenza and GAS pharyngitis, and new evidence suggests that POCT conducted in community pharmacies can reduce the need for GP consultation and may reduce antibiotic prescribing . Challenges to POCT implementation include cost and training. Despite these challenges, POCT for pharyngitis has become widely available in pharmacies in some countries and may represent a strategy to contain AMR and contribute to AMS [112].

2.4.1.5 Clinical decision support systems

The CDSS tools which have the potential to enhance AMS employed in the included trials were electronic alerts or reminders [214], antimicrobial guideline information [218], a checklist to guide antimicrobial selection, dose, and duration for a particular infection or patient [215]. Having these tools available at the point of prescribing, including a requirement for justification for use of non-recommended antibiotics, efficiently prompts prescribers to select the right treatment based on individual patients' clinically relevant factors, such as prescribing indication, available microbiology culture results, susceptibilities, antibiotic allergies, drug-drug interactions, renal function, medical history and cost or insurance coverage. Prescribers were educated before and during the implementation phase to optimise uptake of the CDSS and utility which was found to be a limitation in most of the included studies. The studies in which the CDSS tool was used, generally demonstrated a favourable reduction in antibiotic prescribing in ARIs [171]. However, it is important to anticipate challenges and barriers associated with CDSS aids when considering their implementation and integration. This is in line with the recommendation of Forrest *et al* that the resolution of technical and administrative issues for smooth integration is important, otherwise prescribers were unlikely to use such tools as they will interrupt workflow, their function is inflexible or they introduce time pressure in the context of consultation and prescribing [237].

2.4.1.6 Delayed prescribing/dispensing

This review identified four studies in which delayed prescribing and/or dispensing was employed as an AMS strategy, either in mild acute otitis media or acute uncomplicated RTIs [119, 179, 180, 219]. The review found that delayed prescribing is another well documented approach to the optimisation of antibiotic use and is an acceptable compromise in place of immediate antibiotic prescribing, particularly when there is patient pressure for an antibiotic. A delayed prescribing strategy is also well advocated in the case of diagnostic uncertainty and when the prescriber perceives that patient satisfaction scores may suffer if an antibiotic is not prescribed, as it is quicker to prescribe than to educate. However, delayed prescribing can be seen as an opportunity to educate the patient and its success also depends on the communication skills of the prescribers [156]. One of the drawbacks of this approach is that patients may feel uncomfortable deciding on their own when the prescription should be filled; usually prescribers advise to delay its use to see if symptoms resolve by their own at first. The major limitation of this approach, for prescribers who use electronic prescribing, is postdating the prescription, which might not be valid or feasible in some countries. Despite the evidence, implementation of this strategy may face some barriers in jurisdictions such as Australia, as related to prescribing regulations. In such cases the prescribers usually add a free text advisory note to the prescription such as "fill on this date if not better". A recent publication reported that delayed prescribing is one evidence based AMS strategy that is underused and entails proper implementation. Further studies are required to explore the best method to properly implement it [238]. Our results are consistent with the live systematic Cochrane review by Spurling *et al*, comprising 11 studies which concluded that delayed antibiotic prescribing resulted in significant reduction in antibiotic use, compared with immediate antibiotic prescribing. The review also reported that using a no antibiotic approach results in the greatest reduction in antibiotic use [239].

2.4.2 Comparison with existing literature

AMS is more well established in hospitals compared with community settings. This fact is supported by a number of studies and reviews, for example, a systematic review undertaken by Davey *et al* in 2017 [15] which included a large number of studies (n-=221) investigating different AMS interventions in the hospital setting and focussed on adverse drug effects, mortality and overall length of stay of the patients in a particular hospital or in a specific unit of the hospitals. AMS programs are not just required in hospital settings but across the continuum of care. However, AMS recommendations from hospital settings cannot be applied in the community setting because the factors which are required for optimal use of antibiotics are different. The most notable of them are diagnostic uncertainty, prescriber time pressures, patient or caregiver's expectations and perceptions. Moreover, in most developed countries, the national accreditation requirements are directed towards hospitals only [93, 94]. Lately, AMS efforts in the community setting are emerging but the literature search found few systematic reviews on different topics of AMS in the community setting. The notable systematic reviews conducted earlier by Arnold *et al* in 2005 [12] reviewed 39 studies. In 2008 Ranji *et al* [149] included 43 AMS studies and in 2015 Drekonja *et al* [63] included 50 studies. Recently (in 2017), Dobson *et al* updated and summarised the available AMS interventional studies and found that one ideal intervention or combination of interventions to optimise antibiotic use is difficult to identify, given the complexity and paucity of comparable data in the community setting; this is in accordance with our review findings [150].

2.4.2.1 Aged Care Facilities (ACFs)

AMS is as important in ACFs as in other community settings, as antimicrobials are amongst the most frequently prescribed medicine, many of which are unnecessary [240]. Antimicrobial-related complications can be severe, leading to higher costs, increased hospitalisation and deaths for persons aged over 65 years [241]. Due to advanced age and frailty, cognitive decline, underlying comorbid conditions and frequent antibiotic use, ACF residents are at higher risk of resistant infections and this makes implementation of AMS programs more challenging [242]. Hence, the ACF specific issues have been neglected yet have significant implications for health services and require particular attention. There are reports of prevalence of high rates of multi-resistant infections in ACFs which can become a major multi-drug resistant organism reservoir for the wider community. The importance of addressing AMS issues in ACFs is particularly pertinent, as in many countries there are more residents in ACFs than patients in the hospitals [241].

Although awareness of appropriate antimicrobial use is gradually increasing, there is still considerable scope for improving AMS in ACFs, [243]. This review found that the resources available in ACFs, such as access to laboratories, GPs and pharmacists with an understanding of AMS and infectious diseases, are limited. This review also found several concerns related to the appropriateness of antimicrobial use, such as availability and timing of the first dose and poor communication at the transitions of care. This review found seven out of eleven studies in which AMS interventions in ACFs achieved significant reductions in antibiotic use, mostly as part of a quality control program. All the trials included in the review employed different educational strategies along with audit and feedback. The results are consistent with the findings of another review conducted in this setting, reporting that multi-faceted interventions, including education, audit and feedback, are the most effective AMS strategies in ACFs [244]. Globally, between 47% and 70% of ACF residents receive a course of an antimicrobial annually, and an estimated 77% to 88% of infections are treated with an antimicrobial, approximately half of which are reported as inappropriate [59]. In the USA up to 75% of antibiotic prescriptions in ACF are inappropriate [245].

Many international, national, regional and local organisations have developed resources including protocols, tools and guidelines for AMS in ACFs but there is still a need for improvement through sustained actionable interventions and this warrants further research to narrow the knowledge gap [244]. In Europe, 39.4% of facilities have AMS resources and guidelines for the appropriate use of antibiotics as compared with 59% facilities in the USA. In Europe and the USA, 24% and 25% of ACFs respectively have a restrictive list of antibiotics[246]. AMS training of nursing staff is undertaken in 73% of ACFs in the USA, compared with 20.7% of ACFs in Europe [247]. In 2015, the Centers for Disease Control and Prevention (CDC) in the USA released the Core Elements of Antibiotic Stewardship for Nursing Homes which include leadership, accountability, drug expertise, action, tracking, reporting and education, and this might help to improve antibiotic use in ACFs in the long run [247]. From November 2017, AMS programs have been mandated in ACFs in the US. Similarly, a significant burden of antibiotic use has been identified in upper respiratory tract infections and asymptomatic bacteriuria in Australia, where the impact of AMS programs in ACFs is unclear and uncertain so far, including the ways to best implement sustained and successful AMS interventions [59] .

2.4.2.2 Role of the community pharmacist in AMS

There is a clear need to find more effective strategies to be included in a comprehensive AMS framework in the community. This could be undertaken by exploring the barriers to and facilitators of implementation, especially ensuring that the scope of AMS studies extends beyond any specific stake holder, indication or intervention because an estimated 90% of human antibiotic use occurs in the community, resulting in an increasing proportion of resistant infections in this setting [248]. Community pharmacists, being primary custodians of medicines, are equipped with an understanding of the intervention modalities relevant to their practice setting, including provision of selfcare advice and delivering medications for uncomplicated infections, as well as having the knowledge and skills necessary to carry out and sustain AMS interventions [112]. This review found that the community pharmacies were not involved in the majority of the studies.

Community pharmacists can be involved in educating the public on the appropriate use of antibiotics and intervening with prescribers when a prescription appears inappropriate. There is also a need to strengthen the collaboration between prescribers and community pharmacists to involve and empower community pharmacists in AMS. For example, most patients with acute URTI require only symptomatic management, using over the counter medicines and monitoring of their symptoms; few will need an antimicrobial [249]. Changes in the community pharmacy structure, retail model and legal framework towards empowering community pharmacists to undertake AMS can improve their capability. Education, incentivisation and persuasion can all assist to enhance the current capacity of the community pharmacist in AMS [250]. Recently a number of publications describing interventions around prescriber-pharmacist collaboration have been published, most notably from the US where, in some states, the concept of collaborative practice agreements (CPAs) is gradually being introduced. It gives community pharmacists autonomy in the care they provide to patients and can serve as a foundation for the implementation of AMS frameworks. A CPA is a voluntary agreement between one or more prescribers and pharmacists which delegates authority under defined conditions and/or limitations toward a common goal. This can be a provider/prescriber making a diagnosis, supervising patient care and referring patients to a community pharmacist under a protocol that allows the pharmacist to perform specific patient care functions which recently included POCT for some regions/states [112].

The other AMS interventions in which community pharmacists have been involved include delayed supply of antibiotics [108, 119], point of care testing [120, 121], prescriber education [122-125], public awareness [126] and the provision of self-care advice [127, 128] to patients with upper respiratory infections. Moreover, the health care system could benefit from the consultation and advisory services of community pharmacists in order to optimise antimicrobial use for urinary tract infections [129-131] and dental practices [132, 133], as well as from enhanced inter-professional collaboration. There are also studies supporting community pharmacists in their involvement in developing practical AMS frameworks for the community through leadership, facilitation and communication initiatives [126, 128, 134].

2.4.3 Limitations

Several limitations of our review need to be acknowledged. Only studies published in English from 2008 to 2020 were included; however, AMS as a term was not widely used before 2008. Furthermore, only two of the included studies [57, 62] discussed that the AMS interventions should be sustained over a long-term. Moreover, publication bias is expected, as studies with positive results tend to be published more often than those with negative findings.

2.4.4 Implications

Given the global threat imposed by increasing AMR, it is important to develop and implement an AMS framework in community settings, even as we await further data. Future large-scale studies, involving multi-faceted interventions, which focus on the sustainability of the outcomes are required if implementation of AMS in the community is to be optimised. The ultimate aim of AMS interventions is to improve health and that can be only achieved with sustained antimicrobial optimisation. Only two articles included in the literature review discussed regarding the sustainability of the AMS interventions [57, 62], hence sustainability of the AMS intervention is a major challenge to address. The reasons for this problem need further elucidation but this literature review found that the impact of AMS intervention(s) levels off and regress with time and lack of monitoring, the Hawthorne effect. Further research is required in this area to determine what can be done to enhance sustainability. It is recommended from this literature review that the long-term evaluation of sustainability should be made a vital part of any AMS intervention to optimise antimicrobial use. It is suggested that high quality randomised clinical trials are required to improve the evidence base for sustained success of AMS interventions and this should be addressed in the research methodology.

Pharmacists are core members of AMS teams in hospitals and have the potential to undertake multiple roles across the patient care continuum. Barriers and facilitators to the AMS role of community pharmacists need to be investigated to understand and present ways for active participation in community AMS initiatives.

Figure 1 Flow diagram of review of literature

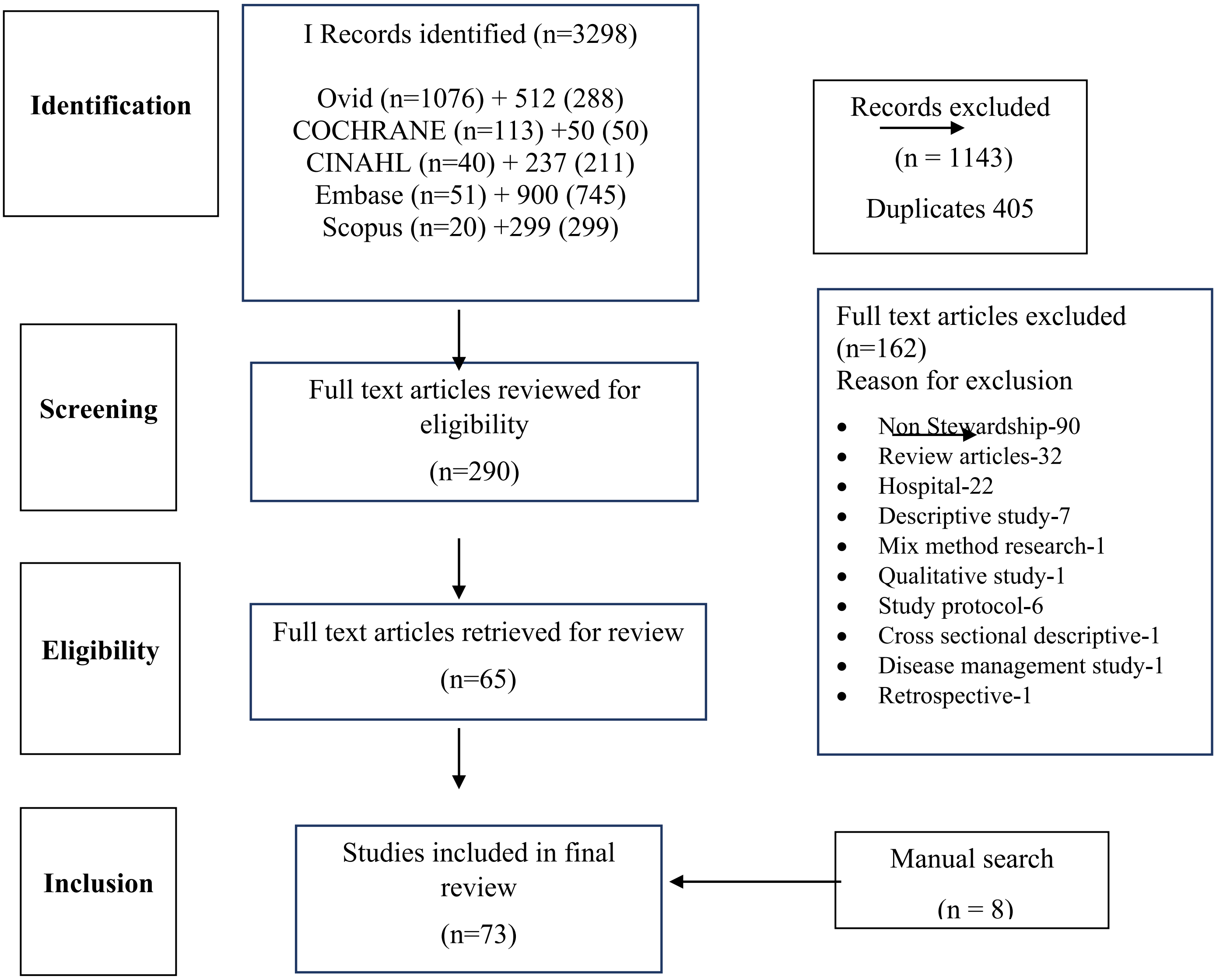

Table 1 Study characteristics

(N = 73)

Variables		No. of studies, n	Successful %	Unsuccessful %
Geographic distribution	Europe	40		
	North America	25	85.7	14.3
	Others	08	100	0
Study design	Cluster randomised controlled trials	29	68.8	31.2
	Randomised controlled trials	20	86.7	13.3
	Quasi experimental studies	17	100	0
	Control before and after studies	07	60	40
Type of infections	Respiratory tract infections	51	77.8	22.2
	General infections	14	100	0
	Urinary tract infections	07	100	0
	Dental infections	01	0	100
Type of interventions	Single component	26	73.3	23.7
	Multifaceted (including ACFs)	36 +11	81.5	18.5

Appendix 1 Search Strategy

<u>Ovid MEDLINE(R)</u>

1. antibiot$.mp. or exp antibiotics/ 2. antimicrob$.mp. 3. exp Anti-Bacterial Agents/ 4. exp Anti-Infective Agents, Urinary/ 5. exp Cross Infection/ 6. exp Community-Acquired Infections/ 7. exp Respiratory Tract Infections/ 8. exp Wound Infection/ 9. exp Catheter-Related Infections/ 10. exp Vancomycin Resistance/ or exp Vancomycin/ or vancomycin.mp. 11. aminoglycosides.mp. or exp Aminoglycosides/ 12. fluoroquinolones.mp. or exp Fluoroquinolones/ 13. broad spectrum antibiotics.mp. 14. carbapenems.mp. or exp Carbapenems/ 15. exp Cephalosporins/or broad spectrum cephalosporins. mp.

16. or/1-15

17. exp Education/or education.mp. 18. information campaign.mp. 19. audit.mp. 20. feedback.mp. or exp Feedback/ 21. dissemination.mp. or exp Information Dissemination/ 22. provider reminders.mp. 23. computerized medical records.mp. or exp Medical Records Systems, Computerized/ 24. exp Physician Incentive Plans/ or financial incentives. mp. 25. discharge planning.mp. 26. guideline implementation.mp. 27. guideline adherence.mp. or exp Guideline Adherence/ 28. exp Quality Assurance, Health Care/ or quality assurance.mp. 29. program evaluation.mp. or exp Program Evaluation/ 30. exp Practice Guideline/ 31. exp Physician's Practice Patterns/ 32. exp Drug Prescriptions/ 33. exp Drug Utilization/

34. or/17-33

35. randomized controlled trial.mp. or exp Randomized Controlled Trial/ 36. controlled clinical trial.mp. or exp Controlled Clinical Trial/ 37. intervention study.mp. or exp Intervention Studies/ 38. Comparative Study/ 39. experiment.mp. 40. time series.mp. 41. pre-post test.mp. 42. (randomized controlled trial or controlled clinical trial). pt. 43. (randomized controlled trials or random allocation or clinical trial or double blind method or single blind method).sh. 44. exp clinical trial/ 45. (clin$ adj25 trial$).ti,ab. 46. ((singl$ or doubl$ or trebl$ or trip$) adj25 (blind$ or mask$)).ti,ab. 47. (research design or placebos).sh. 48. (placebo$ or random$).ti,ab. 49. exp Double-Blind Method/ 50. exp cohort studies/ or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or comparative study/ or follow-up studies/ or prospective studies/ or cohort.mp. or compared.mp. or multivariate.mp. (4148897) 51. (“time series” or pre-post or “Before and after” or intervention).tw.

