Patterns and determinants of community antibiotic use in Australia: observational studies using large electronic health datasets

Zhuoxin Peng

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Thesis Title and Abstract sheet

Thesis Title

Patterns and determinants of community antibiotic use in Australia: observational studies using large electronic health datasets

Thesis Abstract

Background: Antibiotic overuse in clinical practice is an important driver for antibiotic resistance. However, there is insufficient granularity regarding Australian community antibiotic prescribing patterns reported in the literature.

Aim and design: I conducted four population-based retrospective observational studies to understand the pattern of antibiotic use and the determinants in the Australian c ommunity. Chapter 2 examined the rate of antibiotic dispensing and microbiology testing in older adults by their comorbidities. Chapter 3 examined the adherence to guide lines in urinary tract infection episodes in general practice when antibiotics were prescribed. Chapter 4 compared the likelihood of antibiotic prescribing for upper respirator y tract infections in regular and after-hours general practice consultations. Chapter 5 examined the general practice-level broad- to narrow-spectrum antibiotic ratio and its association with patients' antibiotic treatment non-response within the practice.

Methods: Chapter 2 was based on the 45 and Up Study, a large cohort study on older Australians linked to routinely collected health databases including antibiotic dispen sing data. Chapter 3 to 5 used MedicineInsight, a national database of electronic health records from Australian general practices. Both descriptive analysis and multivaria ble modelling were used to identify determinants of antibiotic use.

Findings: 1) There was a discord between the high antibiotic dispensing rate and low microbiology testing rate among older people with chronic respiratory diseases, sug gesting potential antibiotic overuse among those subgroups. 2) Some patient groups who are recommended to have routine urine testing in urinary tract infection episode s, e.g., patients aged <5 years, with recurrent urinary tract infections, or living in nursing homes, had a lower likelihood of testing than comparable patient groups. 3) After- hours consultations were associated with a higher likelihood of immediate antibiotic prescribing for upper respiratory tract infections in general practice. 4) The ratio of pres cribing of broad- to narrow-spectrum antibiotics at the practice-level was a predictor for patients' antibiotic treatment non-response in respiratory tract infection episodes, e ven if the patients had no previous individual-level antibiotic exposure.

Conclusion: These findings could provide implications for developing targeted antibiotic stewardship programs in the Australian community.

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Publication Details #1

Full Title:	Microbiology testing associated with antibiotic dispensing in older community-dwelling adults
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Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 2 contains the original work. The study I present in this chapter addresses Objective 1 of my thesis: to estimate the community dispensing rate of antibiotics with high potential of resistance in the older Australian population who are particularly susceptible to antibiotic-resistant infections and compare it with the rate of microbiology testing among the study populations.

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Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 3 contains the original work. The study I present in this chapter addresses Objective 2 of my thesis: to examine the adherence to the recommendations in clinical guidelines regarding routine urine testing and antibiotic treatment for patients at low or high risk of complicated urinary tract infections in general practice.

Publication Details #3

Full Title:	After-hours consultations and antibiotic prescribing for self-limiting upper respiratory tract infections in general practice
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Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 4 contains the original work. The study I present in this chapter addresses Objective 3 of my thesis: to examine the association between after-hours consultations and the likelihood of antibiotic prescribing for self-limiting upper respiratory tract infections in general practice.

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Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 5 contains the original work. The study I present in this chapter addresses Objective 4 of my thesis: to quantify the independent contributions of general practice- and patient individual-level antibiotic prescribing to subsequent antibiotic treatment non-response in respiratory tract infections.

Candidate's Declaration

I confirm that where I have used a publication in lieu of a chapter, the listed publication(s) above meet(s) the requirements to be included in the thesis. I also declare that I have complied with the Thesis Examination Procedure.

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List of tables

Table 1.1 Quality indicators for assessing the appropriateness of antibiotic use suggested from earlier research (Page 13)

Table 1.2 Correlation between antibiotic resistance in the Global Antimicrobial Resistance Surveillance System (GLASS) priority pathogens and the use of antibiotics (Page 26)

Table 1.3 Summary of studies in the thesis (Page 40)

Table 1.4 Comparison of the 45 and Up Study and MedicineInsight data (Page 41)

Table 4.1. Proportion of first-time upper respiratory tract infections (URTI) episodes with immediate antibiotics prescribed (Page 88)

Table 4.2 Multivariable analysis evaluating the association between temporal factors and the proportion of immediate antibiotic prescribing in upper respiratory tract infection (URTI) episodes (Page 89)

List of abbreviations

aIRR: adjusted incidence rate ratios

aORs: adjusted odds ratios

APDC: Admitted Patient Data Collection

ATC: Anatomical Therapeutic Chemical

AURA: Antimicrobial Use and Resistance in Australia

CheReL: Centre for Health Record Linkage

CI: confidence intervals

COPD: Chronic obstructive pulmonary disease

DDD: Defined Daily Doses

DHS: Department of Human Services

DID: Defined Daily Doses per 1000 inhabitants per day

DUSC: Drug Utilisation Sub-Committee

FDA: Food and Drug Administration

GEE: generalised estimating equations

GLASS: Global Antimicrobial Resistance Surveillance System

GP: general practitioner

ICD-10-AM: International Classification of Diseases, 10th version, Australian Modification

ICU: intensive care units

MBS: Medicare Benefits Schedule

MRSA: methicillin-resistant *Staphylococcus aureus*

NSW: New South Wales

PBS: Pharmaceutical Benefits Scheme

RACF: residential aged care facilities

RBDM: Registry of Births, Deaths and Marriages

RTIs: respiratory tract infections

UNSW: University of New South Wales

URTIs: upper respiratory tract infections

UTIs: urinary tract infections

WHO: World Health Organization

Abstract

Background: Antibiotic overuse in clinical practice is an important driver for antibiotic resistance. However, there is insufficient granularity regarding Australian community antibiotic prescribing patterns reported in the literature.