52. or/35-51

53. 16 and 34 and 52

54. limit 53 to English language

55. limit 54 to humans

56. limit 55 to yr= "2008 -Current"

57. (influenza$ or antimalar$ or malaria$ or prophylax$). mp.

58. 56 not 57.

Chapter 3: Tasmanian study

A manuscript describing the pilot study conducted in Tasmania has been published in the International Journal of Clinical Pharmacy. An electronic reprint is provided.

Rizvi T, Thompson A, Williams M, Zaidi STR. 'Perceptions and current practices of community pharmacists regarding antimicrobial stewardship in Tasmania'. Int J Clin Pharm, 2018. Oct;40(5):1380-1387. doi: 10.1007/s11096-018-0701-1. Epub 2018 Aug 2. PMID: 30069668; PMCID: PMC6208572

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RESEARCH ARTICLE

Perceptions and current practices of community pharmacists regarding antimicrobial stewardship in Tasmania

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Abstract

Background Despite increasing interest in antimicrobial stewardship (AMS), little is known about the related practices and perceptions of community pharmacists. *Objective* To develop and validate a questionnaire to measure the current practices of, and barriers to, community pharmacists' participation in AMS. *Setting* Community pharmacists in Tasmania, Australia. *Method* A questionnaire to explore AMS knowledge, current practices and perceptions of community pharmacists was developed. It was designed after a rigorous literature review, expert opinion and feedback from a group of community pharmacists. A convenience sample of 140 Tasmanian community pharmacists was used for this study. Cronbach's alpha and exploratory factor analysis (EFA) were used for reliability and validity. The questionnaire was hosted online, a link to which was sent by invitation e-mails, fax and post to community pharmacists in Tasmania, Australia. *Main outcome measure* Current AMS practices, perceived importance, barriers and facilitators of AMS. *Results* Eighty-five pharmacists responded to the survey yielding a response rate of 61%. EFA identified one factor solution for each of three perceptions scales and showed acceptable reliability. The Cronbach's alpha of perceived importance-understanding was 0.699; perceived importance-motivating was 0.734; perceived support from GPs was 0.890; operational barriers was 0.585; general facilitators was 0.615. Most pharmacists reported that they counselled patients on adverse effects (86%), drug interactions (94%) and allergies (96%). In contrast, less than half (43%) intervened with prescribers, regarding antibiotic selection. Lack of training, lack of access to patients' records, limited interactions with general practitioners and absence of a reimbursement model were major barriers limiting community pharmacists' participation in AMS. *Conclusion* The questionnaire was of acceptable reliability and validity; a larger study will further contribute to its reliability and validity. Future studies utilising the questionnaire at national and international levels may provide further insights into the determinants of community pharmacists' involvement in AMS.

Keywords Antimicrobial · Australia · Perception · Pharmacist · Practice · Antimicrobial stewardship · Survey

Impact of findings on practice statements

- An improved understanding of routine practices and perceptions of community pharmacists related to antimicrobial stewardship can assist in the development and implementation of antimicrobial stewardship related initiatives in community settings.
- Community pharmacists are willing to and capable of playing an important role in helping optimise antimicrobial use by educating patients and effectively interacting with prescribers, although a number of barriers may currently be limiting their participation.
- Knowledge surrounding current practices and perceptions of community pharmacists regarding antimicrobial stewardship are limited. Future research into the barriers to and facilitators of community pharmacists optimising antimicrobial use is required.

Electronic supplementary material The online version of this article (https ://doi.org/10.1007/s1109 6-018-0701-1) contains supplementary material, which is available to authorized users.

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Introduction

Increasing antimicrobial resistance (AMR) is a major global threat to human health [1]. If not tackled urgently, AMR will cause 10 million deaths annually by 2050 [2]. Antimicrobial stewardship (AMS) refers to the coordinated interventions designed to measure and improve the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug, dose, duration of therapy and route of administration [3]. AMS is high on the agenda of global health organisations and currently there is an increasing interest in community based AMS initiatives, as this is where the majority of antibiotic use occurs, much of which is inappropriate [4].

Community pharmacists can play an integral role in AMS programs within community settings for various reasons. Firstly, pharmacists are delivering value added services beyond their traditional dispensing duties [5]. Secondly, they are one of the most frequently seen healthcare professionals and serve as the first point of contact for seasonal viral respiratory tract infections - the most common conditions in which inappropriate use of antibiotics has been noted [6]. Thirdly, community pharmacists often liaise between patients and various service providers, and are well positioned to operationalise any AMS framework. Little is known about the current practices of community pharmacists in the developed world. An improved understanding of these issues can assist in the development and implementation of AMS initiatives in community settings. Some of the previous studies were conducted in countries where antibiotic prescribing and dispensing are neither reimbursed nor well regulated, thus making these research findings less applicable in developed countries [7, 8].

In Australia, approximately 27 million antibiotic prescriptions are dispensed annually [9] and antimicrobial use is 20% above the average of countries in the Organisation for Economic Cooperation and Development [10]. To address this issue, the Australian government released its first antimicrobial resistance strategy in 2015 [11]. The Australian government-funded National Prescribing Service MedicineWise (NPS-MW) is playing an important role to reduce antibiotic use in the community by raising awareness through educational initiatives such as the "Resistance Fighter Campaign" and "Antibiotic Awareness Week" [12]. In Australia, strict regulatory restrictions exist and antibiotics cannot be dispensed without a prescription [13]. However, once a prescription is issued, it is generally valid for one year and in many cases prescribing software automatically defaults to including a repeat. Furthermore, dispensing software in Australian community pharmacies has no interface with the prescribing software and therefore, pharmacists cannot access a patient's clinical information or laboratory data [13]. This further limits Australian community pharmacists' participation in AMS initiatives. Little is known about the current practices and perceptions of pharmacists working in the community sector.

The primary aim of our study was to develop and validate a questionnaire to measure the perceptions and practices of Australian community pharmacists regarding AMS. A secondary aim was to determine community pharmacists' awareness of and engagement with NPSMW's initiatives designed to reduce AMR. The study was conducted in the Australian state of Tasmania, which has a population of around 520,000 and a geographical area similar to that of the Republic of Ireland. The study findings can help to inform AMS frameworks for community pharmacists in Australia.

Ethics Approval

This study received approval from the Tasmanian Human Risk Ethics Committee (HREC) in April 2016 (H0015673).

Method

Survey development

We generated an item pool based on a thorough literature review with key words related to antimicrobial stewardship, community and pharmacists [7, 11, 14–20]. STRZ reviewed, modified and organised this item pool according to Australian pharmacy practice. A demographic section was also introduced at this stage. The questionnaire was then reviewed by AT and a section on items related to the NPSMW initiatives was included. Following the initial review, the questionnaire was edited, based on limited piloting with researchers and practising pharmacists working in the Division of Pharmacy at the University of Tasmania. The final questionnaire is available as supplementary material. A Likert-type agreement scale was used for questions around current practices and perceptions.

Survey deployment

The questionnaire was hosted online using the Lime Survey® portal. A convenience sample of 140 community pharmacists across Tasmania was invited to participate in the study via e-mail, fax and post during the first week of May 2016. Subsequently, copies of the questionnaire, with a standard invitation letter, were faxed and posted to pharmacies from where there had been no initial response and a paper survey with a self-addressed reply paid envelope was posted. The invitation letter included a web link to the questionnaire and a mobile-enabled scanning code (QR code) directing participants to the questionnaire. Two reminders were sent on a fortnightly basis after faxing/posting. Participants were offered the chance to win one of five gift cards selected by a draw conducted at the end of the study.

Data analysis

Exploratory factor analysis (EFA) was used to examine the internal structure and construct the validity of the perception scales. Maximum likelihood technique with the oblique rotation was employed. The items having a rotated factor loading of at least 0.55 or above [21] were retained for each factor. Qualitative feedback from the participants was discussed amongst the investigators when loadings were ambiguous. Cronbach's alpha was used to determine the reliability of individual factors. Qualitative comments were analysed using a constant comparative approach to identify various themes, under the guidance of STRZ, without any specific software. Univariate linear regression was employed to identify variables and factors associated with the participants' scores on the current AMS practices section of the survey. Variables with a p value ≤ 0.20 were included in the multivariate linear regression model. All statistical analyses were performed using SPSS version 22 (IBM Inc., Chicago, IL).

Results

85 of the 140 community pharmacists responded

Table 1 Demographics of survey respondents

Categories	Total (%)
Gender (n = 63)	
Female	41 (65%)
Male	22 (35%)
Age (n = 62)	
21–30	10 (16%)
31–40	21(34%)
41–50	14 (23%)
51 and above	17(27%)
Experience as community pharmacist (n = 64)	18(28%)
Less than 10 years	15 (23%)
10–19 years	13 (20%)
20–29 years	18 (28%)
30 years or more	
Education (n = 65)	52 (80%)
Bachelor's degree in Pharmacy	3 (5%)
Master's degree in Pharmacy	3 (5%)
Doctorate degree in Pharmacy	7 (10%)
Other	
Location (n = 65	40 (62%)
Metro	25 (38%)
Rural	

to the survey, yielding a response rate of 61% with the majority of respondents being female (65%) (Table 1). A wide distribution of age and experience was noted among the participants ranging from 23 to 70 years and 1–50 years respectively. Most participants (80%) had an undergraduate pharmacy degree as their highest qualifications.

Validity and reliability of the survey tool

Appendix 1 in "Electronic supplementary material" shows the results of EFA and Appendix 2 in "Electronic supplementary material" shows the results of reliability analysis, including total item statistics. The rotated solution for the perceived importance scales showed two factors comprising perceived understanding of AMS and perceived motivating factors of AMS (Cronbach Alpha 0.699 and 0.734 respectively). The EFA of the perceived barriers scale yielded a two-factor solution comprising perceptions regarding support from GPs and operational barriers (Appendix 1 in "Electronic supplementary material"). The Cronbach's alpha of the perceived support from GPs and the operational barriers scale was 0.89 and 0.58, respectively. The EFA of perceived facilitators scale yielded one-factor solution. The Cronbach's alpha of the general facilitators' scales was 0.615. Items on monetary compensation and public image of pharmacists' role in AMS were retained because of a strong support from the qualitative feedback on these issues.

Results of the study

Awareness of NPS-MW initiatives

The majority (63%) of pharmacists knew the term 'antimicrobial stewardship', although 75% reported an improved understanding after reading the provided definition. Most respondents were aware of the general (80%) and specific (72%) NPS-MW quality initiatives, although less than half (45%) were aware of the resources available to them. Around a quarter of the respondents reported that they are taking more interest (24%) and making more interventions (27%) regarding antibiotic use due to the NPS-MW's initiatives. Lastly, nearly half of the participants (53%) reported that they would be willing to participate in future AMS initiatives if resources were to be made available.

Current practices of AMS

Pharmacists frequently contacted prescribers relating to allergies, dosing or drug interactions (Table 2). On the

Table 2 Current AMS practices of Tasmanian community pharmacists

Scale and items	Participant's response, %		Median (IQR)
	Scoring ≤ 3	Scoring ≥ 4	
Current AMS practices			
Providing clear messages on expected side effects (n = 72)	13.9	86.1	4 (4–5)
Providing clear messages what should be done if the patient experiences side effects (n = 72)	22.2	77.8	4 (4–5)
Contacting the prescriber if the patient is allergic to the prescribed antibiotic (n = 72)	1.4	98.6	5 (5–5)
Contacting the prescriber if the antibiotic dose/frequency is too high or too low (n = 71)	14.1	85.9	5 (4–5)
Contacting the prescriber if the prescribed antibiotic involves a drug interaction (n = 70)	2.9	97.1	5 (5–5)
Contacting the prescriber if the choice of antibiotic may not be optimal (n = 71)	53.5	46.5	3 (2–4)
Recommending OTC/self-care treatment to patients with symptoms of infection not needing antibiotics (n = 71)	4.2	95.8	5 (4–5)
Referring patients to a general practitioner when symptoms are suggestive of an infection (n = 69)	1	99	5 (5–5)
Providing advice when it would be appropriate to use the repeat (n = 70)	17.1	82.9	4 (4–5)
Discussing with the patient to determine if it is appropriate for them to use the presented repeat (n = 72)	30.6	69.4	4 (3–5)

Current practices measured on a scale of 1–5, where 1 = do not practise at all and 5 = practise all the time *n* Number of participants, *IQR* inter quartile range

contrary, pharmacists less commonly contacted prescribers if they considered the choice of antibiotic to be inappropriate.

Respondents indicated that they were referring patients to see GPs if they suspected an infectious presentation that might need an antibiotic prescription but, when this was not the case, pharmacists reported that they were invariably managing patients by offering over the counter medicines (95.8%). Pharmacists were commonly ascertaining the need for an antibiotic when a patient presented a repeat prescription (82.9%).

Perceptions and association with AMS practices

Most pharmacists agreed that AMS programs in community pharmacy would lead to a reduction in inappropriate antibiotic use and the costs associated with managing infections (Table 3). Similarly, pharmacists believed

Table 3 Perceived importance and barriers to participate in AMS in community pharmacy

Scales and items	Participant's response, %		Median (IQR)
	Scoring ≤ 4	Scoring ≥ 5	
Perceived importance of AMS-understanding of the role			
Community pharmacists can play an important role in AMS (n = 68)	2.9	97.1	7 (5–7)
AMS will reduce health care costs associated with infections (n = 68)	21.6	78.4	7 (5–7)
AMS will reduce inappropriate antibiotic use (n = 68)	17.6	82.4	5 (5–7)
Perceived importance of AMS-motivating forces			
AMS will enhance the public image of pharmacists (n = 67)	20.9	79.1	6 (5–7)
AMS will enhance the job satisfaction of pharmacists (n = 67)	17.9	82.1	6 (5–7)
Perceived barriers of AMS-operational barriers			
I do not have the required training to participate in AMS (n = 66)	63.6	36.4	4 (3–5)
I do not have enough time to participate in AMS (n = 64)	75	25	3 (3–5)
Limited access to patient records to review the appropriateness of antibiotic prescriptions (n = 65)	4.6	95.4	6 (5–7)
There aren't any standard guidelines to implement AMS (n = 62)	33.9	66.1	5 (4–6)

Perceived barriers of AMS-perceived support from GPs			
GPs are not receptive to pharmacists intervening on the choice of an antibiotic (n = 63)	34.9	65.1	5 (5–6.25)
GPs are not receptive to pharmacists intervening on the dose and dosage form of an antibiotic (n = 64)	64.1	35.9	3 (3–6)
GPs are not receptive to pharmacists intervening on the duration of an antibiotic (n = 62)	75.8	24.2	3 (3–6)

Perceived importance and perceived barriers were measured on a scale of 1–7, where 1 = strongly disagree and 7 = strongly agree *n* Number of participants, *IQR* inter quartile range that they could play an important role in implementing AMS initiatives and their participation in AMS programs would lead to a better public image and enhanced job satisfaction. Pharmacists also indicated that the lack of access to patients' medical records and objective laboratory information limited their participation in AMS. Pharmacists also felt that GPs do not welcome their intervention regarding choice of antimicrobial prescription (Median = 5, IQR 5–6.25 Scale 1–7). On the contrary, interventions related to the dose, duration or dosage form of antibiotics were perceived as welcomed by GPs. Pharmacists were mostly neutral about their lack of training as a barrier to their participation in AMS. Likewise, most of them did not consider lack of time as a barrier in their AMS role (Table 3). Facilitators related to public awareness campaigns, collaboration with GPs, access to antibiotic guidelines and patients' clinical and laboratory data, were all considered as most helpful in increasing pharmacists' AMS involvement (Table 4).

The univariate linear regression analysis identified three variables that showed some degree of association with the total scores for the AMS practices section of the survey (p value ≤ 0.2). The three variables were: willingness to participate in future AMS initiatives, total scores of general facilitators scale and perceived importance scale. The multivariate linear regression analysis did not identify any of these variables as having a significant association with the AMS practices of the community pharmacists (Table 5).

Qualitative feedback

Qualitative comments were analysed using a constant comparative approach to identify various themes under the guidance of STRZ. Pharmacists showed great interest in providing qualitative feedback via free text comments. The main themes from the qualitative feedback were: contextual limitations of community pharmacists, improper use of repeat prescriptions, need for public awareness, lower than recommended dose of antibiotics in children and the impact of AMS on the business model of the pharmacy. Software was not used for qualitative analysis. Details of these comments are presented in Table 6.