Aim and design: I conducted four population-based retrospective observational studies to understand the pattern of antibiotic use and the determinants in the Australian community. Chapter 2 examined the rate of antibiotic dispensing and microbiology testing in older adults by their comorbidities. Chapter 3 examined the adherence to guidelines in urinary tract infection episodes in general practice when antibiotics were prescribed. Chapter 4 compared the likelihood of antibiotic prescribing for upper respiratory tract infections in regular and after-hours general practice consultations. Chapter 5 examined the general practice-level broad- to narrow-spectrum antibiotic ratio and its association with patients' antibiotic treatment non-response within the practice.

Methods: Chapter 2 was based on the 45 and Up Study, a large cohort study on older Australians linked to routinely collected health databases including antibiotic dispensing data. Chapter 3 to 5 used MedicineInsight, a national database of electronic health records from Australian general practices. Both descriptive analysis and multivariable modelling were used to identify determinants of antibiotic use.

Findings: 1) There was a discord between the high antibiotic dispensing rate and low microbiology testing rate among older people with chronic respiratory diseases, suggesting potential antibiotic overuse among those subgroups. 2) Some patient groups who are recommended to have routine urine testing in urinary tract infection episodes, e.g., patients aged <5 years, with recurrent urinary tract infections, or living in nursing homes, had a lower likelihood of testing than comparable patient groups. 3) After-hours consultations were associated with a higher likelihood of immediate antibiotic prescribing for upper respiratory tract infections in general practice. 4) The ratio of prescribing of

broad- to narrow-spectrum antibiotics at the practice-level was a predictor for patients' antibiotic treatment non-response in respiratory tract infection episodes, even if the patients had no previous individual-level antibiotic exposure.

Conclusion: These findings could provide implications for developing targeted antibiotic stewardship programs in the Australian community.

Table of contents

Acknowledgements VI

List of tables VIII

List of abbreviations IX

Abstract XI

Preface 3

Chapter 1: Introduction 9

1.1 Literature review 10

1.1.1 Mechanisms of antibiotic resistance 10

1.1.2 Prevalence of antibiotic use in clinical practice 11

1.1.3 Determinants of antibiotic use 18

1.1.4 Antibiotic-associated adverse events 25

1.1.5 Methods applied in previous literature 30

1.1.6 Knowledge gaps and rationales for my research projects 31

1.1.7 Description of general practices in Australia 32

1.1.8 Summary 33

1.2 Thesis objectives 34

1.3 Methods 34

1.3.1 Data sources 35

1.3.2 The comparison of 45 and Up Study and MedicineInsight data 39

1.3.3 Ethical approval 39

1.4 References 41

Chapter 2 Microbiology testing associated with antibiotic dispensing in older community dwelling adults 60

Chapter 3 Microbiology testing and antibiotic treatment for urinary tract infections in general practice 71

Chapter 4 After-hours consultations and antibiotic prescribing for self-limiting upper respiratory tract infections in general practice 80

4.1 Summary 81

4.2 Introduction 83

4.3 Methods 84

4.3.1 Data sources 84
4.3.2 Ethical approval 84
4.3.3 URTI episodes and immediate antibiotic prescribing 84
4.3.4 Temporal variables and covariates 85
4.3.5 Statistical analysis 86
4.4 Results 86
4.5 Discussion 90
4.6 Conclusion 92
4.7 References 92
Chapter 5 Practice- and individual-level antibiotic prescribing associated with antibiotic treatment non-response in respiratory tract infections 96
Chapter 6 Discussion and Conclusions 107
6.1 Major findings in the thesis 108
6.2 The original contribution in the context of existing literature 110
6.3 Implications for practice and future research 111
6.3.1 Improving general practitioners' awareness of guideline-based antibiotic prescribing in certain circumstances 111
6.3.2 Increasing organisation-level support for quality antibiotic prescribing 112
6.3.3 Using validated quality indicators to monitor antibiotic use and assess the effectiveness of antibiotic stewardship programs 113
6.3.4 Antibiotic stewardship in the era of COVID-19 113
6.3.5 Recommendations for future research 114
6.4 Strengths and limitations 115
6.5 Overall conclusion 118
6.6 References 119
Appendix 1. Supplementary methods, tables and figure for Chapter 2 124
Appendix 2. Supplementary methods, tables and figure for Chapter 3 139
Appendix 3. Supplementary methods and tables for Chapter 4 158
Appendix 4. Supplementary methods and tables for Chapter 5 166

Preface

Antibiotics are agents used to inhibit bacterial pathogens and treat bacterial infections [1]. The use of antibiotics in clinical practice is considered one of the most important medical milestones in the 20th century [2]. It was estimated that the introduction of antibiotics has increased the average human life expectancy by 23 years [1]. However, the emergence of antibiotic resistance may erode the progress made in the battle against infectious diseases. Antibiotic-resistant organisms refer to organisms such as bacteria that have adapted to antibiotics and can survive when they are exposed to antibiotics [3]. With the selective advantage under the environmental pressure of antibiotics, antibiotic-resistant organisms will gradually predominate and finally result in eliminating the effectiveness of antibiotic treatment [4]. There is a large health burden globally due to antibiotic-resistant infections, as they usually lead to a longer length of symptoms, higher risk of complications and death if compared with antibiotic-susceptible infections [5]. There are approximately 700 000 deaths each year associated with infection caused by antibiotic-resistant organisms in the world [6]. The additional health care cost due to antibiotic resistance in the US was estimated at 55 billion US dollars in 2012 [7]. This cost was estimated to be 77 billion US dollars in China according to a national survey in 2017 [8]. The prevalence of antibiotic resistance varies among different geographical regions. Hashiguchi et al. analysed the susceptibility of bacterial isolates from patients' blood or cerebrospinal fluid in 52 countries and estimated the average proportion of eight priority antibiotic-resistant organisms for each country [9]. They found that Nordic countries and the Netherlands had the lowest average proportions of antibiotic-resistant microorganisms (5%) whereas India, Russia, China and Romania had the highest proportions (40%); Australia has a relatively low

proportion of third-generation cephalosporin-resistant *K. pneumoniae* (6%), carbapenem-resistant *Pseudomonas aeruginosa* (3%), and penicillin-resistant *Streptococcus pneumoniae* (6%) as well as a relatively high proportion of methicillin-resistant *Staphylococcus aureus* (18%) and vancomycin-resistant *Enterococcus faecalis* (21%).

When bacteria are exposed to a type of antibiotic for a period of time, the growing resistance to the antibiotic will naturally occur [10]. Discovering a new generation of antibiotics and reducing unnecessary antibiotic use are two basic solutions for the emergence of antibiotic resistance [11]. However, the development of new antibiotics has slowed in recent years. Between 1983 and 1987, there were 16 new antibiotic agents approved by the U.S. Food and Drug Administration (FDA) for clinical use [2], while between 2016 and 2020, only 8 new antibiotic agents were approved by the FDA [12]. Considering the dramatic increase in antibiotic resistance rates around the world since the 1990s [13], developing new antibiotics is not sufficient to address the current threat of antibiotic resistance [2]. Therefore, preserving the effectiveness of existing antibiotics and reducing unnecessary antibiotic use is important for stopping the acceleration of antibiotic resistance. Antibiotic prescribing in primary care settings is one of the most important drivers for antibiotic resistance, which accounts for 80% to 90% of total antibiotic prescribing for clinical use [11, 14, 15]. Furthermore, a large proportion of antibiotic prescribing behaviours in primary care settings may not be necessary or appropriate. A study in the US showed that approximately 75% of antibiotic prescribing in primary care settings were not consistent with clinical guidelines [16]. Similarly, an Italian study in general practices showed that 67% of antibiotic prescriptions in respiratory tract infection episodes were not indicated by clinical guidelines [17]. For nursing home residents, it was reported that the proportion of inappropriate outpatient antibiotic prescribing was 49% for all infections and 58% for urinary tract infections [18]. All these findings suggest that understanding the pattern of antibiotic prescribing behaviours and reducing antibiotic overprescribing in the

community are urgent issues for the control of antibiotic resistance.

To provide a better understanding of the pattern and the determinants of antibiotic use in the Australian community, I conducted four population-based epidemiological studies using large electronic health databases, which form the body of my PhD thesis. Two large-scale population-based databases in Australia, the 45 and Up Study [19] and the MedicineInsight programme [20] were used in my thesis. The detail of these two databases will be described in the introduction chapter.

In the first year of my PhD program, I had access to the 45 and Up Study. But there is a lack of information on reasons for prescribing in the database. Therefore, my focus in the Project 1 was on antibiotic use and patients' comorbidities which are included in the 45 and Up Study. From the second year of my PhD program, the MedicineInsight database became available to me. This dataset had the advantage over the 45 and Up Study as it contains further clinical details regarding the visit where antibiotics were prescribed in the community and allowed me to investigate potential reasons for antibiotic prescribing. Therefore in the following three projects, I extended my research projects to focus on factors related to antibiotic prescribing patterns in specific infections in the community, including respiratory tract infections and urinary tract infections. I selected these infections because they are commonly diagnosed and treated in the community (See Section 1.1.2.3) and there are various gaps in our understanding of antibiotic prescribing behaviours in primary care (See Section 1.1.6).

Chapter 1 of the thesis provides a literature review that introduces the mechanisms of antibiotic resistance, previous work on the measurement of antibiotic usage, the determinants for antibiotic prescribing, the potential adverse effects of antibiotic use, methodologies applied in the research area of antibiotic use, as well as knowledge gaps in this research area in Australia. It also outlines the objectives of the thesis, the data sources, study populations, and methods used in my studies.

Chapter 2 is an original research article published in a peer-reviewed journal that estimated the community dispensing rate of antibiotics with high potential of resistance

in the older Australian population who are vulnerable to antibiotic-resistant infections and compared it with the rate of microbiology testing using a large cohort or Australian adults, the 45 and Up Study.

Chapter 3 is an original research article published in a peer-reviewed journal that examined the adherence to the recommendations in clinical guidelines regarding routine urine testing and antibiotic treatment for patients at low or high risk of complicated urinary tract infections in Australian general practice. This study used an electronic general practice database, MedicineInsight.

Chapter 4 includes a study that examined the association between after-hours consultations and the likelihood of antibiotic prescribing for self-limiting upper respiratory tract infections in Australian general practice using MedicineInsight data. The manuscript has been submitted for peer-review publication.

Chapter 5 is an original research article published in a peer-reviewed journal that quantified the independent contributions of general practice- and patient individual-level antibiotic prescribing to subsequent antibiotic treatment non-response in respiratory tract infections in Australia using the MedicineInsight data.

Chapter 6 includes a summary of key findings from the previous chapters, the discussion of results, the strengths and the limitations of the studies, the implications for practice and future research, and the overall conclusion of the thesis.

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Chapter 1: Introduction

1.1 Literature review

In this literature review, I will first give a brief introduction to the mechanisms of antibiotic resistance. Then I will review the current methods applied for measuring antibiotic use in clinical practice. After that, I will present the current trends in antibiotic use in the world and Australia. Next, I will discuss the determinants of antibiotic use and the potential adverse effect of antibiotic overuse. Finally, I will summarise the common study designs, current healthcare systems in Australia, and knowledge gaps in this research area.

1.1.1 Mechanisms of antibiotic resistance

Antibiotics play an important role in treating and preventing bacterial infections. However, the emergence of antibiotic resistance increases the likelihood of antibiotic treatment failure and severely threatens human health [1]. Under the selective pressure from antibiotic use, bacteria with genetic traits against antibiotic effect are more likely to spread in the environment and finally result in decreased effectiveness of antibiotics. However, usually there will be a fitness cost when bacteria develop antibiotic resistance, which means when the pressure of antibiotic prescribing lifts, non-resistant strains can return to dominance [2]. There are several important mechanisms that bacteria have evolved to cope with the effect of antibiotics. Bacteria can produce enzymes to degrade antibiotics [3]. The most common examples of these kinds of enzymes are beta-lactamases which can break the structure of beta-lactam antibiotics [3]. Bacteria can also modify their antibiotic-binding sites so that the antibiotics cannot interfere with the bacteria, such as vancomycin-resistant *enterococci* [4]. Some bacteria like *Escherichia coli* have developed an efflux system so that they can pump antibiotics out, which is the major mechanism for the development of tetracycline resistance [5].