Discussion

We report the development and validation of the first questionnaire to measure the current practices and perceptions of AMS amongst Australian community pharmacists. The mixed method approach of using EFA, expert opinion and qualitative feedback to validate the survey tool was found useful in retaining important items for each section, while reducing the size of the questionnaire to a manageable length. The three perception scales demonstrated

Table 4 Perceived facilitators of AMS in community pharmacy settings

Scales and items	Participant's response, %		Median (IQR)
	Scoring≤3	Scoring≥4	
Perceived facilitators of AMS-general facilitators			
Increased provision of education activities regarding AMS (n = 65)	6.2	93.8	5 (4–5)
Better collaboration with local GP practices (n = 65)	1.5	98.5	5 (4–5)
Clarifications of the duties of pharmacists' professional organisations (n = 63)	27	73	4 (3–5)
Better access to patients' clinical and laboratory data (n = 64)	7.8	92.2	5 (4–5)
Perceived facilitators of AMS-operational facilitators			

Public awareness initiatives highlighting community pharmacists in AMS (n = 66)	10.6	89.4	5 (4–5)
Monetary compensation for the time involved in AMS programs (n = 64)	18.8	81.2	4 (4–5)

Perceived facilitators measured on a scale of 1–5, where 1 = unhelpful and 5 = most helpful *n* Number of participants, *IQR* Inter quartile range [a] Items not loaded on any factor but retained based on qualitative analysis as participants were very vocal about the issues covered by these items

Table 5 Multivariate linear regression analysis: predictors of Tasmanian Community Pharmacists' participation in AMS (n = 59)

Predictor	Unstandardised β	Standardised β	*P* value	95% CI range
Willingness to participate in future AMS initiatives	0.13	0.05	0.07	− 0.56–0.82
Total scores on the perceived importance scale	0.53	0.25	0.20	− 0.06–1.12
Total scores on the general facilitators scale	0.46	0.17	0.70	− 0.25–1.18

Table 6 Qualitative feedback from the Tasmanian Community Pharmacists

Theme	Example statements
Contextual limitations	Unlike hospital settings, implementation of AMS is certainly a challenge in the community. GPs prescribe antibiotics due to the pressure of patients. Are there any ID consultants involved in community AMS? Who is going to give approval and decide the duration?
	Not sufficient information about ailment or patient to make a call about appropriateness of antibiotic
	Until we are provided full history, pathology and diagnosis, very difficult to implement
	It is not always easy to determine what infection is being treated in a patient, as we have not made the diagnosis and if the patient can communicate this appropriately then ensuring the most suitable antibiotic can be difficult as it may be specific to a sputum sample, culture etc. This could be a hurdle in AMS.
	I think you cannot have an AMS program in community pharmacies without any prior agreement with the prescribing doctors for those pharmacies, otherwise will cause client confusion, and worsen the relationship with doctors. Also considering that pharmacists lack diagnostics skills, it is the role of the doctor to determine the need for an antibiotic and not the pharmacist to question the doctor's decision.
Increase public awareness	I always explain the expected duration whether it is less than or more than an initial supply and discourage the use of repeats weeks after the original has been filled.
	Many patients still expect to come away from a doctor's appointment with an antibiotic prescription, especially for a child with respiratory symptoms or middle ear infection-despite these often being self-limiting.
	I believe that more public education is necessary for people to understand when antibiotics are appropriate and when they are not.
Policy support to define pharmacist's role	Pharmacists are definitely in an ideal position to be able to intervene when inappropriate antibiotic use is evident—however, the means by which the program is introduced is essential.
	Pharmacists already have the knowledge and correct attitude to reduce antibiotic misuse, we just need the authority.
	I genuinely think most people are unaware of what pharmacists are able to do and what we are supposed to do.
Improper use of repeat prescriptions	A good start would be modifying the prescribing software to force prescribers to actually decide whether a repeat is necessary or not, rather than automatically defaulting to a repeat for every patient.
	I think that antibiotic scripts should have a two week expiry—unless for a long-term condition. It would save repeats being saved and presented at other times …
Lower than recommended dose of antibiotics in children	Often once a week have to call doctor to adjust dose of antibiotic for children as often under dosed. Often doctors don't tell if they need repeat or not.
	Notice lower then recommended children antibiotic doses, when double check with doctors they prefer to use lower doses anyway
Impact of AMS on the business model of pharmacy	There is absolutely a need to have better remuneration for pharmacies involved in AMS programs—if the pharmacist involved is effectively performing their role, they may in fact be reducing script volume of antibiotics and thus negatively affecting the pharmacy's takings. For instance, if a pharmacist encourages a doctor to cancel a prescription for an antibiotic that is unnecessary, the pharmacy is missing out on (for example) a $10 sale. The whole process of contacting the GP, then discussing the decision with the patient may take up 15–20 min of the pharmacist's time and ultimately the pharmacy is down $10.
	We are time poor, with rapidly reducing income with health dept. and govt. who do not respect us. But still expect us to enable initiatives with little or no remuneration

reasonable internal validity as evident from the results of EFA and an acceptable reliability demonstrated by a Cronbach's alpha of > 0.5 [21]. Khan *et al*. [7], Erku [8] and a recent study by Sarwar *et al*. [22] have surveyed Malaysian, Ethiopian and Pakistani community pharmacists about AMS, respectively. The contexts of pharmacy practices in these countries are significantly different from those found in most Western countries, including Australia where antibiotics are available only with a valid prescription. Additionally, based on the reported results, the authors have not conducted a formal exploratory factor analysis to examine the internal structure of the questionnaire.

Principal findings of the pilot survey

Our findings highlight that Australian pharmacists contribute to triaging common infectious presentations, determining those conditions that may require medical attention and those which are minor ailments amenable to self-care or management with over the counter medicines. This particular role of community pharmacists is not as widely appreciated in Australian settings as it has been in other countries. For example, provision of advice for minor ailments is considered a reimbursable activity in the United Kingdom [23]. We found that pharmacists were less comfortable about intervening with the choice of antibiotics or advising patients on the use of repeat prescriptions when compared with other activities, such as intervening on the dose and duration of antibiotics and counselling patients regarding the adverse effects of antibiotics. Qualitative comments provided further clarification about the contextual limitations of the Australian community pharmacy practice in determining the appropriateness of antibiotics or contacting GPs for interventions related to paediatric antibiotic dosing. These findings are not surprising, as community pharmacists in Australia do not have access to a patient's clinical and laboratory data. Additionally, unlike the UK and most of Scandinavia, community pharmacies in Australia do not operate within a healthcare network which may be limiting one-on-one interaction between GPs and pharmacists [24].

Most pharmacists in this study rated the importance of AMS highly, considering it a source of motivation and learning, potentially enhancing the public image of the profession. Likewise, pharmacists also believed that AMS programs in the community will reduce inappropriate antibiotic use and healthcare costs. Our results are consistent with the study of Burger *et al*. [25] in which the majority of respondents indicated that AMR is a worldwide problem and pharmacists have an important role to play in tackling this problem. The perceived barriers pharmacists reported in the study included lack of access to patient's clinical and laboratory data, and lack of co-operation from the GP when the community pharmacist intervenes regarding selection of antibiotics, both of which can be inter-related. Our findings are in line with a systematic review by the National Institute of Health Research, England [26] which reported that barriers to implementing AMS include lack of resources, patients' expectations regarding antibiotics and the influence of colleagues on the selection of antibiotics. Most of the respondents believed that educational activities targeted towards pharmacists and patients will enable them to perform AMS duties efficiently. Similarly, most of the community pharmacists suggested improved collaboration with prescribers and having access to patients' clinical and laboratory data would be helpful, enabling them to better participate in AMS. This is consistent with the updated statement from the International Pharmaceutical Federation which stressed the importance of pharmacist and public educational initiatives in implementing AMS [27].

Awareness of AMS and national quality initiatives

The findings of the pilot study identified a gap between AMS awareness and utilisation of available resources by community pharmacists. More efforts to engage pharmacy students, interns and pharmacists are required to develop community pharmacists' competency in AMS. The majority of respondents were not regularly referring to the resources and activities of NPS-MW. Almost half of the respondents reported that they are not currently utilising the educational resources available to them but would definitely employ them if they could gain easy access. Globally, an increasing number of learning and training courses and toolkits are offered by public and private organisations, institutions and countries [28–31], some of which are free web-based online courses and others are inter-professional curricula to increase pharmacists' competency in AMS. There is a clear a need for such initiatives to help fill this AMS knowledge gap for Australian community pharmacists.

Limitations and strengths

The findings of our study should be interpreted with some caution. We only examined the views of pharmacists from one Australian state (Tasmania) and the views may not be generalisable to all Australian community pharmacists. Given the traditionally poor response rate with survey studies, we utilised a convenient sample drawn from a pool of pharmacists whose details are on file in the Division of Pharmacy, at the University of Tasmania, and this may further limit the generalisability of our findings. In contrast, a few specific strengths of the study should also be highlighted. To the best of our knowledge, this is the only study to report the development and validation of a questionnaire to measure community pharmacists' perceptions of, and barriers to, AMS in the community setting. We employed a robust process combining quantitative and qualitative data, while supplementing it with expert opinion to develop and refine the questionnaire.

Conclusion

The newly developed questionnaire to measure pharmacists' perceptions of and barriers to, AMS in community settings demonstrated acceptable reliability and validity. Pharmacists were supportive of their involvement in the AMS, although they highlighted some important barriers limiting this involvement. A future Australia-wide study, employing this newly developed tool, will provide more data to examine the questionnaire's reliability and validity, while also providing further insights into the perceptions and practices of community pharmacists regarding AMS at a national level.

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Conflicts of Interest None.

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Chapter 4: National Study

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Validation and implementation of a national survey to assess antimicrobial stewardship awareness, practices and perceptions amongst community pharmacists in Australia

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ABSTRACT

Objectives: Antimicrobial stewardship (AMS) programmes are well established in hospitals, yet such programmes have not been widely implemented in the community. Understanding current practices and perceptions of community pharmacists about AMS may provide insights into the implementation of AMS in community pharmacies. The aims of this study were to validate a questionnaire to measure community pharmacists' perceptions of AMS and to explore barriers and facilitators to their involvement in community-based AMS initiatives.
Methods: A 44-item survey questionnaire comprising sections on demographics, AMS practices and perceptions of community pharmacists, and barriers and facilitators to AMS was hosted online. Community pharmacists were recruited through social media pages of community pharmacist groups across Australia. Cronbach's alpha and exploratory factor analysis were used to measure the reliability and validity of the survey tool, respectively.
Results: A total of 330 community pharmacists started the survey, with 255 of them completing at least one question. Pharmacists were more likely to intervene with general practitioners (GPs) (≥80% of the time) for allergies, dosing and drug interactions and were less likely to intervene if they felt the choice of antibiotic was inappropriate (45%). Major barriers limiting pharmacists' participation in AMS were lack of access both to patient data (82.6%) and to a standard guideline to implement AMS programmes (72.1%). Almost all pharmacists (98%) reported that better collaboration with GPs would improve their participation in AMS initiatives.
Conclusion: Future studies utilising the knowledge gained from this study may provide a framework for AMS in community pharmacy settings.

1. Introduction

The World Health Organization (WHO) has declared antimicrobial resistance (AMR) a major global threat. One of the strategies to reduce AMR is to control inappropriate use of antimicrobials [1]. Antimicrobial stewardship (AMS) is a set of co-ordinated interventions and initiatives to promote the appropriate and judicious use of antimicrobials without compromising patients' quality of healthcare [2]. The Australian Commission on Safety and Quality in Health Care (ACSQHC) recommends AMS programmes (ASPs) in hospitals [3], and pharmacists have a routine and recognised role in these programmes [4].

However, AMR is becoming a growing concern in the community, which is where most antimicrobials (88%) are prescribed, and one-half of these prescriptions are considered inappropriate [2]. Hence, there is an urgent need for engaging suitable resources and stakeholders, including community pharmacists, to support the implementation of such AMS initiatives in the community. Community pharmacists are currently offering several professional services such as health screening, vaccination and chronic disease management, suggesting their desire and willingness to translate their traditional supply-centred role into a more advanced clinical role [5,6].

There is an unmet need to ensure that measures are in place for effective participation of community pharmacists in AMS activities [6,7]. Therefore, to assess the current knowledge and perception of community pharmacists regarding AMS, we developed and tested a questionnaire in one state of Australia (Tasmania) [8]. The

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Table 1
Demographic characteristics of survey respondents (*N* = 255).

Characteristic	*n* (%)
Sex (*N* = 227)	
Male	78 (34.4)
Female	148 (65.2)
Prefer not to disclose	1 (0.4)
State/territory (*N* = 228)	
NSW	62 (27.2)
QLD	54 (23.7)
VIC	45 (19.7)
ACT	6 (2.6)
SA	20 (8.8)
WA	28 (12.3)
TAS	8 (3.5)
NT	5 (2.2)
Highest level of pharmacy education completed (*N* = 229)	
Bachelor's degree	177 (77.3)
Master's degree	33 (14.4)
Doctorate degree	3 (1.3)
Other	16 (7.0)
Age (*N* = 225)	Median 29 years (IQR 26–36 years)
Experience (*N* = 225)	Median 6 years (IQR 4–12 years)
Geographical location of work (*N* = 228)	
Metropolitan	158 (69.3)
Rural	63 (27.6)
Remote	7 (3.1)

IQR, interquartile range; NSW, New South Wales; QLD, Queensland; VIC, Victoria; ACT, Australian Capital Territory; SA, South Australia; WA, Western Australia; TAS, Tasmania; NT, Northern Territory.

resources were present (22%). Most of the respondents responded positively regarding the likelihood of pharmacies utilising the resources provided by the NPS MedicineWise (61%).

3.3. Current practices

The most frequent AMS activities reported by community pharmacists were contacting the prescriber about drug interactions (95.2%), allergies (98.4%) and antibiotic doses (83.8%) (Table 2). Pharmacists were less likely (44.8%) to contact prescribers if they considered the selection of an antibiotic to be inappropriate. Most of the respondents reported that they frequently guided patients regarding over-the-counter treatment options (88.9%) and referred patients to a general practitioner (GP) if symptoms were suggestive of infection (76.6%) (Table 2). Participants reported that they frequently provide clear messages on expected side effects (80.0%), however comparatively fewer reported that they explain what should be done if a patient experiences a side effect (74.5%). Similarly, most of the respondents frequently advise patients when it is appropriate to use an antibiotic repeat (85.1%), but fewer reported that they discuss with patients the appropriateness of a repeat antibiotic prescription at the time of dispensing (68.5%).

3.4. Validity and reliability of the perception scales

The survey results related to perception scales are outlined in Tables 3 and 4. The values of the Kaiser–Meyer–Olkin test and Bartlett's test of sphericity were 0.53 and $P < 0.001$, respectively, indicating the suitability of exploratory factor analysis (EFA) in the study sample [11] (see Appendix 2). PAF was used for extraction, and Oblimin with Kaiser Normalisation was used as a rotation technique. The rotated solution for the three perception scales yielded four factors: perceived importance of AMS, comprising 5 items (Cronbach's α = 0.787); perceived operational barriers to AMS, comprising 3 items (Cronbach's α = 0.637); perceived barriers related to GPs' support, comprising 3 items (Cronbach's α = 0.740); and perceived facilitators, comprising 6 items (Cronbach's α = 0.671) (see Appendix 2). The item related to monetary compensation did not load on any factor but was kept as a standalone item owing to its support in the qualitative data and as per the authors' opinion.

3.5. Perceived importance

Most respondents (94.8%) agreed that community pharmacists could play a vital role in implementing AMS in the community setting. Furthermore, a similar proportion of respondents perceived that the associated healthcare costs would be decreased (93.1%) and that inappropriate use of antibiotics would be reduced (91.9%) by improved community AMS. Pharmacists indicated that AMS initiatives in the community setting would increase job satisfaction (83.3%) and enhance the public image (80.9%) of community pharmacists.

3.6. Perceived barriers

The major barriers identified by the respondents were lack of access to patients' records to review the appropriateness of antibiotic prescriptions (82.6%) and lack of access to standard guidelines to implement AMS. Most pharmacists believed GPs are not receptive when pharmacists intervene regarding the choice of antibiotic (78.3%). However, most respondents did not consider lack of time (60.3%) or lack of training (54.4%) as barriers to AMS activities.

3.7. Perceived facilitators

The major facilitator identified by the respondents in carrying out AMS activities in the community was better collaboration with

Table 2
IQR of item scales: current antimicrobial stewardship (AMS) practices in community pharmacies.[a]

Scale/item	Participant's response [*n* (%)]		Median (IQR)
	Scoring ≤3	Scoring ≥4	
Providing clear messages on expected side effects (*n* = 255)	51 (20.0)	204 (80.0)	4 (4–5)
Providing clear messages on what should be done if a patient experiences a side effect (*n* = 255)	65 (25.5)	190 (74.5)	4 (3–5)
Contacting the prescriber if the patient is allergic to the prescribed antibiotic (*n* = 252)	4 (1.6)	248 (98.4)	5 (5–5)
Contacting the prescriber if the antibiotic dose/frequency is too high or too low (*n* = 253)	41 (16.2)	212 (83.8)	5 (4–5)
Contacting the prescriber if the prescribed antibiotic involves a drug interaction (*n* = 251)	12 (4.8)	239 (95.2)	5 (5–5)
Contacting the prescriber if the choice of antibiotic may not be optimal (*n* = 250)	138 (55.2)	112 (44.8)	3 (2–4)
Recommending OTC/self-care treatment to patients with symptoms of infection not needing antibiotics (*n* = 252)	28 (11.1)	224 (88.9)	5 (4–5)
Referring patients to a GP when symptoms are suggestive of an infection (*n* = 253)	6 (2.4)	247 (97.6)	5 (5–5)
Providing advice on when it would be appropriate to use the repeat prescription (*n* = 255)	38 (14.9)	217 (85.1)	4 (4–5)
Discussing with patient to determine whether it is appropriate for them to use the presented repeat prescription (*n* = 254)	80 (31.5)	174 (68.5)	4 (3–5)

IQR, interquartile range; OTC, over-the-counter; GP, general practitioner.
[a] Current practices measured on a scale of 1–5, where 1 = do not practice at all and 5 = practice all the time.

response of the pilot study was limited and therefore there was a need to validate the questionnaire on a larger scale. Hence, the objectives of this study were to implement and test the survey questionnaire at a national level in order to identify gaps in knowledge and to explore community pharmacists' current practices and perceptions regarding AMS.

2. Methods

2.1. Questionnaire

Data were collected through an online questionnaire that was developed and tested in another similar, but smaller, study (Fig. 1), details of which have been published elsewhere [8]. In brief, the

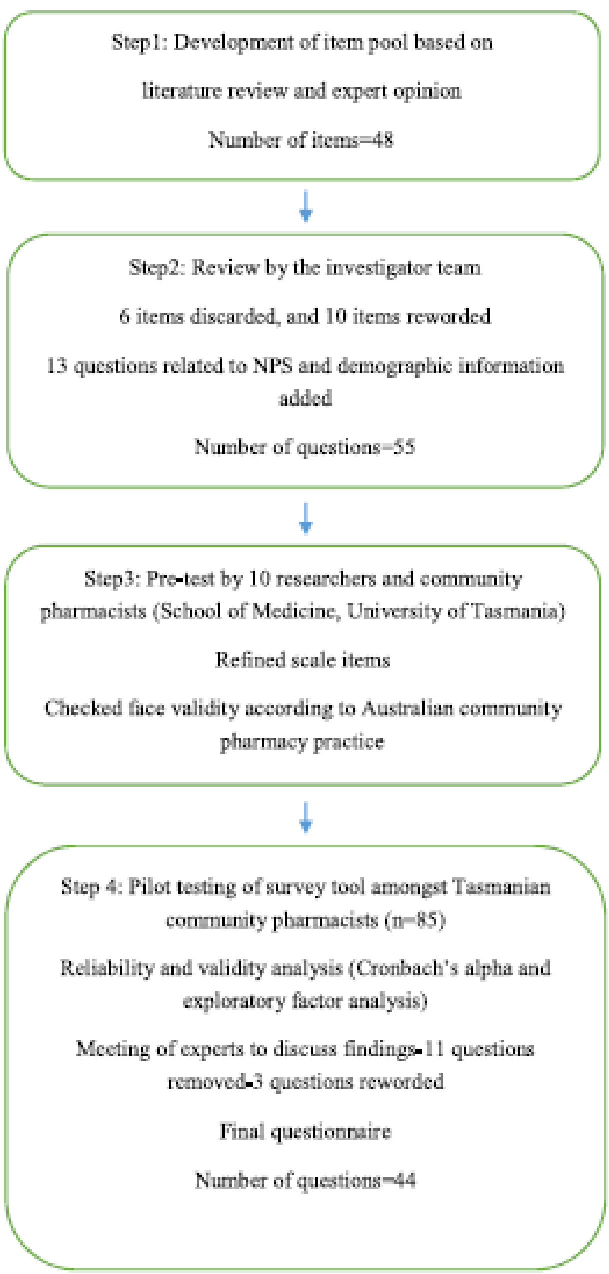

Fig. 1. Development of the questionnaire.