Antibiotics can be divided into narrow-spectrum or broad-spectrum antibiotics according to the range of pathogens they are effective against [6, 7]. Narrow-spectrum

antibiotics, e.g. penicillins and first-generation cephalosporins, are often only effective against a certain group of bacteria while broad-spectrum antibiotics, e.g., amoxicillin & clavulanate, second- or third-generation cephalosporins, and quinolones, can be effective against a wider range of bacteria [8]. Since broad-spectrum antibiotics may act on both the causative pathogens and other non-pathogens in the treatment of infectious diseases, they will exert higher selection pressure on the host microbiome and bring a higher risk of antibiotic resistance [6]. Therefore, current clinical guidelines recommended that in most conditions narrow-spectrum antibiotics should be used as first-line treatment and broad-spectrum antibiotics should only be used when narrow-spectrum antibiotics are not effective [9-11]. The volume and appropriateness of broad-spectrum antibiotic use are regarded as key indicators for assessing the quality of antibiotic prescribing in clinical practice [12].

Exposure to antibiotics is one of the most important drivers of accelerating antibiotic resistance [1]. Antibiotic prescribing in healthcare directly exerts selection pressure on human pathogens [13]. Apart from clinical use, antibiotics are commonly used in agriculture and veterinary medicine [14]. Environmental microbes with antibiotic resistance are widespread in water, soil, animals, and plants [15]. When humans contact antibiotic-containing food products, animals with antibiotic-resistant bacteria, or even water and soils contaminated by antibiotic-resistant bacteria, the risk of antibiotic-resistant infections may also increase [16]. Although there is a difference between antibiotic classes used in food production and human medicine, the positive correlation between antibiotic use in agriculture and the rate of antibiotic-resistant infections in humans has been observed in previous studies [17]. Therefore, surveillance and research on antibiotic use inside and outside health care facilities are important for controlling antibiotic resistance.

1.1.2 Prevalence of antibiotic use in clinical practice

1.1.2.1 Measuring the volume and quality of antibiotic use in clinical practice

An essential issue when conducting surveillance on antibiotic use in clinical practice is to determine proper indicators of measuring antibiotic use. The most common indicator used in surveillance programs is the total amount of antibiotics prescribed per person-time. The rationale of using this simple indicator is mainly based on the concept that antibiotic use in most conditions is in fact not appropriate and a reduction of total antibiotic use can be directly regarded as a reflection of improvement in antibiotic prescribing [16]. The World Health Organization recommends the number of Defined Daily Doses (DDD) as a measurement unit in its guideline for drug consumption [18]. DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" [19]. The estimation of DDD, e.g., DDD per 1000 inhabitants per day (DID) or DDD per 1000 occupied-bed days, is widely used to assess the total amount of systemic antibiotic use or a specific type of systemic antibiotic in different healthcare settings around the world [12, 20, 21]. Another important measurement unit in antibiotic usage assessment is the number of consumed or dispensed antibiotic prescriptions. One common example of this kind of indicator is the prescriptions or packages per 1000 inhabitants per day. At present, many surveillance reports and studies on antibiotic use in Europe use prescriptions per person-day together with DID, mainly due to the fact that the DDD may be questionable when it is applied to special patient groups who are not suitable for a standard dose, such as children or patients with renal insufficiency [22]. A previous study in Australia found that the measurement of prescriptions per person-day can correlate well with DDD in general practice [23].

A limitation of simply using the measure of total antibiotic usage is that the variation of total antibiotic use may be due to the seasonal or annual variation in infectious diseases rather than the appropriateness of antibiotic prescribing. The ideal method is to directly identify the number of antibiotic prescriptions inconsistent with therapeutic guidelines case by case. Several studies adopted this method to monitor the appropriateness of antibiotic usage in clinical practice [24-28]. They usually required a group of experts to

review the medical records to determine whether a treatment was appropriate or not. The process of this kind of "peer-review" is often time-consuming and not feasible for studies based on large scale databases.

An alternative way to determine the appropriateness of antibiotic prescriptions is to design a set of specific quality indicators according to key points in clinical guidelines which are feasible for coding. According to previous studies [29-31], I classified the quality indictors which could be used as measures of antibiotic use in outpatient and impatient settings into six types: 1) the proportion of antibiotic volume by specific classes; 2) antibiotic choice for specific indications; 3) proportion of antibiotic treatment directed by laboratory testing results; 4) dose; 5) routes of administration; 6) duration of antibiotic treatment; 7) sound documentation of indication and therapy plan. The types and examples are shown in Table 1.1. A good example of these kinds of programs in Australia is the National Antimicrobial Prescribing Survey which assessed the appropriateness of antibiotic use at scales in surgical, hospital and aged care settings in Australia [32].

Table 1.1 Quality indicators for assessing the appropriateness of antibiotic use suggested from earlier research.

Indicators	Examples
Proportion of specific antibiotic classes	"Ratio of No. of items for quinolones to No. of items for all antibiotics" [31]
Antibiotic choice for specific indications	"Use of quinolones for acute bronchitis" [29]
Laboratory-directed therapy	"Before starting systemic antibiotic therapy in hospitalised adults with a suspected bacterial infection, at least 2 sets of blood cultures should be taken" [30]
Dose	"Dose and dosing interval of antibiotics should be adapted to renal function" [30]

Routes of administration	"Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 48–72 h on the basis of the clinical condition and when oral treatment is adequate" [30]
Duration of antibiotics treatment	"The maximum duration of empirical systemic antibiotic treatment should be 7 d." [30]
Documentation	"An antibiotic plan should be documented in the case notes at the start of systemic antibiotic treatment" [30]

1.1.2.2 Global antibiotic usage

There has been an increasing trend in global antibiotic use in recent years. According to a study based on the antibiotic consumption data of 76 countries from 2000 to 2015 [33], the consumption of antibiotics per person increased 39%, from 11.3 DDD per 1000 inhabitants a day to 15.7 DDD per 1000 inhabitants a day; this study also indicated that the total antibiotic consumption has increased 65% from 21.1 billion DDDs in 2000 to 34.8 billion DDD in 2015, and will rise threefold in 2030 if policies of antibiotic stewardship do not substantially change [33].

There are disparities in antibiotic usage among different countries. In general, populations in high-income countries consume more antibiotics than people in middle- and low-income countries, but the growth rate of antibiotic consumption in middle- and low-income countries, especially those middle-income countries with high economic growth, such as China, Brazil and Russia, is much more rapid than high-income countries [33, 34]. Not only the use of antibiotics but also the pattern of antibiotic stewardship largely varies among different regions. High-income countries often have comprehensive and evidence-based national policies, guidelines and standards for antibiotic stewardship, e.g. EU Guidelines for the Prudent Use of Antimicrobials in Human Health [35], and Core Elements of Hospital Antibiotic Stewardship Programs in the US [36]. Antibiotic stewardship programs are usually poor or even absent in low-income countries [37]. In

India and China, many broad-spectrum antibiotics can be accessed by patients over the counter, which means prescriptions from doctors are not needed in the process of dispensing, resulting in high antibiotic use and a reduction in opportunities for antibiotic stewardship [34].

In 2015, the most consumed antibiotic class in the world was amoxicillin and clavulanate, accounting for 39% of total antibiotic consumption, followed by cephalosporins, quinolones, and macrolides, which accounted for 20%, 12%, and 12% of total antibiotic consumption, respectively [33]. Different antibiotic classes showed different trends in their usage. A national report on inpatient antibiotic use in the US from 2006 to 2012 revealed that, although the trend in total antibiotic use did not significantly change over time, there was an increasing trend of broad-spectrum antibiotic use, especially glycopeptides, 3rd and 4th generation cephalosporins, and penicillin & β-lactamase inhibitor combinations [38]. The preference for narrow- vs broad-spectrum antibiotics among clinicians varies among different countries. A cross-national study in Europe reported that the ratio of broad- to narrow-spectrum antibiotic prescriptions was only 0.6 in Denmark but as high as 120.2 in Italy [39].

1.1.2.3 Antibiotic use in Australia

In Australia, the most comprehensive monitoring program is the Antimicrobial Use and Resistance in Australia (AURA) Surveillance System established by the Australian Commission of Safety and Quality in Healthcare in 2016 [12]. The commission routinely releases comprehensive data on trends in national antibiotic use and resistance in the community and hospitals, which is comparable to surveillance data in other countries and can be used to guide future antibiotic stewardship in Australia [12]. According to the AURA report in 2019, there was a downward trend in the total antibiotic use in the community between 2013 (1208 prescriptions per 1000 inhabitants a year) and 2017 (1067 prescriptions per 1000 inhabitants a year) in Australia[12]. Meanwhile, the national antibiotic resistance rate of most priority pathogens has

remained stable in recent years [12]. The major concerns have been the increasing rate of fluoroquinolone-resistant *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA) in community settings [12]. However, when compared with other high-income countries, the volume of community antibiotic prescriptions in Australia (22.7 defined daily doses [DDDs] for 1000 inhabitants a day in 2018) is higher than the average rate of EU countries (18.7 DDDs for 1000 inhabitants a day), and double the rate in Sweden (10.8 DDDs for 1000 inhabitants a day) and the Netherlands (8.9 DDDs for 1000 inhabitants a day) [40, 41]. The gap between Australia and EU countries reflects the potential for further reducing community antibiotic prescribing in Australia.

In Australian general practice, the most common reason for antibiotic prescribing is upper respiratory tract infections, followed by urinary tract infections and skin & soft tissue infections [42]. Cefalexin, amoxicillin, and amoxicillin & clavulanate were the three most frequently prescribed systemic antibiotics in Australian primary care settings [43]. The AURA report suggested that particular concerns about community antibiotic prescribing in Australia include antibiotic overprescribing for common infections (especially upper respiratory tract infections which are mostly of a viral origin) and non-adherence to national antibiotic treatment guidelines in clinical practice [12]. The report suggested that research should particularly focus on the quality use of amoxicillin & clavulanic and quinolones; besides, clinicians should be cautious when prescribing antibiotics to patients who have chronic obstructive pulmonary diseases or live in aged care facilities, as these populations have a high risk of recurrent and complicated infections and they may not respond well to first-line antibiotic treatment [12].

Antibiotic stewardship is defined as a system-wide approach to improve antibiotic prescribing behaviours and preserve the effectiveness of antibiotics [44], which include four core elements: to measure and monitor the appropriateness of antibiotic prescribing; to improve the diagnosis of infectious diseases and minimise antibiotic misuse; to optimise antibiotic selection, dose, course, and route of administration; and to promote rational antibiotic use among clinicians and patients [36]. In Australia, the