44-item survey questionnaire, comprising sections on: demographics; current AMS practices; the perceived importance of, barriers to and facilitators of AMS; as well as a section about the awareness of NPS MedicineWise initiatives (see Appendix 1). NPS MedicineWise is an Australian not-for-profit independent organisation that is leading national initiatives to reduce inappropriate antibiotic prescribing [9]. The MedicineInsight programme, Resistance Fighter campaign and Antibiotic Awareness Day are some of the key initiatives of NPS MedicineWise to make stakeholders aware of the AMR threat and to educate them regarding rational antibiotic use [9].

2.2. Survey implementation

The survey was hosted on the web survey platform LimeSurvey®, which is an open-source survey tool, between November 2016 to February 2017 [10]. Community pharmacists were invited through e-mails to the leading pharmacy chain stores and the Pharmaceutical Society of Australia. Advertisements on Facebook pages of pharmacist communities representing various states of Australia were also posted. The invitation e-mails and advertisements contained a link to the questionnaire along with a mobile-enabled scanning code (QR code) and details on how to enter a draw to win one of twenty A$50 gift cards. At the end of the survey, the winners of the draw were randomly selected.

2.3. Data analysis

Data collected via LimeSurvey® was exported to Microsoft Excel® (Microsoft Corp., Redmond, WA, USA) and IBM SPSS Statistics v.22 (IBM Corp., Armonk, NY, USA) for analysis. A mixed methods approach was adapted to analyse the results of different sections of the survey. Demographics were tabulated as numbers, frequencies, percentages and averages. Principal axis factoring (PAF) technique was used to determine the validity of perception scales, namely perceived importance of, barriers to implementation and facilitators of AMS in community pharmacies. Cronbach's alpha (α) was used to determine the reliability of the identified factors.

3. Results

3.1. Demographics

Table 1 presents the demographic characteristics of the community pharmacists who participated in the survey. A total of 330 community pharmacists accepted the invitation by clicking on the link, with 255 of them completing at least one question (as participants were able to skip questions). There was a proportionate distribution of responses from different Australian states and territories, with the majority (69.3%) from metropolitan areas. The median age of respondents was 29 years and their median experience was 6 years. The majority (74%) of participants felt that they were aware of the term 'AMS', although 86% of them reported a better understanding of AMS after reading the formal definition.

3.2. Awareness of the national quality initiatives

Most of the respondents knew about the resources provided by NPS MedicineWise related to rational use of antibiotics (74%) and were aware that NPS MedicineWise has dedicated 1 week for antibiotic awareness (73%). Most respondents knew about the 'Resistance Fighter' campaign co-ordinated by NPS MedicineWise (62%). However, fewer respondents reported using the patient education resources available from the NPS MedicineWise website (39%), whilst some respondents were not even aware that such

Table 3
IQR of item scales: perceived importance of and barriers to antimicrobial stewardship (AMS) in community pharmacies.[a]

Scale/item	Participant's response [n (%)]		Median (IQR)
	Scoring ≤4	Scoring ≥5	
Perceived importance of AMS			
Community pharmacists can play an important role in AMS (n = 248)	13 (5.2)	235 (94.8)	6 (5–7)
AMS will reduce healthcare costs associated with infections (n = 247)	17 (6.9)	230 (93.1)	7 (6–7)
AMS will enhance the public image of pharmacists (n = 246)	47 (19.1)	199 (80.9)	6 (5–7)
AMS will enhance the job satisfaction of pharmacists (n = 245)	41 (16.7)	204 (83.3)	6 (5–7)
AMS will reduce inappropriate antibiotic use (n = 248)	20 (8.1)	228 (91.9)	6.5 (5–7)
Perceived barriers to AMS: operational barriers			
I do not have the required training to participate in AMS (n = 239)	130 (54.4)	109 (45.6)	4 (3–5)
I do not have enough time to participate in AMS (n = 239)	144 (60.3)	95 (39.7)	4 (3–5)
Limited access to patients' records to review appropriateness of antibiotic prescriptions (n = 241)	42 (17.4)	199 (82.6)	6 (5–7)
There are no standard guidelines to implement AMS (n = 233)	65 (27.9)	168 (72.1)	5 (4–6)
Perceived barriers to AMS: perceived support from GPs			
GPs are not receptive to pharmacists intervening on the choice of antibiotic (n = 240)	52 (21.7)	188 (78.3)	6 (5–7)
GPs are not receptive to pharmacists intervening on the dose and dosage form of antibiotic (n = 240)	86 (35.8)	154 (64.2)	5 (4–6)
GPs are not receptive to pharmacists intervening on the duration of antibiotic (n = 240)	86 (35.8)	154 (64.2)	5 (4–6)

IQR, interquartile range; GP, general practitioner.
[a] Perceived importance and barriers were measured on a scale of 1–7, where 1 = strongly disagree and 7 = strongly agree.

Table 4
IQR of item scales: perceived facilitators of antimicrobial stewardship (AMS) in community pharmacies.[a]

Item	Participant's response [n (%)]		Median (IQR)
	Scoring ≤3	Scoring ≥4	
Increased provision of education activities regarding AMS (n = 234)	22 (9.4)	212 (90.6)	4 (4–5)
Public awareness initiatives highlighting community pharmacists in AMS (n = 234)	11 (4.7)	223 (95.3)	5 (4–5)
Access to guidelines for common community infections (n = 232)	6 (2.6)	226 (97.4)	5 (4–5)
Better collaboration with local GP practices (n = 234)	4 (1.7)	230 (98.3)	5 (4–5)
Clarification of the duties of pharmacists' professional organisations (n = 229)	38 (16.6)	191 (83.4)	4 (4–5)
Better access to patients' clinical and laboratory data (n = 234)	16 (6.8)	218 (93.2)	5 (4–5)
Monetary compensation for the time involved in AMS programmes (n = 231)	29 (12.6)	202 (87.4)	5 (4–5)

IQR, interquartile range; GP, general practitioner.
[a] Perceived facilitators measured on a scale of 1–5, where 1 = unhelpful and 5 = most helpful.

local GP practices (98.3%). Mirroring some of the responses to questions about barriers, pharmacists reported that facilitators would be the availability of one standard antibiotic guideline for prescribers and pharmacists, access to patients' clinical and laboratory data, public awareness campaigns, and provision of AMS-related educational activities for community pharmacists. Other facilitators considered somewhat helpful included monetary compensation and clarification of AMS duties expected of pharmacists by their professional organisations.

3.8. Qualitative analysis

A thematic analysis of the qualitative comments is presented in Appendix 3. The major issues highlighted by the respondents in carrying out routine AMS activities included: lack of access to patients' records and laboratory data; inappropriate use of antibiotic repeats; use of different antibiotic guidelines by prescribers; and lack of clarity regarding the AMS role of community pharmacists. Respondents further stressed that their limited role in AMS is due to lack of access to patients' records, which causes uncertainty as to why an antibiotic is in a given dose, dosage form and duration, hence they hesitate to intervene. Respondents also pointed out limited public awareness regarding AMR that leads to unnecessary demand for repeat antibiotic prescriptions. They specifically pointed out inconsistencies and apparent mistakes in doses prescribed for paediatric patients. Participants also pointed out operational limitations in carrying out AMS-related activities and they suggested that community pharmacists should be professionally recognised and compensated for the provision of AMS services. Participants reported that unnecessary prescribing of and consumer demand for antibiotics is gradually decreasing, but that this could be further reduced if a comprehensive AMS model is introduced in the community.

4. Discussion

The proven benefits of pharmacists in ASPs in hospital settings suggest that they can also play an important role in community pharmacy AMS services [12–15]. Whilst pharmacists are willing to contribute to AMS [16], so far the majority of AMS studies involving primary care interventions have been aimed only at GPs working in the USA, Europe or North America [17]. The results of the present study provide an insight into the AMS knowledge as well as the current practices and perceptions of Australian community pharmacists. A mixed methods approach was used to validate the survey tool developed in the pilot study published elsewhere [18]. Reliability analysis and EFA helped to examine the internal structure of the questionnaire.

4.1. Main findings

The results of this national study found that the majority of Australian community pharmacists are aware of the term 'AMS' but do not have an in-depth understanding of it. They need better access to AMS educational resources provided by the pharmaceutical bodies and agencies tasked with improving quality use of medicine, such as NPS MedicineWise. The study found that the majority of pharmacists perceive that the AMS resources of NPS MedicineWise are not effectively promoted and they are unable to easily access them. AMS education, policies and regulations in community settings are still evolving in other countries as well. According to the US Society of Infectious Diseases Pharmacists

(SIDP), pharmacists have an essential role in the implementation of ASPs and, without relevant knowledge of AMS, community pharmacists cannot play their desired role [6,19]. The current findings are in accordance with other studies in which community pharmacists were found to be willing to participate in educational activities related to AMS [20,21]. However, AMS-related educational intervention studies involving implementation of antibiotic guidelines, diagnostic skills and communication skills focus only on clinics and prescribers practicing in them, and there is a paucity of data regarding the role of community pharmacists in AMS [6].

While carrying out their routine pharmacy activities, most respondents agreed that they regularly provide patients with information regarding side effects and how to effectively use repeat antibiotic prescriptions, and guide patients to non-antibiotic symptomatic therapy alternatives. These results can be compared with the studies of Dyar et al. and Blanchette et al. confirming that community pharmacists are playing an important role in patient education, particularly about when and how to take prescribed antibiotics [6,22]. The survey participants also reported that they frequently intervene with prescribers if the dose, dosage form or duration of antibiotic is not appropriate and if there is a potential of drug interaction or allergy. However, pharmacists less frequently intervene with prescribers regarding choice of antibiotics. These results are similar to a study conducted in the USA regarding the role of pharmacists, where most of the pharmacists could not change the selection of antibiotics even knowing that it is not appropriate [23]. This finding may also relate to the lack of access to patients' records by pharmacists, thus not being aware of the exact diagnosis hindering the pharmacist from contacting the prescriber. Presently, community pharmacists in Australia cannot access patient's clinical data to confirm the appropriateness of prescribed antibiotics, but there are a number of initiatives taken recently by national and international bodies aiming to improve community AMS practices. The most recent of these in Australia is that pharmacists will be able to access patients' electronic health records [24]. However, maximum benefits can only be achieved when complete information and ease of access to these data is given to community pharmacists [25].

The majority of responding community pharmacists believe that they can play an important role in AMS and can help reduce inappropriate antibiotic use and healthcare costs. However, most of the survey respondents did not agree that it would help in further professional recognition or enhance their public image in the community. It may be because there is no professional degree or AMS course for specialisation in AMS. This is unlike the situation in the USA [6], North America [26] and Europe [27] where AMS as a specialised community pharmacy service is an emerging and growing profession.

The major barriers identified in this survey were lack of access to patients' records and lack of any standard guideline to practice AMS. Some of the respondents also highlighted the need for better collaboration with GPs regarding dose, duration, dosage form and particularly choice of antibiotic. In 2015, Bryant conducted a survey in Australia and New Zealand which found that physicians and pharmacists perceive lack of education, lack of dedicated staff, and lack of willingness to change as reasons for slow implementation of AMS [28].

The responses of the facilitators scale mirrored the responses of the barriers scale. Most of the pharmacists agreed that professional AMS training, public awareness campaigns, better pharmacist–GP collaboration and access to patients' records would be helpful in effectively carrying out AMS activities.

4.2. Practice implications

The best AMS practices for community pharmacies in Australia, like in many other countries, are not yet defined. The current study provides an insight into the practices, perceptions and awareness of community pharmacists regarding AMS. These findings can help overcome challenges related to the implementation of an effective AMS model in the community. Most of the perceptions of community pharmacists are directing us towards changing the professional behaviours and systems for effective AMS activities. Organisations interested in developing and implementing AMS initiatives in community settings should consider addressing some of the barriers identified in this study so that community pharmacists can be engaged in such initiatives in a meaningful way.

4.3. Limitations

Although responses were received from all the states and territories of Australia, we acknowledge the limitations of response bias thus limiting the generalisability of the findings. Certain community pharmacists are less likely to respond to online surveys, hence having only a limited spectrum of respondents was one of the limiting factors of this study. Similarly, it was difficult to take a representative sample population based on visits to social media website and e-mail links. Owing to an acceptable but low Cronbach's α of the perceived operational barriers and perceived facilitators scales, there is a need that the questionnaire should be confirmed for validity in another confirmatory survey.

5. Conclusions

Here we report the findings of a survey development and validation study to measure the perceptions of Australian community pharmacists regarding AMS. Once validated, the survey tool may assist other researchers who are interested in measuring the perceptions of community pharmacists about AMS in their practice. Pharmacists in this study regarded their role as antimicrobial stewards as an important one, although several barriers related to the practice settings, patients' perceptions and their interaction with GPs were limiting their participation in AMS. Organisations interested in implementing AMS initiatives in community settings should address such barriers to encouraged greater involvement of community pharmacists.

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Competing interests

None declared.

Ethical approval

This study was approved by the Tasmanian Human Risk Ethics Committee (HREC) in April 2016 [approval no. H0015673].

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2019.08.025.

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Chapter 5: Factors affecting community pharmacists' participation in Antimicrobial Stewardship-A qualitative inquiry

5.1 Abstract

5.1.1 Background

Limited literature on the perceptions of community pharmacists about antimicrobial stewardship (AMS) is focussed on survey research. Qualitative inquiry into factors affecting community pharmacists' participation in AMS informed the implementation strategies of AMS in primary care. We aimed to explore the barriers and enablers of community pharmacists' participation in AMS.

5.1.2 Methods

One-on-one semi-structured telephone interviews were conducted with a purposive sample of community pharmacists across Australia. Interviews were transcribed verbatim and analysed using Framework analysis method.

5.1.3 Results

Twenty pharmacists, the majority of whom were female (70%), representing urban, regional and remote areas of Australia participated in the study. Pharmacists identified a discord between the clinical needs of patients and practice policies as the primary source of excessive prescribing and dispensing of antibiotics. The fragmented nature of the primary health care system in Australia is limiting information exchange between community pharmacists and general practitioners about antibiotic use and this was encouraging inappropriate and, at times, unsupervised use of antibiotics. The existing community pharmacy funding model, in which

individual pharmacists were not benefiting from any financial incentives associated with clinical interventions, was also discouraging their participation in AMS. Pharmacists suggested restricting default antibiotic repeat supplies, reducing legal validity of antibiotic prescriptions to less than 12 months and adopting a treatment duration-based approach to antibiotic prescription, instead of the 'quantity-based' approach in which the quantity prescribed is linked to the pack size of the antibiotic.

5.1.4 Conclusions

Structural changes in the way antibiotics are prescribed, dispensed and funded in the Australian primary care settings are required urgently to discourage widespread misuse of antibiotics by members of the public. Modifications to the current funding model of the pharmacist-led cognitive services which favour pharmacists are necessary to motivate them to participate in AMS initiatives.

5.1.5 Keywords

Antimicrobial resistance; Antimicrobial stewardship; Community pharmacists; Qualitative study; Antibiotics, Australia.

5.2 Introduction

Antimicrobial stewardship (AMS) is a coordinated set of interventions directed towards maximising the benefit of antimicrobial treatment while minimising harm [38]. The majority of AMS initiatives are developed and implemented in secondary care and are equally important in primary care where the majority of antibiotic prescribing occurs [112]. Globally, it is estimated that up to 50 percent of antibiotics prescribed in primary care are unnecessary [37].

In Australia, antibiotic prescribing in primary care is above the average of the Organisation for Economic Co-operation and Development (OECD) countries [251], yet there is no AMS framework for the primary care sector in Australia [252]. The role of community pharmacists as antimicrobial stewards is under-recognised in Australia and globally, despite their essential role in supporting the quality use of medicines and medicines optimisation [253]. Community pharmacists are often the first point of contact for the public seeking selfcare advice and symptomatic relief from minor ailments, such as self-limiting respiratory tract, urinary tract, eye, skin, soft tissue and vulvovaginal infections [250]. In other situations, for example, when a patient already has an antibiotic prescription, the community pharmacist may also be the last point of professional contact and have an opportunity to promote appropriate antibiotic use [254].

Despite the current and potential role of community pharmacists as antimicrobial stewards, limited research has been undertaken to explore determinants of their involvement in AMS [255-257]. Our earlier investigations identified a number of barriers and facilitators to Australian community pharmacists' participation in AMS [256, 258] although the inherent limitations of surveys prevented us from developing a deeper understanding of such barriers and facilitators within the context of clinical practice. This qualitative study was undertaken to develop an in-depth understanding of the various barriers limiting community pharmacists' role in AMS and to identify recommended solutions to overcome such barriers, in order to facilitate greater involvement of community pharmacists in AMS initiatives.

5.3 Methods

Community pharmacists who participated in an earlier national survey (Ethics approval reference: H0015673) were invited to participate in this follow-up qualitative study. Sixty participants expressed their interest by providing their email addresses, although only 10 out of 60 responded to the invitation email. A sample of 14-16 participants is often recommended to achieve saturation in homogenous groups. As community pharmacists in Australia may be considered a homogenous group, we recruited ten additional community pharmacists, using professional community pharmacists' groups, using the social media platform, Facebook®.