AURA monitoring system routinely reported the status of antibiotic use and resistance in both community and hospital settings [12]. Besides, the Drug Utilisation Sub-Committee (DUSC) in Australia also report community antibiotic dispensing data from the Pharmaceutical Benefits Scheme (PBS), a national medication subsidy program for Australian citizens supported by the Australian government [43]. The *Therapeutic Guidelines: Antibiotic* is the national evidence-based guideline providing advice regarding infection management and antibiotic treatment for healthcare providers in Australia [11]. Apart from recommendations for antibiotic regimens, it also includes guides to assist in shared decision making when clinicians encounter patients with self-limiting upper respiratory tract infections, flowcharts outlining differential diagnosis between infections of viral and bacterial origins, and specific antibiotic prescribing strategies for particular patient groups such as residents in aged care facilities and Aboriginal and Torres Strait Islander Australians [11]. Besides, there are also national and local programmes to enhance antibiotic prescribing in Australia. For instance, NPS MedicineWise, a not-for-profit organisation supporting quality use of medicines which is funded by the Department of Health in Australia, used to provide a national prescribing auditing program for Australian general practitioner (GP) participants; GPs can receive feedback regarding the quality of their recent antibiotic prescribing and improve antibiotic prescribing behaviours [45]. The Antimicrobial Awareness Week in Australia is an example of antibiotic awareness campaigns for the public [45]. Supported by the Australian government and the Australian Commission of Safety and Quality in Healthcare, the patients and consumers can participate in the educational activities organised in the week to increase the awareness of the threats of antibiotic resistance and the importance of rational antibiotic use. However, there are concerns regarding the availability and sustainability of those antibiotic stewardship programs in Australia. The Therapeutic Guidelines is only available by subscription to general practitioners, and a number of practitioners in Australia have no access to the flowcharts and prescribing guidelines. The NPS MedicineWise quality improvement program for

antimicrobial stewardship is discontinued in recent years and therefore currently GPs cannot not receive regular feedback about their appropriateness of antibiotic prescribing.

1.1.3 Determinants of antibiotic use

1.1.3.1 Age

Age is regarded as an important predictor of antibiotic use. A common pattern of antibiotic usage in Australia is that children and older people are more likely to be dispensed antimicrobial prescriptions than other age groups [12]. A similar association between age and antibiotic use was reported in other regions around the world. A study based on national primary care administrative databases in seven European countries also observed greater use of antibiotics among people aged under 9 years and over 80 years [46]; A time-series study between 2007 to 2014 based on a national insurance database in South Korea showed the highest rate of antibiotic prescribing was among children under 6 years old, followed by people aged over 65 years old [47]. This pattern can be ascribed to the low immunity and high susceptibility to infectious diseases among these populations. But results from some studies have suggested that the older population might have less awareness of antibiotic resistance, which could also lead to more requests for antibiotic prescriptions in clinical encounters [48, 49].

1.1.3.2 Sex

Previous studies have reported that women were more likely to use antibiotics than men. A cross-sectional study on one-year antibiotic use in Denmark found that women obtained 11% more prescriptions than men in general practice [50]. By measuring the crude rate of DDD of antibiotics per 1000 inhabitants per day, a study using health care databases from five European countries also found that women used more doses of

antibiotics than men [39]. Smith et al. adjusted for potential confounding factors and analysed the difference in antibiotic prescribing patterns between men and women in the UK [51]. They indicated that when comparing men and women with similar numbers of consultations there was no difference in antibiotic prescribing between men and women, and the greater use of antibiotics among women can be mostly explained by more frequent consultations among women. Meanwhile, Bagger et al found that there was no sex difference in the likelihood of unnecessary antibiotic use in the treatment for upper respiratory tract infections in Denmark[52]. The authors suggested that the higher rate of antibiotic use among women may be mainly due to their greater rate of general practice visits [51, 52]

1.1.3.3 Ethnicity

Ethnicity can be another important predictor of antibiotic use. In the US, white adults were found more likely to be prescribed broad-spectrum antibiotics for acute respiratory tract infectious diseases than other races [53]. Similarly, a US cohort study in paediatric emergency departments showed that black and Hispanic children were less likely to use antibiotics for viral illnesses, compared with white children [54]. There are few studies regarding the quality of antibiotic use among Aboriginal and Torres Strait Islander populations and other ethnic groups in Australia. In a case-control study performed in New Zealand, the Maori Indigenous people were dispensed fewer antibiotics prescriptions than other populations [55]. Those results suggest that socioeconomically disadvantaged minorities in multiethnic societies may face a different issue in antibiotic use. They are usually high-risk groups for infectious diseases but may have limited access to healthcare services [55]. The potential underuse of antibiotics should be of concern in the antibiotics stewardship and policy-making process for these populations.

1.1.3.4 Socioeconomic factors

As discussed, there are different patterns of antibiotic use in high-income and middle-/low-income countries. Individual-level socioeconomic status also affects antibiotic use at the individual level. The relationship between socioeconomic factors and antibiotic use can be complex. This is because socioeconomic status comprises numerous aspects, including the level of education, income, housing conditions, and remoteness of residence, etc. The interactive relationship among those factors also increases the difficulty of verifying the effect of socioeconomic factors on antibiotic use. Currently, the most frequently used study design for this issue is the ecological study based on data in middle- or high-income countries. Evidence based on individual-level data and from low-income countries is relatively scant. Some studies suggest that the use of antibiotics is positively correlated with income level [56, 57], while other studies came to the opposite conclusion [58, 59]. In addition, lower education level [57], urban residence [56], and smaller household size [60] were also identified as potential determinants for greater antibiotic use.

1.1.3.5 Access to healthcare facilities

Accessibility of healthcare facilities may be an important mediating factor that can help explain the association between antibiotic use and ethnicities and socioeconomic factors, as poor access to healthcare services among specific ethnic groups, patients living in rural areas, or patients with low socioeconomic status will lead to fewer chances to visit clinicians, and therefore receive fewer antibiotic prescriptions. A study on US medical insurance claim data found that variation in primary care visits can explain 45% of gaps in outpatient antibiotic prescribing after adjusting for other demographic factors [61]. However, in many low- and middle-income countries where antibiotics can be accessed without clinicians' prescription and antibiotic dispensing without prescriptions is even more common than antibiotic dispensing with prescriptions [62], this factor may have a weaker impact on actual antibiotic dispensing in the community.

1.1.3.6 Seasonality

Seasonal effects must be considered in studies examining trends in antibiotic use. According to previous studies, the number of antibiotic prescriptions usually increase in winter: Sun et al. reported a strong correlation between the winter months and antibiotic use in US community settings [63]; the winter peak of outpatient antibiotic use was also observed in European countries [64]. Meanwhile, a time-series study in Switzerland found that regions with more DDDs of overall antibiotics had higher seasonal variations in antibiotic prescribing [65]. The seasonal pattern of antibiotic use was particularly strong among older adults than other age groups, according to a study on US Medicare health data [66]. It is believed that the greater use of antibiotics in winter is related to the seasonal outbreak of upper respiratory tract infectious diseases. Since only 10% to 20% of upper respiratory tract infections are of bacterial origins [67], it can be considered a reflection of increased antibiotic overprescribing in the winter season [63, 66].

1.1.3.7 Healthcare settings

The pattern of antibiotic use can vary among general practices, hospitals, aged care facilities, and other healthcare settings. A meta-analysis reported that variations in antibiotic prescribing in DDD per 1000 inhabitants in intensive care units (ICU) are much larger than in outpatient settings, which could be due to greater heterogeneity in the types of patients, guideline recommendations, illness severity, and prescriber behaviours [68]. Long-term residence in aged care facilities, or nursing homes, is an independent risk factor for high use of antibiotics among the elderly. A large-scale retrospective cohort study among British residents compared the use of antibiotics in aged care facilities and the community and found that the average annual number of prescriptions of antibiotics per 100 inhabitants over 75 years old was 199 for those living in aged care facilities, significantly higher than those not living in the aged care facilities (142 prescriptions per

100 inhabitants) after adjusting for age, sex and health conditions [69]. A cohort study in Canada observed an extreme variation among nursing homes in antibiotic use: the prevalence of antibiotic prescribing in the highest-use nursing home can be as much as nine times higher than the lowest-use nursing home; and not surprisingly, living in high-use nursing homes was a significant predictor for antibiotic-associated adverse outcomes like antibiotic resistance or *Clostridium difficile* infections [70]. Inappropriate antibiotic treatment for asymptomatic bacteriuria and other urinary tract infections may largely contribute to the overuse of antibiotics in aged care settings [71].

The type of hospital, department, and clinician is also associated with the pattern of antibiotic prescribing. An ecological study on the determinants of antibiotic use in intensive care units in Germany found that the university-affiliated hospitals and hospitals with a greater number of beds were two independent predictors for higher antibiotic use, although they did not control for patient's illness severity in their analysis [72]. A cross-sectional study in US hospitals reported that critical care units, such as surgical critical care units and paediatric critical care units had much greater antibiotic use than other wards outside critical care units [73]. Patients admitted to the hospitals with those predictors are often in more severe conditions, thus they will consume more antibiotics. Compared with junior clinicians, senior clinicians have a lower rate of antibiotic prescribing in Australian general practice [74]. Besides, different types of clinicians may have different patterns of antibiotic prescribing. For example, infectious diseases specialists were reported to have a lower rate of inappropriate antibiotic prescriptions than other specialists in Turkey [75]. It is also reported that the co-attendance of a nephrologist can help increase the quality and appropriateness of antibiotic prescribing for patients with chronic kidney diseases in Canadian primary care settings [76].

1.1.3.8 Infection types

The type of infection is directly associated with antibiotic use. Antibiotics are only effective for bacterial infections and therefore are not supposed to be used for treating

viral infections, fungal infections, and non-infectious diseases. However, antibiotic overuse without indication is one of the most common patterns of inappropriate antibiotic prescribing in clinical practice. Although secondary bacterial infections may occur following viral respiratory tract infections [77], antibiotic treatment is not recommended in 80% to 90% of upper respiratory tract infection episodes in clinical guidelines as they are often self-limiting [11]. A study based on an elderly Australian population found that 56% of laboratory-confirmed influenza episodes in general practice had antibiotic prescriptions dispensed [78]. Although an exacerbation of asthma is not an indication for antibiotic prescribing in current clinical guidelines [79], 58% of patients hospitalized for exacerbations of asthma actually received antibiotic treatment according to a national study in the US [80]. It was estimated that more than 90% of acute rhinosinusitis cases are viral infections or self-limiting bacterial infections and therefore antibiotic therapy should be withheld in most conditions, but the actual antibiotic prescribing rate for acute rhinosinusitis was 41% in Australian general practice [67]. These data suggested the need for improving the appropriateness of decision making in antibiotic prescribing for these conditions in healthcare settings.

1.1.3.9 Chronic non-communicable diseases

Major chronic non-communicable comorbidities, e.g., diabetes, cancers, chronic kidney diseases, and cardiovascular diseases can also influence the use of antibiotics. On the one hand, patients with major chronic diseases are more susceptible to infections and therefore receive more antibiotics [81, 82]. A Danish national study showed that patients with Type 2 Diabetes had more antibiotic prescriptions than general populations without diabetes in the community [83]. There is a higher antibiotic prescribing rate among patients with cancers, as antibiotics for prophylaxis are routinely prescribed in surgery and chemotherapy for malignant tumours in the US [84]. On the other hand, the use of antibiotics should be restricted, adjusted, and cautiously reviewed among patients with chronic diseases for avoiding adverse side effects, e.g., antibiotic-associated kidney

damage and macrolide-associated cardiac arrhythmias [85, 86].

1.1.3.10 Vaccination and the use of other drugs

Alternatives to antibiotics such as vaccines and probiotics can help prevent infectious diseases and decrease the use of antibiotics as well as the probability of developing antibiotic resistance. The role of pneumococcal conjugate vaccination in reducing antibiotic prescribing has been widely reported by researchers, as several studies reported that there was a decreasing trend in antibiotic use for respiratory tract infections after the introduction of pneumococcal conjugate vaccination among children [87-89]. Knight et al. even found that influenza vaccines, although not directly targeting bacterial infections, may also help reduce antibiotics prescribed for patients, especially those inappropriate prescriptions for viral illness in Africa [90]. Lactobacillus rhamnosus GG, a type of probiotic, was reported to help decrease the use of antibiotics for gastrointestinal infections by improving gut microbiota in Finnish children [91]. Besides, some non-antibiotic drugs, e.g. statins, may also have anti-infective effects and can be used as potential adjunctive antibiotics to help decrease antibiotic resistance [92]; whereas other non-antibiotic drugs, especially immunosuppressant drugs like steroids, were identified as a risk factor for increasing antibiotic use and resistance in population-based cross-sectional studies [93, 94]. Limitations of these studies include the small sample size and unmeasured confounding factors such as patients' comorbidities. Therefore, those relationships between the non-antibiotic drugs and antibiotic resistance still require verification by clinical trials or large-scale observational studies.