An interview guide based on the findings of our national survey [256], was used to direct the interviews. TR piloted and modified the interview guide by conducting six mock interviews with the guidance of AT, three research pharmacists and three community pharmacists, before conducting the first interview. All interviews were conducted by TR, using a smartphone with a built-in audio recorder. A participant information sheet and a consent form were then sent to the participants. All interviews were transcribed verbatim and transcripts were verified by the participants before data analysis. Participants were offered a gift voucher worth AUD $20 as a token of acknowledgement for their time.

Interviews were analysed using the Framework Method [259, 260]. STRZ and TR independently analysed the first interview and discussed the differences in the coding approach to reach an agreement. Following that, TR analysed four additional interviews and STRZ reviewed all the codes, discussed disagreements and sought explanations when applicable. TR and STRZ co-developed the initial thematic framework based on the first five interviews and this was reviewed by MW and AT. TR applied the thematic framework to the remaining interviews while accommodating additional codes or themes. No new codes emerged after the sixteenth interview. Qualitative data analysis software QSR's NVivo V.12 and later V.20 were employed for coding and organising the qualitative data.

5.4 Results

The majority of the participants were female (70%) and represented a range of early and mid-career, and senior pharmacists representing urban, regional and remote areas of Australia. The interviews ranged from 16 to 43 minutes with an average interview lasting 29 minutes. Further details about the participants are provided in Table 1. The perspectives of the participants in this study indicated that community pharmacists are facing several challenges which limit their participation in AMS. Several interesting themes emerged from the interviews; Table 2 provides quotes for each sub-theme and a detailed breakdown of the themes, sub-themes and associated quotes is provided as Appendix 1.

5.4.1 Clinical and practice paradox

Many participants raised concerns about the way antibiotics are prescribed, dispensed and consumed in the Australian primary care setting; this may be grouped collectively under the term 'clinical and practice paradox'. We defined this as 'clinical misuse of antibiotics due to practice related limitations'. Participants not only shared the problems arising from this paradox but also suggested innovative solutions to overcome such problems.

5.4.2 Repeat authorisation

In Australia, a prescription can be issued with 'repeats', that is, the same prescription may be used for a further supply of medication without consulting with the original prescriber. Participants believed that repeatable antibiotic prescriptions are encouraging the misuse of antibiotics in the community.

The participants reported that quite often repeat prescriptions were generated because the settings in electronic prescribing software automatically defaulted to issuing a repeat unless the GP chose not to issue one (Table 2, 1.1). Unnecessary repeats are encouraging patients to self-medicate with antibiotics for future episodes of 'similar illnesses'. Pharmacists reported several incidences when patients have presented repeat antibiotic prescriptions, several months after the original prescription (Table 2, 1.1). A few participants suggested a change in the default setting of the antibiotic prescribing to zero repeats, in order to avoid the unintentional generation of automatic repeats.

5.4.3 Pharmaceutical Benefits Scheme quantity

Pharmacists reported that the pack sizes of some antibiotics are inconsistent with the recommended duration of antibiotic treatment, as per the antibiotic guidelines. Participants stated that the discrepancy between the recommended duration and the pack size was often giving patients access to a surplus of antibiotics, thus encouraging overuse and self-medication (Table 2, 1.2). Some participants suggested that patients should be given antibiotic quantities for a given condition, as per clinical needs rather than the pack size.

5.4.4 Validity of antibiotic prescriptions

The third factor responsible for inappropriate antibiotic use was the default legal validity of antibiotic prescriptions. Once written and issued, antibiotic prescriptions in Australia remain valid for 12 months. This is appropriate for chronic medications such as antihypertensive or anti-diabetic agents; however, having the same validity period for antibiotics provides patients with an 'open prescription' to be used whenever they feel like using it (Table 2, 1.3). Some participants reported some positive trends, for example, acknowledging that doctors are increasingly writing set duration scripts (Appendix 1).

5.4.5 Fragmented healthcare system

Many statements made by the participants pointed towards a lack of communication between multiple care providers and a disconnect between general practice and pharmacy. We define 'fragmented healthcare' as 'a healthcare system in which one healthcare provider is unaware of all episodes of patient care, involving a range of other healthcare providers'. The participants mentioned several clinical care issues that arise because the GPs and the pharmacists are working in their separate silos.

In Australia, patients are not required to register with a general practice and therefore, some will visit multiple practices and consequently, multiple prescribers. Patients are also free to visit multiple community pharmacies with their prescriptions. Participants reported that the lack of a reliable and complete prescribing and dispensing history for a given patient was contributing to antibiotic misuse (Table 2, 2.). Participants noted that some patients attend a different doctor to get antibiotic prescriptions if they are unsatisfied with the outcome of their initial consultation. Several suggestions were made by the participants to overcome the problems arising from the fragmented healthcare system (Appendix 1). These include introduction of an antibiotic surveillance program similar to that in place in Australia for pseudoephedrine. Such a system would enable monitoring and help ensure that the dispensing of each antibiotic is recorded in a sharable database.

One of the specific examples in which a lack of coordination between community pharmacists and GPs was evident is the way delayed prescribing is being implemented in Australian primary care. The participants reported that, although they are increasingly seeing the trend of 'delay prescribing' being applied in the general practice, it is only seen in low-risk situations. In such cases, patients, despite the prescriber's suggestion to withhold, ask the pharmacist to dispense the antibiotic immediately (Table 2, 2.1).

5.4.6 Scope of community pharmacy practice

Several comments made by the participants were related to the scope of community pharmacy practice in Australia. Community pharmacy runs as a business and community pharmacists are largely reimbursed for activities on a fee for service model, whether these are dispensing or professional services.

5.4.7 Funding model

The participants felt that the existing funding model in Australia favours community pharmacy, as the benefits of any clinical intervention go to pharmacy owners instead of employee pharmacists.

Moreover, the proliferation of discount chains in the Australian community pharmacy sector, and a further decline in funding for dispensing services, were reported as adding pressure to the quality of care provided by the community pharmacists (Table 2, 3.1). Due to the changing landscape of community pharmacies, pharmacists are fearful of losing 'customers' to other pharmacies if they try to educate patients or contact prescribers, as those who are impatient could go to another pharmacy (Table 2, 3.1).

5.4.8 Inadequate infrastructure

Pharmacists felt that the current infrastructure of the community pharmacy is often restrictive of an advanced role in AMS. Apart from the retail nature of the community pharmacy, lack of access to patients' history and laboratory data, and patients being unaware of or not recalling such information, were noted as other common limitations to community pharmacies supporting AMS (Table 2, 3.2).

5.4.9 Time pressures of being the last stop on patients' journey

Most patients or their carers, after consulting the GP, expect that the prescribed antibiotic will be dispensed in the shortest possible time. Participants reported that, due to this patient pressure, most of the time they were usually unable to check the details as to whether the indication or duration is appropriate or not (Table 2, 3.3). Explaining it further, the participants also attributed 'lack of time' as one of the main reasons for not approaching the GP, despite identifying an obvious need to seek further clarification or intervening on a prescription.

5.4.10 Knowledge base for antimicrobial prescribing

In Australia, the Therapeutic Guidelines (TG) is widely recognised as the definitive source of information on antimicrobial prescribing. However, participants were concerned that some GPs are not adhering to the recommendations in TG when prescribing antibiotics (Table 2, 4).

Furthermore, some participants also commented that not all pharmacists have access to TG either. According to the participants, the lack of adherence to guidelines may lead to serious issues, particularly in relation to children's antibiotic doses (Appendix 1).

5.4.11 Patients' understanding and behaviours

Participants reported that patients lack an understanding of the consequences, implications and effects of antimicrobial resistance and that this leads to an undue demand for antibiotics. The participants stressed the need for a better public understanding of the concept that antibiotics will become ineffective if used unnecessarily. Participants pointed out the need for simpler and more accessible messages to create greater awareness (Table 2, 5).

5.5 Discussion

The present study provides useful insights into the role of community pharmacists as antimicrobial stewards. Our participants noted system wide issues that are contributing to inappropriate antibiotic use, making these findings highly relevant to the broader healthcare community and organisations which are interested in implementing AMS in primary care.

5.5.1 Healthcare system related issues

We identified several issues affecting the prescribing and dispensing of antibiotics that are related to the wider healthcare system in Australia. Firstly, we noted that the clinical intention of treating an episode of infection was implemented in an illogical manner, in order to meet the restrictions imposed by the medicine funding methods of the Pharmaceutical Benefits Scheme (PBS) of the Australian Department of Health [261]. The PBS dictates the quantity of each prescription (including a repeat/refill authorisation) under a particular prescribing and dispensing code. The prescribing and dispensing software in primary care, as well as the commercial packaging of antibiotics from manufacturers, are all designed to issue quantities aligned to the PBS schedule. The community pharmacist faces major barriers to developing their AMS role due to the flow-on effects of computer generated unnecessary antibiotic repeat prescriptions. The issue of repeat prescriptions was also highlighted in other Australian studies as a potential contributor to antibiotic misuse and overuse [262-264]. Although Australia's National Prescribing Service MedicineWise (NPS MedicineWise) took the initiative to educate prescribers regarding software settings, the results were not sustained [265].

Secondly, the current legal validity of an antibiotic prescription is another major source of inappropriate antibiotic use by the public. We found that patients were keeping their prescriptions for future use and getting these dispensed several months after the date of issue. The majority of acute infections in the community can be treated with a single three-day or seven-day course of antibiotics; a shorter validity of antibiotic prescriptions will reduce the chances of self-medication. A study conducted in 2017 reported that one in ten antibiotics was dispensed from prescriptions that were more than a month old, although they were intended for short term treatment of acute infections [264].

Thirdly, we found that community pharmacists' inability to access the diagnosis and pathology data is an important limiting factor in carrying out their AMS role. Likewise, the inability of doctors to access patients' records from other healthcare providers whom the patient may have seen, is also limiting essential information from the doctors who are prescribing antibiotics. Integrating community pharmacies with the broader health system was strongly suggested to overcome this issue. This issue of a fragmented healthcare system has been reported in other studies and requires system wide changes to include community pharmacists in the primary healthcare team, giving them access to patient records [127, 266, 267].

Fourthly, inconsistent and contradictory practices in delayed antibiotic prescribing is also hindering community pharmacists from assisting with AMS. Our findings revealed that not all doctors were providing explicit directions about delayed prescribing. This led to patients demanding antibiotics to be supplied, undermining the prescribers' intentions, and potentially hoarding them for later use. This issue was predicted by Sargent *et al* in 2016 as the potential disadvantage of delayed antibiotic prescribing [238]. To overcome this, introduction of a procedure to withhold antibiotic dispensing is required but again this necessitates legislative changes in the health system.

Lastly, despite the availability of a standard antibiotic guidelines in the form of Therapeutic Guidelines [268], the resource was not unanimously used by the pharmacists and doctors as the primary reference. Instead, a number of doctors were referring to the Monthly Index of Medical Specialities (MIMS) [269] and there were considerable differences in terms of dosing and other medicine information between MIMS and the Therapeutic Guidelines. Our findings are in line with a recent study conducted by Saha *et al* [270] which reported non-adherence by GPs to the Therapeutic Guidelines.

5.5.2 Business related barriers to pharmacists' involvement in AMS

Unlike hospital pharmacy services, in which AMS has become an essential component of a pharmacists' role, community pharmacies are small businesses in which the primary aim of their owners is to generate profits. Pharmacists in our study reported that their skills, knowledge and clinical capabilities are not currently being utilised as businesses were more focussed on generating income related activities. The lack of any specific funding for AMS initiatives means that there is no clear financial incentive to refuse the dispensing of antibiotic prescriptions beyond the index infection when a patient presented an older script or a repeat prescription. Another obvious concern prohibiting the refusal of dispensing such prescriptions was that patients may easily go to a neighbouring pharmacy to get their antibiotics dispensed. Pharmacists also felt that the current funding arrangements only favours pharmacy owners and any limited incentives from clinical interventions are not passed on to the pharmacists doing such interventions. The current issues of this funding model imposing a perverse barrier to prudent use of antibiotics were also reported by Lum in 2017 [271]. The pharmacy funding models of the United Kingdom and Canada, with respect to the role and the scope of pharmacists to address areas of AMS, are more inclusive and more efficient as community pharmacists are involved in patient care teams related to self-care and minor ailments [272].

The overall impact of discount pharmacies on the quality of pharmacy services is also affecting community pharmacists' motivation to intervene on antibiotic prescriptions. In Australia, there is an unprecedented infiltration of discount pharmacies in which the business model is mainly 'volume oriented' instead of service delivery [273].

5.5.3 Public awareness

Pharmacists often have to deal with patients who seek antibiotics for the wrong reasons, that is, for viral infections, for self-medication or for the treatment of other minor self-limiting illnesses. This shows poor public awareness of AMR as a real threat to public health and the consequences of inappropriate antibiotic use. Our findings are largely in line with two other studies conducted in Australia in 2017 and 2019, in which limited health literacy regarding AMR was identified, despite there being mass education campaigns [274, 275]. The participants suggested smart, short and simple message content to correct patients' understanding of bacterial and viral infections, self-medication and minor self-limiting illnesses. Our findings are supported by another study reporting that patients should be provided with more specific and targeted information so that they only demand an antibiotic from their pharmacist when it is required. [271]. A sustained, concerted effort of public awareness is crucial to minimise resistance development and its spread.

Despite the considerable challenges outlined above, it was encouraging to see a general willingness and enthusiasm from community pharmacists for their role in community-based AMS initiatives. Provided that adequate resources and support are available, pharmacists were keen to participate in educating patients, collaborating with general practices and triaging patients with respiratory symptoms to discourage antibiotic use for viral infections. Educational interventions to facilitate short consultations and counselling with the patients by the community pharmacists through information leaflets have been successful in European countries and may be applied in the Australian context [127, 276].

To the best of our understanding, this is the first qualitative study of the Australian community pharmacists which explores specific barriers to their participation in AMS initiatives. Our participants represented various regions of Australia, ranging from remote regional areas to major metropolitan centres. Likewise, a range of age and experience was represented, thereby providing diverse opinion on the study matter. The student researcher was supervised for the test and initial interviews, transcripts were verified by the participants, and the thematic framework used for coding was verified with independent double coding by an experienced researcher (STRZ). This is a single country study and therefore, views expressed by the Australian community pharmacists may not represent the global community pharmacists' perspectives, although most modern community pharmacies in the Western world may relate to our findings. Similar to any cross-sectional study, our study may have a selection bias as the community pharmacists in our study may have a desire to become involved in AMS.

It is humbling and encouraging to note the recent changes announced by the PBS which are in line with our earlier studies [256, 258]. The maximum quantity and repeats for five commonly prescribed PBS-listed antibiotics (amoxicillin, amoxicillin-clavulanic acid, cefalexin, doxycycline and roxithromycin) have been restricted under the PBS by the Pharmaceutical Benefits Advisory Committee (PBAC) since April 1st, 2020 [111, 277]. We are hopeful that the publication of this qualitative study will provide additional support for legislative changes, in order to limit the validity of antibiotic prescriptions to three instead of 12 months.

5.6 Conclusion

Health system related conflicts, role-based limitations, interprofessional dynamics and resource constraints in the community, if not addressed, will continue to significantly limit the ability of Australian community pharmacists to participate in AMS. If community pharmacists are allowed to practise at their full scope, they can have a greater role in the primary healthcare system, especially in enhanced antibiotic governance, that is, AMS. Community pharmacists can play a vital AMS role in more appropriate antibiotic use in Australia. However, a number of changes in health policy and practice are required so that community pharmacists can fulfill their AMS role.

5.7 Acknowledgements

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5.8 Funding

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5.9 Transparency declarations

Nothing to declare.

Table 1 Participants Demographic Information

#	State	Gender	Experience	Area	Pharmacy Size
1	NSW	F	6 years	Urban	Medium
2	NSW	M	8 years	Urban	Small
3	SA	F	7 years	Rural	Large
4	NSW	F	11 years	Regional	Medium
5	NSW	M	30 years	Rural	Small
6	VIC	M	9 years	Metropolitan	Large
7	VIC	F	3 years	Urban	Medium
8	WA	F	24 years	Urban	Medium
9	TAS	F	4 years	Rural PHARIA 2	Medium
10	WA	F	>1 year	Suburban	Large
11	WA	F	9 years	Metro	Large
12	QLD	F	4 year	Metro/Regional	Large
13	WA	F	9 years	Urban	Small
14	ACT	F	3 years	Urban	Medium
15	NSW	M	10 years	Urban	Large
16	QLD	F	8 years	Urban	
17	QLD	F	10 years	Regional	Large
18	QLD	M	2.5 years	Urban	Medium to large
19	QLD	M	16 years	Metro/Regional	Medium
20	TAS	F	3 years	Suburban	Large

Table 2 Summary of themes, sub-themes and relevant quotes of the participants

Themes and Sub Themes	**Quotes**
1. Clinical and practice paradox	
1.1 Repeat authorisation	*"They are getting access to something they should not have access to, that is getting a repeat."* *"GP's computer just automatically prints a repeat, even if [they] said that 'it is for five days', ----- they just give it to the patient."* *"Somebody comes in and says they got this script that the doctor wrote six months ago, and I've got a chest infection, is it the right one?"* *"Get rid of that automatic repeat or put an expiry on repeat prescriptions."*
1.2 Pharmaceutical benefit scheme quantity	*"A very common example is a treatment for UTI: Trimethoprim they say it is for three days. But I think in dispensing software it comes in packs of seven."* *"We know that they do not need the balance of the medication and obviously at the end of the day, what they do with it we do not know."* *"We have to have a course duration of all antibiotic treatments for patients, and we only give them what they need for that course."*
1.3 Validity of antibiotic prescriptions	*"A lot of the time the patient just grabs an antibiotic script from like half a year ago and then when you ask them what reason is that for? Then you start to realise that it might not actually be the right antibiotic for that*

	type of infection." *"I am seeing more and more some of those 'set durations' being applied, which makes it much easier for us as pharmacists to provide that information."*
2. Fragmented healthcare system	*"--in community pharmacy, it is much harder to implement those kinds of systems, collaboratively with GPs, where we are working over the course of these different settings."* *"If people travel from one pharmacy to another, you then have to rely on what the patient tells you."* *"They have a script for erythromycin from one GP. They were not happy with it, saw another doctor, pretended that they have not seen a doctor and that doctor prescribed them Augmentin Duo Forte. Then they come and see you and they say 'oh, I have these two, what is the difference, which is better?"*
2.1 Delayed prescribing	*"You can feel that they've been pressured and bullied by the customer, because now a lot of doctors' scripts will have 'withhold for 72 hours, do not treat unless fever above 38.5C'. And then the patients come in the same day, saying 'the doctor said not to take it, but I'd rather take it anyway."*
3. Scope of community pharmacy practice	
3.1 Funding model	*"There is no push in doing so. So, whether you do that or whether you do not [reference-AMS] that it is alright yeah. It's like still there is no initiative for you to do that [AMS]."*

	"if we tell them that no, this is not the right antibiotic. You are sending away business in the commercial pharmacy setting."
3.2 Inadequate infrastructure	*"In terms of knowledge, we definitely have it------we do not have access to full patient's medical records."*
3.3 Time pressures of being the last stop on patients' journey	*"It is not all the time I get the doctor immediately, so if the doctor is busy and then the patient is in a hurry, we usually end up with what has been prescribed, which is not appropriate."*
4. Knowledge base for antimicrobial prescribing	*"All the GPs that I've called use eMIMS, released once and never updated."* *"They don't weigh the child and they just prescribe the dose based on the standard. So, I do not know which guideline they use to write but not based on the child's weight."*
5. Patients' understanding and behaviours	*"Lots of patients are saying, 'No, no, there is just too much information'. They want something in a sentence or two. They don't want a leaflet/pamphlet about resistance."*

Appendix 1 Thematic Framework of the study "Factors affecting community pharmacists' participation in Antimicrobial Stewardship-A qualitative inquiry"

Themes and Sub-themes	**Quotes**
1-Clinical and practice paradox	
1.1 Repeat authorisation (Patients are using the repeat of an earlier prescribed antibiotic without the knowledge of their doctor.)	"still seeing those repeats where they are not needed" 03* "as soon as you start giving people more tablets than they need and repeats, I just think they need to come and get them. You know, all they hold on to, is to bring them back, four months later and say, oh it's the same thing at it was four months ago, and you say "well, it's probably not and you're probably fine", but they don't want to hear it" 04 "somebody comes in and says they got this script that the doctor wrote six months ago, and I've got a chest infection, is it the right one? Well, it might be the appropriate one if it's a properly diagnosed and recognised infection, but you're still guessing, from our perspective" 05 "we are having same symptoms, same signs, same problems we are having as last time, then this medication worked last time, so it should work this time. But the chances are, it is not always the case. So, yeah, it can become quite challenging too, just to talk to the patient" 06 "if they need 20 tablets, just 20 tablets, but they have to do seven days plus one repeat which is a bit confusing for the customers" 08 "they will come after a couple of weeks with the repeat and I'm like, you should have completed the course, you know, the 10-day course" 08 "a lot of customers when they come in with repeat don't know. When you ask them, do you want

	the repeat now? The doctor said how long to take it. No, he did not say anything. He just gave me the script. So, they do not know how much they need for the course, there is nothing on the prescription to say how long the antibiotics to continue for the one repeat. They don't know whether it's for the same course or whether it's to be repeated again at some stage later so that information is not given to them when repeat scripts are issued" 08 "I think, that is the worst prefill prescribing software in the history of prefills. I am quite a vocal advocate against the automatic application of a repeat prescription on an antibiotic, it also gives the power to the patient to make the assumption that all they used and the amount of people that I've met that say I got this in the cupboard at home. Thankfully, they are coming in and asking can I use? I say no you can't." 09 "The doctor told me to keep holding on to this repeat so that if something happens just fill this repeat no need to go back and see them" 10 "patients in Australia tend to have a humongous build-up of everything" 15 "they are getting access to something they should not have access to, that is getting repeat" 17 "when the patient come to us to see us and if the doctor has written five days, and there are 20 capsules in Amoxicillin pack and accidentally they put a repeat on it, we don't dispense. So, we talk to the doctor and say, "if you give it to them for five days why to put a repeat on it" 19 "GP's computer just automatically prints a repeat, even it said that. "it is for five days" and they have to actually go in and put zero repeat on it because otherwise it just will print by default, and they just because they are busy, they just give it to the patient" 19 "They bring the repeat, they don't want to spend money and go and don't want to see the doctor again. So they just bring the repeat because they just want to treat themselves" 20 "they just write for the standard course of five days and one repeat" 20
1.2 Pharmaceutical benefit scheme quantity	"if I see a script coming in, one twice a day for the next 10 days, I would give that person 20 capsules, regardless of if the doctor ordered 50" 04 "won't like doing set number of tablets, they much rather grab a box with 20 in it, you get 20" 04

(Antibiotic prescriptions are not indicated for days of treatment rather pack size, due to which there are two problems: 1) Unnecessary repeats due to default settings of the prescribing software or 2) Required repeats due to duration of treatment as doctor may wish to give seven days of treatment and one box only has five or six days For example, Amoxicillin - one dose minus seven days is for infection not for disease and cannot be taken again without proper clinical assessment. But the system generates repeat scripts valid for 12 months and the pharmacist cannot decline the patient's request. Pharmacist can only advise or counsel.)	"it will default for full pack size, and the doctor will write for three days, or 20 tablets or whatever. So, or you know, five days in a packet, but no, say for three days, in which case they get the full packet because that's what they prescribed" 05 "a very common example is treatment for UTI: Trimethoprim they say it is for three days, but I think dispensing software comes in packs of seven, which is what doctor might just have seen, and selected what is on the screen. But in practice what I tend to do I just give them three days of Trimethoprim tablets" 06 "PBS scripts, we have to dispense according to what's on the script" 08 "GPs wouldn't give us a quantity on the script, what they would do is give us a course for five days or seven days and then one repeat, that repeat will cover the full box quantity even though the course is for ten days. For that we would dispense the full box quantity" 08 "the only reason pharmacists dispense full packs is because of the way prescriptions are written. We know that they don't need the balance of the medication and obviously at the end of the day, what they do with it we don't know, whether they continue taking it or whether it is handed over to someone else, whether it's thrown away" 08 "it is also cost effective for the government in a way. You need 20 tablets, you know for ten days if you are using it once twice a day, but you are giving up two full packs. The customer may use half and throw away half. So, every patient coming in with a repeat script is basically throwing away half the tablets. When we do not need to. It is something that needs to be directed to PBS with regards to the guidelines for antibiotics and all possibly, getting the companies to change the pack sizes of antibiotics to suit a ten-day pack size" 08 (Solution) "if you have, for example, a five-day course of cefalexin, and you've got a box of 20 and you are taking it QID you will finish that course and you will not have any tablet remaining" 09 (Solution) "if the doctor puts Alprim seven tablets, once daily for three days', we still have to give seven" 11

	“we have to go with what the doctor prescribes, and often that's a full pack. I wish I could break down a packet and go, “This is exactly how many, the quantity that you need, only take that.” We get so many returns of unfinished antibiotics. We look at the label and it is only used for three days, they were given a seven-day packet, and with a repeat for that. That is a waste of PBS, that is a waste of time. I'd rather be giving the quantities required rather than what is the manufacture box” 12 “I was absolutely shocked by this process that pharmacies are so used to dispensing the original package” 15
1.3 Validity of antibiotic prescription (Infections are treated as an acute medical condition. However, the legal validity of an antibiotic prescription is 12 months, just like any other medicine. This is raising system wide problems and, therefore, it is suggested that the validity of antibiotics prescriptions is capped to one month unless otherwise specified.)	"I can't remember for what I saw the doctor for, but I've got this, will that still work?" 05 “the medication is actually for kids, for example, so even the dose prescribed at that time would have been different from what that may be now, because kids they do grow. Every different thing, their body weight for example, apart from whether the indication is correct or not” 06 “a lot of the time the patient just grabs an antibiotic script from like half a year ago and then when you ask them reason what that is for? Then you start to realise that it might not actually be the right antibiotic for that type of infection” 07 “when there are leftovers at home either somebody had a bad reaction, most of the time, and they popped it aside. Or someone else in the family hasn’t finished a course of those antibiotics and they are floating around for that reason” 09 “still have customers who dig up unfinished antibiotics; ‘this has expired two months ago; can I still use it? I am going to take it anyway’ ” 11 “someone says they’ve got Cephalexin and they’ve had this script and then they might come back a few months later and say, yes, I’ve got another UTI and I'm going to get my Cephalexin again and it might not be appropriate for them” 14 “I am seeing more and more some of those “set durations” being applied, which makes it much easier for us as pharmacists to provide that information” 03
a. Solutions	Various solutions were suggested to restrict and monitor access to antibiotics.

i-Set duration scripts	“it is very important that the GP prescribe just enough for the whole course and then if they want it like so that they don’t actually have a chance to like to keep the repeat for the next time” 01 “we have to have course duration of all antibiotic treatment for patients, and we only give them what they need for that course” 04 “for antibiotics I would expect the prescribing doctor to actually state the duration of treatment. If it is for 10 days then it should be for just 10 days if it is for 3 days that just for 3 day” 06 “I have seen some prescribers actually write on the prescription, antibiotic only like prescription, this particular antibiotic prescription only for like a month or something like that, so, do not dispense it after the month” 07 “there needs to be some limits around, not necessarily number of repeats, but that, because you don’t want to be limiting patient access. When they have an infection, they think I have to go back and see the doctor again to get a script for a UTI, when I know it’s a UTI, recurrent UTI, for example” 14 “the doctor should have to specify the “duration of the antibiotic” they want patient to take, and only that quantity should be supplied” 17 “this prescription is only valid for two months or six months” 18 “emphasising on the duration of therapy and not to, you know, not to continue therapy until they come back and see the doctor” 19 “getting doctors do not write a script that will last for more than two or three months unless it is for like a chronic infection or something” 20
ii-No repeats, no expiry on repeats, no authority to approve repeats or no putting controls on antibiotics such as S11/S8	“get rid of that automatic repeat or put an expiry on repeat prescriptions” 03 “stop giving PBS repeats” 04 “we have to stop giving PBS repeats. We need to make sure that people are only getting the amount of medication that they need for the course that the doctor is prescribing for” 04 “don't put repeats on prescriptions, of antibiotics scripts, unless somebody has got sort of recurrent, yeah, like a recurrent UTI or something” 05 “legislation, if you're at all yet, all antibiotics cannot be used after like, six months” 07

	"I did see some scripts that doctor actually wrote, either do not give repeat, repeat expire after this lot, something like that. So, pretty much then I realised that when the doctor actually writes clear instructions the patient follows it" 10 "they need a telephone authority or something like that to authorise repeat" 17 "they can just put the default as zero especially for products like antibiotics" 19 "like all antibiotics probably have two months expiry or something" 20
iii-Real time monitoring (e.g. Project STOP style real time monitoring)	"same type of monitoring process as what we have in hospital in terms of what is restricted" 06 "a safe script is really useful for community pharmacy, because it's checked. You can check what has been spent and what has been dispensed and what has been prescribed by patients across multiple prescribers" 07 "But ultimately, it's a bit sad, but just like you've got the SafeScript monitoring on trial in Victoria for Benzo's - I really think antibiotic resistance is so important. It is important enough to go for something like that, to do a script monitoring, I think more so for the prescriber." 11 "whether it was filled or not, but he'd be able to see that Mrs Smith saw a doctor two postcodes away for the flu symptom and prescribed Augmentin Duo, but then she saw the ED doctor at Sir Charles Gardner Hospital, who gave her Ibilex and then she's come and seen you today for the same thing. If the doctor knew the history then I think they would be more - the more information, the more educated they are to know what's happening" 11 "Project STOP where you can track exactly which pharmacies, how many days it had been" 12
2-Fragmented healthcare	
This theme is about barriers which community pharmacists are facing due to a lack of continuity of care and poor communication with GPs. It also covers issues of not having one pharmacy or one GP for every patient. Therefore, the community pharmacist is not aware of the diagnosis and indication information of the patient and has only the dispensing history (in some instances even that is also not present), whereas GPs may not have the prescribing history from other doctors. There is a lack of a single health care system.	"a safe script is really useful for community pharmacy because it's checked. You can check what has been spent and what has been dispensed and what has been prescribed to the patients across multiple prescribers" 07 "I've had customers come in with the script from the hospital, which is to complete an antibiotic course, which started off in hospital, but they come two days later with the prescription" 08 "So, there is a gap at the hospital level as well where they send them home with the balance of medication. Or if you're giving them a script, they need to be told, it needs to be continued and completed" 08 "when I photocopy the script and patient history to send to the most current doctor, I get a call and

	say 'I didn't' know she saw a doctor last week and the week before; I treated her based on what she presented to me, so that's on the patient'. The GP will not say 'oh if that's the case, withhold my Augmentin and go on with Clarithromycin' or whatever, some hospital script they have kept going with. He will just say that 'my script is based on the signs and symptoms that the patient presented to me for that day, so it is up to that patient to follow my instructions.' " 11 "We do truly see the elderly come in, they have five scripts - because they look old and they're all from different doctors" 11 "They have a script for erythromycin from one GP, they weren't happy with it, saw another doctor, pretended that they hadn't seen a doctor and that doctor prescribed them Augmentin Duo Forte. Then they come and see you and they say 'oh, I have these two, what's the difference, which is better? 11 "if people travel from one pharmacy to another, you then have to rely on what the patient tells you" 13
2.1 Delayed prescribing	"lots of just in case repeats" 03 "watch and wait approach" is good that I heard about a few years ago years, you know, doctors were stamping scripts saying take if not better in 48 hours, go get your script" 04 "when it is not a clear-cut diagnosis, I think and they are "just in case" prescription, they frustrate the hell out of me basically" 04 "some of the doctors here are definitely doing that for the delay scripts, giving them scripts but telling them to hold on to it, you know "just wait" but still there's definitely still that perception in the community that you get an infection, you go and get antibiotics and it sorts it out" 05 "I haven't seen any stamps; it seems to be a verbal thing" 05 "I am happy to put it through, which is the case most of the time anyway, but then you do see a patient that is actually, who not even coming back for prescription, so either they are not coming back because they don't need it or they have got that filled somewhere else, that can be a different story" 06

	“A lot of times doctors give it out to patients like as sort of “in case” if you don't get better after three days then start antibiotic” 08 “But the patient would just do it straight away, even though we say oh, no, you don't need it now. All I'm trying not to, telling them hypothetically not to use it first. Just because you don't really want to use it right now but they say oh I just want to grab it and for the duty of care and everything we just have to be right okay. Just counsel them because the doctor said to use it only when you start getting the signs and symptoms.” 10 “we are equipped intelligence-wise but to do with the bullying from the customer we are not equipped, and there is no education on it. Somehow the general public they do not even realise that we need a degree to be a pharmacist. I am sure a lot of people will say ‘yeah, give me a Ventolin, I’m side-tracking a bit’. Ventolin is meant to be only given if referred from the doctor. I will tell you countless times they say, ‘just give it to me.’ ” 11 “And then the patients come in the same day, saying ‘the doctor said not to take it, but I’d rather take it anyway” 11 “Occasionally, it depends on the condition, but yes we do have prescriptions that say to be dispensed if the symptoms occur or should be dispensed next month or just things like that but that would be very condition dependent” 18 “I will not say majority but I have seen this trend lately” 19
3-Scope of community pharmacy practice (This theme is the context in which pharmacists are working in the community. The scope of pharmacy practice in the community is broader but community pharmacists are not given access to patients’ data. Pharmacists have PBS approval numbers and they are agents. They are not providers of cognitive services. The community pharmacy agreement is linked to owning a pharmacy business. The patient has an understanding of the GP consultation but the pharmacist has no means to collect objective information.	
3.1 Funding model	“there can be incentives put in place again, it's difficult but I know, a long time ago in the UK, there was incentives for GPs, for practices, not for the GP, but for the practices they were trying to reduce the use of something, might have been antibiotics, can’t remember but they got an incentive for the practice. If they reduced their usage for those pharmacies, in the early days when pharmacists were going into doctors’ practice, to, sort of, improve prescribing habits you can do something like that, because money does talk” 05

	"And that's often the case it is the GP, the practice, gets the incentive, but the pharmacist does the work and it's all nice and warm and fuzzy but pharmacists should be paid for their work as well" 05 "there is no push in doing so. So, whether you do that or whether you do not that it is alright yeah. It's like still there is no initiative for you to do that [AMS]" 07 "if we tell them that no, this is not like the right antibiotic, you are, you're sending away business in the commercial pharmacy setting" 07
3.2 Inadequate infrastructure	"In terms of knowledge, we definitely have it, definitely have the capacity to do that, but just I want to mention as before, the only thing worrying is we do not have access to full patients' medical records" 06 "If we were to provide complete service then we should have access to all the information that we need" 06 "when you are only presented with just a prescription like most of the time you don't know what is going on in the background. It really makes it hard to, just to give like a proper recommendation" 06 "education wise and skill wise, I think pharmacists are equipped with the knowledge and they know basically what needs to be done. It's just we don't have the facilities or the support" 08 "it's confusing for us because we don't know the entire picture" 08 "I certainly like the extensive accurate history for somebody when prescribing or dispensing those medications, that is always helpful" 09 "You can't tell the whole story sometimes in community pharmacy" 13 "In hospital it is received a lot better, because you obviously would take your due diligence and you would look at the patient notes and look at a diagnosis, look at their blood culture, their lab tests, whatever else and you'll get a well-informed clinical decision. Whereas in community you do not have access to any of that, so you'll question a prescriber and they'll sort of be like, you don't know what you're talking about, you don't have the information" 14

	"Definitely a framework would be good. But I think there needs to be support from the managers and the owners of the community pharmacies who enable the pharmacist to do, to have enough time to provide that clinical review, it might almost be like a consultation. When a patient presents a script, they take them into the private consulting room and just get a bit of background information, use the My Health Record to g*et al*l the lab results and feedback. It's going to take more time for the patient" 14 "when we don't have the diagnosis, or what actually happened at hospital or the doctor's room, it's really hard for pharmacists or other allied health healthcare professionals to read, understand if this antibiotic is appropriate or not" 15 "in community, it is a lot harder because you don't always get a full picture of you know what the infection is" 16 "Our friend Chemist Warehouse will be worst because they don't even know, confident, they don't even care that what they do is ….oo UTI.. so you can have Alprim, there you go, see you later bye bye" 02 "if you take the Chemist Warehouse I don't regard them as community pharmacy" 02 "So let's say for instance you know conjunctivitis, Chlorsig eye drops was actually available as OTC …instead of prescription but a lot of workshops, lots of guidelines you know.. set and now I am confident based on that it can be prescribed for conjunctivitis but still you know I worked with Chemist Warehouse people, they don't care, they say oh red eye go go, see you later" 02 "you really need to have specific guidelines on specific condition of what pharmacists you know can do or even like strict policies and focus because our friend Chemist Warehouse is going to abuse it" 02 "They are just churning scripts out" 04 "in a community pharmacy often you are on your own, like you might be one or two pharmacists. I mean, some pharmacies you might have three or four, but they're the discounters, and that's a different model altogether" 04 "the amount workload. If you work in like a, for example, discount chemist, which is like a

	pharmacy model for many pharmacists at the moment. I just guess the workload doesn't really allow them to efficiently evaluate the patient's clinical situation" 07 "you're working in pharmacy in a discount model then you are pushed to dispense like over 100 to 200 scripts in a day" 07 "The problem is, unfortunately we do have things like Chemist Warehouse. They don't spend the time on patients with Chlorsig" 13 "our services have been devalued to the point of Chemist Warehouse" 13 "hard to get access to pharmacists" 15 "everyone is working as a robot" 15 "especially the discount model, where they don't really work on services and providing and going through the details. They just want to increase their volume and put them through pressure on pharmacists" 19 "This is the type of direction they get from their management that if there is a problem, send the patient back to the GP, instead of, which is very annoying, because you will have to have a consultation again which will delay the therapy and then cause problems" 19 "we are always very busy so most of the time we just have to rush through everything" 20
3.3 Time pressures of being the last on patients' journey	"because sometimes you know you are the only pharmacist on duty. You don't always have the privilege to be going through every single patient with antibiotic" 01 "I feel that this is one of the challenges that the pharmacist is facing. It's not about if we have the knowledge or not, but it's about if we have the time or not" 01 "sadly, we are in a retail environment and there are a lot of pressures put on community pharmacists. And you know, that, sadly, the aim is to get the scripts out as quick as possible. And so unfortunately, sometimes clinical decision-making processes are missed and that's a shame" 04 "we might have a bit more time to explain things because it just takes time when you're telling somebody they don't need antibiotics for an upper respiratory tract infection" 05 "If we are going to believe that this is the level of service the pharmacy is providing, I guess, moving forward from plain dispensing service to a more clinical service then definitely would have to factor that in, like manpower" 06

	"there is no time to actually call a doctor if anything went wrong and you are just forced to cut corners" 07 "a lot of the times the time factor comes into play when you're busy and you have lots of scripts to dispense and you don't have the time. Like antibiotics are quite frequently prescribed so every second third prescription over the flu season will be for an antibiotic, but we don't have the time to deal with every customer the same way where we can explain all of that to them" 08 "Sometimes we don't have enough staff members on duty at the same time so that we can take that five minutes extra and explain to the customer how to properly use antibiotics" 08 "when we do have time, then we will ring up the doctor and confirm for them but we are not able to do it in every instance" 08 "because of whole rush and definitely not enough pharmacists we just do the most important counselling points" 10 "We tell people, we need time to be able to do this" 12 "We're limited by time, so obviously the time is a factor. We're limited by the fact that we've got competing priorities in the community pharmacy setting. So, it doesn't mean that we don't want to do something. It's that something else might have to be done first" 13 "I guess sometimes you just don't have enough time to ask and have that conversation or they might not feel comfortable especially if the customer is angry or in a hurry" 14 "don't have time to really focus on this" 15 "I might try to tailor my advice a bit more based on what I know but I don't think I reject it because, you know, time pressure" 16 "We're kind of limited in actually preventing any, you know, antibiotic resistance, because we have to give it out. Often you need to wait for call back while you have got a patient at your store, getting annoyed and because they just want to come in and come out" 17

	"I probably say with current workload within pharmacy. To have an antimicrobial stewardship pharmacist within a hospital environment would be justifiable setting but if you are doing same amount of antimicrobial prescriptions in community pharmacy it just could not be justifiable in terms of the pay" 18 "I don't think they justify that time doing that. I think the other KPIs at the moment, everything else needs to be done. I don't think they justify the time on AMS activities as opposed to other things that bring more profit for the pharmacy" 18 "it is a delicate balance, you know, between dispensing medications or checking them and then providing information but this is how you have to organise your workflow" 19 "They are not doing the clinical job like prescription being dispensed by a pharmacy assistant, they just have to check and provide information" 19 "there are other pharmacies who are not close to GPs or are not inside medical centre, in a different area where the GP is far away, where they're receiving the script from someone you know, so it will be really hard and that's the main barrier for them to ring them because either they don't have time or if they ring them GPs don't have time. So these are the type of major barriers for both pharmacists and GPs to actually communicate with each other in this situation" 20 "it is not all the time; I get the doctor immediately, so if the doctor is busy and then the patient is in hurry, we usually end up with what has been prescribed which is not appropriate" 20 "we are always very busy so most of the time we just have to rush through everything" 20
4. Knowledge base for antimicrobial prescribing	
Issues arising due to differences in guidelines or use of the wrong reference	"I use eTG quite a lot. And I have access to that online. I use that in my community work quite often when I'm supporting patients. Not all my colleagues have that" 03 "our prescribers did not have access to eTG" 03 "Some doctors are very accepting of our recommendations; they would be very friendly. I guess it is a dual process because we may recommend something but at the same time, we are also learning

	from them because they may have a different experience and may have seen different resources and etc." 06 "All GPs should have access to therapeutic guidelines, although what I find some I guess more experience GPs or older GP, they tend to have like different references, I don't know whether that is part of what they learn through their career or it could be just using older references that are not quite up to date" 06 "With paediatrics, doctors can prescribe a higher dose depending on what's being treated. So, we generally would go after weight of the patient, we get the weight and just check dose range is appropriate for the weight. If there is an issue then we ring the doctor to confirm if we feel the dose is not what we think it should be" 08 "If we don't use AMH we use the MIMS online, but I'm not too sure what the doctors are using" 08 "I am not too sure whether they use the therapeutic guidelines for antibiotics or if they are using something online" 08 "Most pharmacists go to the Australian Medicine Handbook, the AMH" 09 "I used AMH and e-MIMS for the indications that are sometimes when I see doctors either underdosing young kids or like sometimes most of the adults they give antibiotics for condition that hasn't happened and yeah then the dose thing is like vary for instance for what that has been considered in AMH or e-MIMS" 10 "Most of the doctors, I realise, they use more e-MIMS than AMH" 10 "We have to refer to eTG and but when we quote eTG overwrites everything" 10 "eMIMS, AMH and APF. We check all three, especially when it's a high dose or an odd dose" 11 "All the GPs that I've called use eMIMS" 11 "At the moment, I'm using your AMH so and also your what do you call it that? What is the (eTG)

	yes eTG which I use a lot of time, because I love that I love that software and the website. We also did the last two of the main things, I also have a quite a few different resources that built at the pharmacy, just use different resources" 15 "I just go through the AMH, I don't have access to eTG, but know that it is the best, it is the best option to use and is probably I assume what prescribers go with that AMH and eMIMS, sort of between the two" 17 "eTG I use majority of the time and other times eMIMS and AMH I will be probably using frequently" 18 "We usually always follow eTG" 19 "Yes and also MIMS which they refer to a lot to, MIMS. I have informed them a lot of times that it is actually a product information from the pharmaceutical companies, it is not an independent reference book. Which is for them is very amazing that they are always looking into eMIMS or MIMS without realising that it is actually a product information from a pharmaceutical company, it is not independent" 19 "I normally use AMH or eMIMS" 20
Outdated or different guidelines are followed by prescribers	"those prescribers are a bit stuck in some old ways" 03 "all GPs should have access to therapeutic guidelines, although what I find some I guess more experienced GPs or older GP, they tend to have like different references, I don't know whether that is part of what they learn through their career or it could be just using older references that are not quite up to date" 06 "We quote the AMH and they say no I use the e-MIMS, and we use to tell them that sometimes e-MIMs is not updated and they will be like, doesn't matter, I used the e-MIMS and just follow what I said" 10 All the GPs that I've called use eMIMS, released once and never updated" 11 "Oh, I use the British Pharmacopoeia from 1851" 12 "I saw older doctors just go by experience and what they learn back in the day, I don't really know

	what guidelines are" 16 "A lot of older doctors are using AMH from probably 20 years ago" 18
Supportive comments regarding eTG	"I think that eTG is one great resource" 03 "eTG, antibiotic guidelines provided, are very good reference and guidelines in terms of antibiotic prescribing" 06 "we have to refer to eTG and but when we quote, eTG over write everything" 10 "therapeutic guidelines were only updated two months ago, by the world leaders in antimicrobial resistance and antimicrobial stewardships, why are you not taking this on board?" 12 "I think there needs to be more of a focus on eTG than AMS, just like getting into the nitty gritty of the technicalities about what antibiotic is most appropriate for what organism" 14 "I don't have access to eTG, but know that it is the best, it is the best option to use" 17 "need to upgrade and update the resources" 18 "eTG I think is better but is not usually available, it is not like I am able to access but when I'm at the pharmacy I get to use eTG" 20
5. Patients' understanding and behaviours	
	"they will be pushing I am a regular customer of yours if you don't do this I will bring the business elsewhere somewhere or tell your owner" 10 "we are equipped intelligence-wise but to do with the bullying from the customer we are not equipped, and there is no education on it. Somehow the general public they do not even realise that we need a degree to be a pharmacist. I am sure a lot of people will say 'yeah, give me a Ventolin, I'm side-tracking a bit'. Ventolin is meant to be only given if referred from the doctor. I will tell you countless times they say, 'just give it to me" 11 "I guess sometimes you just don't have enough time to ask and have that conversation or they

	might not feel comfortable especially if the customer is angry or in a hurry" 14 "I am not really not person known to say no to dispensing antibiotic even I might dispense it, but I might try to tailor my advice a bit more based on what I know but I don't think I reject it because you know time pressure, and also because boss might not be happy, you know patient might be angry because they say what right you have to reject, you know, when prescribed by the doctor. It is bit difficult to reject the supply" 16 "often you need to wait for call back while you have got a patient at your store, getting annoyed and because they just want to come in and come out" 17 "they can often storm out or, you know, make some remark that, you know, they are not coming back here" 17 "but unfortunately, people don't want to receive it" 04 "something I am generally aware of, but I don't make the habit of going or reading on a regular basis or anything" 05 "no, I do not see much of it, like rarely. Usually I get newsletter rarely I get it though I get newsletters for other things but have not seen antibiotics or antimicrobial stewardship coming through. So, yes, I rarely go to the website" 10 "All this NPS MedicineWise, all this Health Direct, no-one listens to it because they think we're all under one umbrella and that we're having a colluding conspiracy against the patient" 11 "Frankly, no. Because they are not suitable to a lot of patients - patients don't want to read. Lots of patients are saying, 'No, I'll research the internet if I want to.' Lots of patients are saying, 'No, no, there's just too much information.' They want something in a sentence or two. They don't want a leaflet/pamphlet about resistance" 13 "Yes, I use that as well, for patients and you know, leave notes or leaflets" 15 "I don't know whether the general public knows that much about it. I mean, like, you know, they see the brochures in the pharmacy but most people do not know what NPS is" 16

	“Just like the accessibility to NPS that would be a very big one. For example, I find it a bit hard hopping on to eTG. Hopping on to other things, this should be a lot easier.” 18

Chapter 6: Discussion, conclusion and recommendations

6.1 Background and Synopsis

Healthcare systems around the world are reactive in managing threats to public health and their own sustainability, instead of being proactive in identifying the upcoming concerns that will eventually become sizeable threats. Antimicrobial resistance (AMR) is one such eminent threat which has been progressively increasing in recent decades. After discovering penicillin as the first antibiotic, Fleming warned the public and healthcare professionals that it is the moral responsibility of everyone dealing with antibiotics to take good care of their usage. Fleming said "*thoughtless persons playing with antibiotics might cause adverse consequences of a good medicine*" [278]. The threat of AMR and its potential harm to individuals in present and future times provide strong moral justification to avoid inappropriate antibiotic prescriptions at every level. All stakeholders should be well-versed, actively involved and feel confident in applying the principles of AMS while taking care of their patients.

Despite the world coming closer with unprecedented communication and frequent travel, there still remains disparities and slow-paced progression in endorsing AMR development. AMR does not discriminate between borders, ethnicity and economies, yet the world's health care systems are still focussing on individual efforts in fighting this menace, in order to deduce solutions rather than working as one coherent entity. The issue of AMR is complex and involves a variety of interacting drivers which were contemplated in this research. A part of the problem is antimicrobial use in humans and animals, not just overuse or misuse but also correct use. In recognising the difficulties in facing the challenging and complex nature of AMR, there is no single solution that can be defined as the best. There is an imperative for a global coalition for coordinated and synergistic strategies to optimise the use of antimicrobials. Although the relative contribution of antimicrobial overuse and misuse to AMR is difficult to estimate, due to its challenging and complex nature, there is a definite need for a global coalition and cooperation for coordinated and synergistic strategies to reduce the use of antimicrobials whenever it is appropriate to do so.

6.2 AMS in primary care and synopsis on AMR

One of the major initiatives to optimise antimicrobial use in human medicine is Antimicrobial Stewardship (AMS), which is defined by Dyer *et al*, as a coherent set of actions which promote responsible antimicrobial use [49]. Both the WHO action plan on AMR and the UK Department of Health's report by Professor Jim O'Neill, regarding the global burden of AMR, stress the need to have AMS in every healthcare setting and the importance of reaching all stakeholders [9, 137]. AMS efforts were initiated in hospital settings and are gradually developing further at the community level. Fewer AMS programs exist in the community and even where they do exist, they have not reached the same level as in hospitals. Community care, sometimes referred to as primary care, accounts for most antimicrobial use, yet the relative proportion of AMS initiatives in primary care has always been smaller than in secondary care [150]. This research was carried at a time when change in the direction of AMS initiatives towards primary care was observed, as evident from a few narrative and systematic reviews

6.3 Pharmacists and AMS

Pharmacists should work to help prevent or reduce the transmission of infections within the healthcare system including the community (for example, among patients and healthcare workers). Methods on how this can be accomplished have been outlined by almost all the Ministries/Departments of Health and Professional Societies including those in Australia and the United Kingdom, and the American Society of Health-System Pharmacists (ASHP) [279]. Pharmacists should also be proactive in promoting vaccination which can decrease the use of antibiotics, both directly, by preventing primary infection, and indirectly, by preventing bacterial superinfection. Similarly, pharmacists have an important role within AMS programs, including:

- developing and managing antimicrobial guidelines;
- reviewing individual patient regimens to optimise therapy;
- educating healthcare staff on the appropriate use of antimicrobials, and
- monitoring and auditing outcomes of antimicrobial usage.

6.3.1 Hospital pharmacists

Pharmacists should be an integral part of the AMS team to ensure active involvement in management of antimicrobials. AMS programmes with a dedicated infectious disease (ID) or AMS pharmacist have been shown to be associated with greater adherence to recommended antimicrobial therapy practices when compared with AMS programmes which relied on ward pharmacists [280]. In the United States, specialty residency and/or fellowship training in ID is the most widely accepted training method, and other methods include the 'Society of Infectious Disease Pharmacists', 'Making a Difference in Infectious Diseases Pharmacotherapy' certification programs and expert professional development programs. However, budgetary considerations, a shortage of ID-trained pharmacists and staffing constraints to allow a pharmacist to complete such a program, have been barriers to the widespread implementation of these robust programs and pose a challenge within hospitals. Due to the shortage of ID-trained pharmacists, the role of non-ID pharmacists in driving an AMS programme cannot be underestimated. Therefore, a growing number of general pharmacists are being offered alternative AMS training options in order to participate effectively in AMS activities. In one study [281], it was found that an introductory-level AMS elective utilised active learning with human patient simulation technology in a PharmD curriculum which was also used to compare and contrast similar antimicrobial agents, in order to define and propose criteria and applicable AMS strategies. Another study [282] found that implementing a mentoring program, in which an experienced ID physician and ID pharmacist offered mentoring, insights and guidance to general pharmacists with unique perspectives, requires the involvement of the hospital administration for its effective development and sustenance. Pharmacists can reduce inappropriate antimicrobial regimens through various AMS strategies, including, but not limited to, optimising prescribing behaviour, monitoring antimicrobial use, infection prevention and education, training and public engagement.

In a study [283] which was conducted in Australia and France, two countries where AMS frameworks are effectively implemented in hospitals, it was found that pharmacists, as part of an infection review team, have a significant impact on facilitating intravenous-to-oral switches and identifying patients who are suitable for discharge on oral therapy or outpatient parenteral antimicrobial therapy (OPAT). For inpatients, once the infection has been controlled, hospital pharmacists actively facilitate early discharge and help patients with suitable oral antimicrobial therapy or OPAT which shows that good clinical governance and AMS practices are in place.

6.3.2 Community pharmacists

In hospitals, as discussed above, there are several resources available for pharmacists to optimise and monitor antibiotic use. However, there is a paucity of research data and a lack of similar systems and frameworks within the community settings; this raises the question of ‘what are the problems and challenges that community pharmacists are currently facing related to AMS?' The answer to this question can help us to understand and improve community pharmacists' involvement in AMS.

6.4 Literature review

Based on the knowledge that a significant research gap exists in the suitability, quality and sustainability of AMS strategies in the community and its methods of development and implementation are not yet fully explored, a first phase literature review was conducted. The literature review provided the international context for various AMS strategies conducted in the community. The main hypothesis of this literature review was that AMS strategies need to be tailored to consider the unique characteristics found in the community sector. Some of the recommendations were specific to local community settings, such as access to point of care testing and use of local guidelines, as main strategies to optimise antimicrobial use. However other strategies, such as education, delayed prescribing, audit and feedback were universal strategies of value, both in the hospital and community settings. The review found that the content and mechanism of action of most AMS interventional studies were to optimise antibiotic use for respiratory tract infections (RTI) in primary care. The main finding of the review was that AMS strategies need to be tailor-made and tested, involving all stakeholders from the planning stage, in order to consider the unique characteristics found in the community sector. The literature review could not identify any study in which pharmacists were actively employed, involved or lead the trial. A 2020 publication by Atkins *et al* [284] also identified a total of 39 interventions of which only eight involved community pharmacy staff.

6.4.1 Geographical distribution

The literature review was undertaken to help understand the current status of AMS within the community setting. It was found from the review that legislations surrounding antimicrobial prescribing and dispensing are different in every country. The most distinctive variation is ease of access to antibiotics. There are many countries where antibiotics are available without prescription and in developing countries, there is lack of data on prevalence and incidence of AMR, as well as on the types of AMR and treatment failures. In addition, there is a scarcity of good quality AMS studies. That is why several limited-resource countries continue to struggle to set up AMS programmes. In contrast, most developed countries have strict regulations and laws to restrict the use of antimicrobials; they can only be dispensed if a registered practitioner prescribes them to the patient. The review was conducted to gather information from the research completed in such countries in order to understand the dynamics of different type of interventions which are commonly used in their primary care. Most of the studies included in the review were conducted in Europe (56%) and more than a quarter of the included studies were conducted in North America (31.5%). In both these areas, antibiotics have status as prescription-only medicines. Results from this literature review contributed to providing essential health intelligence to guide the next phase of quantitative and qualitative studies in order to explore the role of community pharmacists in AMS.

6.4.2 Types of intervention

A number of AMS interventions in the community setting were identified and were categorised, to aid an understand of their effectiveness. The majority of the trials incorporated complex interventions with more than one intervention group. Most of the studies involved patients with RTIs, as evidence suggests that most inappropriate antibiotic prescribing is for viral RTIs. Mostly trials were directed to change the behaviour of the prescriber and the patient through education. Educational interventions which were investigated/reviewed related to prescribers for the promotion of guideline adherence, communication skills and persuasive strategies used for decision making. Educational interventions were also found to be directed towards parents, patients and the public for better awareness regarding antibiotics and AMR. The rest of the interventions were restrictive, aiming to direct and guide the prescribers not to give antimicrobials when they are not required. These included points of care testing, clinical decision support systems, audit, feedback and delayed prescribing.

6.4.3 Community pharmacists in aged care facilities

From the literature review, we found that residents of aged care facilities (ACF) are at an increased risk of healthcare-associated infections, and around 50–80% of ACF residents are prescribed at least one course of antimicrobial per year. In three community ACFs, the introduction of a weekly prospective audit and feedback strategy encountered several barriers to effective implementation, despite having an ID physician and ID pharmacist available once a week for reviews [285]. A modest decrease in antimicrobial utilisation was observed but there were several missed opportunities for intervention and low acceptance rates when recommendations were made. Therefore, it is critical to have continued medical education on AMR/AMS for ACF staff, in combination with a prospective audit and feedback strategy, in order to reduce the inappropriate use of antimicrobials. A systematic review of five studies, which were evaluating pharmacist-led interventions on medication prescribing in older adults receiving primary care, found that pharmacist-led interventions, including access to medical notes and medication reviews, in conjunction with feedback to physicians, and computer alerts identifying potentially inappropriate medications, can improve appropriateness of prescribing [286].

6.5 Community pharmacists' involvement in AMS

6.5.1 Tasmanian Study

After conducting the initial literature review, we searched in addition for interventional studies, or any qualitative or quantitative study, to investigate the involvement of community pharmacists in AMS. It was revealed that there was paucity of studies regarding the role of community pharmacists in AMS. Therefore, a survey questionnaire was developed to find answers regarding the current knowledge, perceptions and practices of community pharmacists of AMS. The questionnaire, once drafted, was trialled amongst expert pharmacists and academics and subsequently, it was tested and validated online amongst community pharmacists in Tasmania, Australia. The major findings of the survey were that Tasmanian community pharmacists have some knowledge of AMS and understand the importance of it. The major barriers were lack of access to patient data, poor access to antibiotic guidelines, lack of collaboration with general practitioners (GP) and a lack of education regarding AMS. This study was published in the International Journal of Clinical Pharmacy. The questionnaire used in this study was found to be of acceptable reliability and validity and the research suggested the need for a larger study to further validate the newly developed questionnaire.

6.5.2 Australian study

A national study of community pharmacists from all states and territories in Australia was conducted in the next phase to further validate the survey questionnaire and to gather more data regarding the barriers and facilitators which community pharmacists face regarding AMS. The survey questionnaire was an improved and reduced version derived of the Tasmanian pilot study. The questionnaire comprised 44 questions in several sections related to current practices, perceptions, knowledge, barriers and facilitators, and was hosted online. The findings of this nationwide study were no different than those found in the Tasmanian study. Major barriers reported by the survey participants were lack of patient data, lack of access to antibiotic guidelines and lack of coordination with the GPs. The major facilitators were mirroring the barriers pointed out by the survey participants. Additionally, the necessity of AMS education was stressed by the participants, and a change in community pharmacy funding and a compensation model to be supportive of AMS were also mandated. The open-ended questions at the end of each section further guided, through qualitative analysis of the responses, the need to explore comprehensively the underlying reasons for the barriers of community pharmacists' participation in AMS. This study has been published in the Journal of Global Antimicrobial Resistance.

In both the Tasmanian and nationwide Australian survey, as presented in the Chapters 3 and 4, the community pharmacists identified, reported and suggested various initiatives, strategies and opportunities that can effectively contribute to AMS in the community setting. Community pharmacists also suggested that development and implementation of a community AMS framework is a key to improving quality and safety activity for their patients. The most dominant and underlying requirement, as recommended by the participants of the survey, was the need for AMS education and training in optimising antimicrobial use.

6.5.3 Qualitative study

Findings from the quantitative studies were then used to inform the subsequent qualitative research presented in the fifth chapter of this thesis, so as to help triangulate findings and gain more in-depth understanding of factors unique to community pharmacists and AMS. The interview guide comprised questions related to community pharmacists' understanding of AMS, repeat antibiotic prescriptions, GP/pharmacist relationships, e-health records, delayed prescribing, and concerns related to patient education, pharmacist knowledge and perceptions. In summary, the qualitative study pointed towards two main themes: a fragmented healthcare system and a clinical and practice paradox. It is envisaged that these key findings will assist and facilitate Australian community pharmacists to:

- address key resource and governance deficiencies;

- specify target prescribing areas;
- motivate change by addressing underlying public and patient's attitudes towards AMS, and
- devise a solution for AMS implementation considering the key features unique to the Australian community pharmacists.

6.5.3.1 Governance structure and AMS resources

It was previously unclear whether community pharmacies in Australia had the resources and an appropriate governance structure for community wide AMS implementation, which is a resource intensive initiative involving a multitude of stakeholders. Results from the Tasmanian and national surveys indicated that community pharmacists are deficient in a number of areas which have been described as critical to the successful adoption of AMS. An example is the absence of a community AMS framework in Australia which can help to establish standards of practice to optimise antimicrobial use. Without any AMS framework, the community sector will continue to experience difficulties in tackling inappropriate antimicrobial prescribing.

The lack of accessible resources for community pharmacists was not only a concern among survey participants, but also among interview participants who felt that community pharmacist support for AMS was not at the same level as that in the hospital sector. The perceived barriers of community pharmacists to conduct AMS activities most likely means that they are not given adequate resources and infrastructure to carry out patient consultations. Hence, addressing this issue may significantly assist in improving community pharmacists' contribution to AMS.

Studies have shown that community pharmacists can play an important role in AMS, with many AMS strategies originating directly from educational and clinical activities which can be led by community pharmacists. Health care systems need to pay attention to the integration of community pharmacies and pharmacists into the AMS process. This can be achieved by dedicating funding for AMS and providing on-going support through provision of AMS education, access to patient data and changes in the community pharmacy infrastructure.

Improving antimicrobial prescribing through community pharmacies requires a multi-pronged approach. There are concerns regarding the ability of prescribing guidelines to permeate into prescribing and dispensing practices. In Australia, the national antimicrobial guidelines (Therapeutic Guidelines: Antibiotic) [199] are well-established to be adapted in their entirety or to produce specific local guidelines. Availability of an electronic version of these national guidelines needs to improve in the community pharmacy sector to allow for better access.

6.6 Summary of the research findings

AMS programs are well established in hospitals to optimise antimicrobial usage and patient outcomes, and to reduce the emergence of antimicrobial-resistant organisms. However, AMS is not well established in the community setting and varies widely, based on local culture, policy and routine clinical practices. Over 90% of antibiotics for human use are dispensed in community health care settings, rather than in hospitals. The prescribers are family physicians, dentists, pharmacists and nurse practitioners who are working across a broad range of private offices, family health teams, urgent care clinics, emergency departments and aged care homes. While many programs have demonstrated pharmacist-led/pharmacist-involved AMS successes in inpatient and emergency department (ED) settings, there is a paucity of literature exploring these initiatives in the community setting. The literature review identified a lack of relevant research/programs. As a result, firstly, contextual factors influencing antibiotic misuse or overuse in the community from the community pharmacists' point of view were explored. Current evidence from the data suggests many barriers which community pharmacists are facing to initiate stewardship interventions in primary care. In this research project, barriers to and facilitators of AMS interventions and their implementation, and ways to address them, were identified. The research findings reflect a number of complex multi-factorial social and behavioural influences on prescribing, dispensing and consumption practices of antibiotics which can be improved with the involvement of the community pharmacists.

6.7 Findings at a glance

1) Community pharmacists value AMS and want to contribute to it. However, they do not always have adequate knowledge, access to resources or the confidence to do it.
2) Community pharmacists are mostly overburdened and very busy doing routine dispensing work; therefore, there is limited or no time for AMS.
3) Community pharmacists perceive GPs are not referring to the current antibiotic guidelines while prescribing antibiotics, especially in the case of children.
4) Community pharmacists perceive that the public, including patients and carers, do not know the serious implications of using left over antibiotics or AMR in general.
5) Community pharmacists are not paid for AMS, as pharmacists in a hospital are paid.
6) The qualitative study further informed us that community pharmacists are restricted in the undertaking of AMS due to the retail structure/funding system of community pharmacies in Australia.
7) The qualitative study also informed us that GPs prescribe inappropriate antibiotics because they have outdated and/or incorrect antibiotic references in their prescribing software.

8) The qualitative study informed us that the automatic repeat prescribing system leads to antibiotic hoarding and overuse. (Australian legislation regarding automatic repeats was changed shortly after conducting this study and now prescribing software does not automatically print repeats as a default option).
9) The qualitative study informed us that most antibiotic box sizes are not appropriate to the length of the infection.
10) The qualitative study informed us that MyHR is not as supportive for AMS as it should be because complete patient information is not present in it.
11) The qualitative study informed us that there is no supportive communication channel or network between community pharmacists and GPs, for rapid clarifications and communication regarding any prescription.
12) The qualitative study informed us that community pharmacists do not have access to information regarding the indication/diagnosis for which an antibiotic has been prescribed, in order to counter check it before dispensing.

These findings informed various AMS interventions to improve antibiotic prescribing practices in the community and confirmed the need to expand AMS to community settings through community pharmacists.

6.8 Recommendations for community pharmacists

AMR is a growing public health threat and community pharmacists have a responsibility to take a prominent role in AMS and other infection prevention and control programs. Community pharmacists can play their part in optimising prescribing behaviour, and monitoring antimicrobial use, infection control and education, even in the presence of current barriers. However, there still remains a need for a well-developed AMS framework and AMS trained pharmacists in community settings in the countries where it is not present, in order to standardise and regulate it. There is a need to:

1) dedicate a greater proportion of time to optimise prescribing behaviour and to monitor antibiotic use;

2) refer to the therapeutic guidelines for each antimicrobial prescription, in order to review each individual patient's regimens so that therapy is optimised;

3) regularly and periodically educate other pharmacy staff about the appropriate use of antimicrobials;

4) organise, involve and participate in education, training and public engagement to optimise antimicrobials; be an easy and accessible source of information and education of antimicrobial use and resistance for the community; be involved and participate actively in public health education and awareness programmes aimed at AMR and infection control in the community;

7) improve coordination with the prescribers and involve them in community awareness programs, so as to influence and support them positively in developing the understanding that antimicrobials are a limited resource which should be reserved for more severe infections;

8) regularly monitor and audit antimicrobial usage of the pharmacy; develop and keep an antibiotic check list to complete when filling an antimicrobial prescription, including age, dose, duration, allergy, interaction and appropriateness;

9) take education and training related to AMS programme/course/framework/new research; if not already present, develop orientation programs, policies and procedures for handling antimicrobial prescriptions, in order to train new community pharmacists; in advance, initiate a calendar of AMS activities, including raising awareness of World Antimicrobial Awareness Week to encourage best practices among the general public; do not reinvent the wheel but use the international, regional and local AMS

resources for continuing pharmacy education on the subject so as to remain updated, and

10) establish competency in the following areas to improve and update clinical knowledge and skills:

a) Pharmacology of anti-infective agents including:

- Spectrum of activity
- Clinical indications
- Principles of pharmacokinetics and pharmacodynamics (PK/PD)
- Therapeutic drug monitoring
- Common adverse effects, as well as those that are rare but significant
- Important drug interactions

b) Basic microbiology and infectious diseases:

- Diagnostic criteria, treatment options and existing clinical guidelines for common infections
- Basic mechanisms of antimicrobial resistance, common resistance profiles with corresponding risk factors, and directed treatment options
- Correct specimen collection techniques
- Limitations of current diagnostic techniques for infectious diseases
- Interpretation of microbiology results and antibiograms, their utility and limitations

c) Basic clinical skills:

- Communication with patients and healthcare providers
- Clinical review and patient evaluation, including severity of infection and patient factors affecting treatment choice
- Clinical documentation and reporting

With all the roles and responsibilities listed above, change in the system and the AMS framework will still be required to facilitate measurements of the outcomes and impact in a systematic manner for the following:

1) The AMS framework will guide a standardised antibiotic monitoring and feedback mechanism across all community pharmacies of a country or a region.

2) The AMS framework will follow regulated and standard process measures and outcome indicators.

3) The AMS framework will be utilised in national, regional and local surveillance of AMR and AMU.

The following types of knowledge and skills are necessary for a community pharmacist to be part of any AMS program:

- Principles of AMS, including aims, ethical considerations, and controversies;
- Quality improvement strategies, and
- Project management skills.

Community pharmacists suggested continuing access to AMS education, point of care assistive tools to guide antimicrobial prescribing and change in the overall infrastructure of the community pharmacy towards AMS supportive policies and procedures.

6.9 Strengths and limitations of the research project

There are many factors which are difficult to control which may have influenced the findings, as Creswell said "*There is the potential for a researcher to bias their research*" [287]. One of the major limitations from the results of this thesis may be sample size, voluntary participation, pharmacy workload and survey fatigue, leading to low response rates. It is likely that participants represented a highly motivated group of individuals, a factor which may also bias results.

The strength of the included studies is the quantitative and qualitative data of the research, which is considered consistent, precise and reliable. While the quantitative studies provided a macro view of all the required details to understand community pharmacists' perceptions regarding AMS, the qualitative study examined the details and in-depth views of community pharmacists about AMS barriers and facilitators, through open-ended and conversational methods.

The research adapted a mixed method approach which is especially useful in understanding contradictions between quantitative results and qualitative findings. This research reflects the participants' point of view and gives a voice to study participants, ensuring that study findings are grounded in participants' experiences.

6.10 Possible future suggestions for research

Antimicrobial resistance is a significant worldwide problem, largely driven by selective pressure exerted through antimicrobial use, which warrants continuing research. Promoting the appropriate use of antimicrobials requires identification of opportunities to safely reduce antimicrobial prescriptions, for example in the management of mild common infections in the community. In terms of AMS, Sweden is a model country having developed the Swedish strategic program against AMR, also known as Strama [288]. This program highlighted the importance of adapting a long-term multidisciplinary approach at both local and national level to contain AMR. The Strama initiatives include active surveillance of AMR, a restrictive approach to antimicrobial prescribing and a broad education campaign to increase public awareness [289]. The main success factor was their bottom-up preventive approach in collection, collation and analysis of the data and later sharing and implementation of infection treatment guidelines with all the stakeholders. Antimicrobial prescriptions in Sweden decreased by overall 43% through Strama and their antimicrobial use is amongst the lowest in the world both in humans and animal healths [290]. The work done by and the lesson from Strama could help inform other countries efforts to tackle AMR.

It is imperative to include community pharmacists who are in unique position to provide triage for the clinical management of infections. Although research on the role of various stakeholders and effective community AMS interventions has been expanded in recent years, additional studies are necessary in order to determine how to scale up such AMS interventions effectively, by involving community pharmacists. To date, most of the studies have been conducted in research networks and outpatient practices associated with large institutions. These studies have been supported with resources that might not be available at an average clinic or community pharmacy, so it would be difficult to inform the clinical management in the community environment about the optimal use of antibiotics.

There is also a need to develop an effective and comprehensive AMS program as part of undergraduate education. Moreover, reinforcing policies, involving community pharmacists, pharmacies, drug supply, distribution and sales, regarding antimicrobial prescribing, dispensing and use, are also urgently required.

6.11 Conclusion

The thesis has fulfilled the aims and objectives as outlined in the introductory chapter. Notably, the thesis has illustrated a need for AMS in the community setting and the importance of the role of the community pharmacist in AMS. It has shown that the burden of antimicrobial use is high and optimisation is required. The studies in this thesis have shown that community pharmacists understand the need for AMS frameworks and they generally do value them. This thesis has also suggested workflow solutions to help guide successful implementation of AMS programs in the community pharmacy. There are now specific recommendations in implementing AMS in community pharmacies, that is, by removing barriers and facilitating changes in the current pharmacy infrastructure in particular, and in health care settings in general. The work presented in this thesis has helped answer a number of important questions regarding the way in which the support of community pharmacists in AMS can be introduced to the community healthcare sector, an area that previously had very little information to guide decisions.

This thesis has provided a mechanism for AMS implementation by way of:

- determining the barriers in knowledge, attitudes, practices and perceptions that need to be overcome;
- identifying a main stakeholder, the community pharmacist, missing from the big picture, and
- providing a means to tailor existing AMS strategies to organisational factors inherent in the Australian community pharmacy sector.

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