1.1.3.11 Antibiotic stewardship programs

Antibiotic stewardship programs are important for healthcare providers to optimize the use of antibiotics and decrease the occurrence of antibiotic resistance. Numerous studies have reported on the effectiveness of antibiotic stewardship programs for reducing

overall antibiotic use and the likelihood of inappropriate antibiotic use in high-income countries. Successful programs have mainly addressed the following five aspects: 1) using electronic approval systems for antibiotic prescribing [95, 96]; 2) auditing the appropriateness of antibiotic prescriptions by expert teams [32, 95, 97-101]; 3) providing educational programmes for clinicians to improve antibiotic prescribing and communication skill with patients [97, 98, 102]; 4) organising public campaigns regarding basic principles of appropriate antibiotic use for patients and the general public [97, 102]; and 5) timely updating clinical guidelines based on the latest research evidence [95, 101]. The primary outcomes of these stewardship programs were the reduction in total antibiotic use (from 6% to 27%) [97, 102-105] or broad-spectrum antibiotic use (10% to 60%) [95, 96, 99, 103]. Secondary outcomes included lower antibiotic resistance rates [96], the reduction of antibiotic cost due to lower use [103, 105], and no increase in patient mortality, length of stay in hospitals, and hospital re-admissions [99, 103, 104].

1.1.4 Antibiotic-associated adverse events

1.1.4.1 Antibiotic resistance

The positive association between previous antibiotic use and the resistance rate of pathogenic bacteria has been widely found in previous studies. The World Health Organisation established a Global Antimicrobial Resistance Surveillance System (GLASS) for monitoring specific pathogens and their resistance to antibiotics [106]. The resistance of all eight priority pathogens in GLASS [106], i.e. *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Salmonella* spp., *Shigella* spp., *Neisseria gonorrhoeae*, and *Acinetobacter baumannii*, have been reported to be associated with high use of one or more antibiotic classes (shown in Table 1.2). A study based on national antibiotic consumption and antibiotic resistance databases in 29 European countries found an association between *Escherichia coli* resistance to

fluoroquinolones, aminopenicillins, and carbapenems and the consumption of corresponding antibiotic classes; this study also showed the association of *Streptococcus pneumoniae* resistance with the use of macrolides, as well as the association of *Klebsiella pneumoniae* resistance with carbapenem and fluoroquinolone use [107]. The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), one of the most important pathogens for healthcare-associated infection [1], was also associated with the higher use of fluoroquinolones in the community [63] and third-generation cephalosporins, glycopeptides, and carbapenems in hospital settings [108]. A meta-analysis reported that another two major pathogens of multi-drug hospital-associated infections, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, were associated with patients' previous exposure to a number of antibiotic classes, e.g., fluoroquinolones, glycopeptides and aminoglycosides [109]. In terms of food-borne infection caused by drug-resistant pathogens, previous fluoroquinolone use is a major significant risk factor for the development of resistance in *Salmonella* spp. and *Shigella* spp. [110, 111]. Wind et al. examined the *Neisseria gonorrhoeae* isolates collected in a sexually transmitted infectious diseases clinic in the Netherlands and found a significant association between patients' history of azithromycin use and a decreased azithromycin sensitivity in *Neisseria gonorrhoeae* isolates [112]. In addition to those priority pathogens in routine antibiotic resistance surveillance, multidrug resistant tuberculosis, which is a severe threat to population health in middle- and low- income countries, is also associated with previous antibiotic treatment [113, 114].

Table 1.2 Correlation between antibiotic resistance in the Global Antimicrobial Resistance Surveillance System (GLASS) priority pathogens and the use of antibiotics

Bacteria	Antibiotics that bacteria have developed resistance to
Escherichia coli	fluoroquinolones, aminopenicillins, and carbapenems[107];
Staphylococcus aureus	fluoroquinolones;[63] third-generation cephalosporins, glycopeptides, carbapenems;[108]
Streptococcus pneumoniae	macrolides[107];
Klebsiella pneumoniae	carbapenems, fluoroquinolones[107];
Salmonella spp	fluoroquinolones;[110]
Shigella spp	fluoroquinolones;[111]
Neisseria gonorrhoeae	macrolides;[112]
Acinetobacter baumannii	fluoroquinolones, glycopeptides, aminoglycosides;[109]

The duration of antibiotic treatment is an important predictor of the likelihood of antibiotic resistance. There have been several studies focusing on the association between the duration of antibiotic treatment and antibiotic resistance. Devasia et al. found that the duration of fluoroquinolone exposure more than 10 days before diagnosis of tuberculosis was associated with fluoroquinolone-resistant tuberculosis [115]; Yusuf et al. investigated the association between different durations (short term: 1-3 days vs. long term >8 days) of antibiotic treatment and antibiotic resistance to *Pseudomonas aeruginosa* and found a significant association of higher resistance risk with long term antibiotic treatment [116]. Guillemot et al. identified an association between long term low-dose antibiotic exposure and antibiotic resistance among *Staphylococcus aureus* nasopharyngeal colonization in healthy children [117]. A similar association was also identified in a randomized trial on a long-term low dose antibiotic prophylaxis regimen for urinary tract infection [118]. A concern about the antibiotic regimens with shortened duration is whether the shortened duration will impact the effectiveness of antibiotic treatment. Several studies have compared the effectiveness of short-term and long-term antibiotic regimens for different types of infection. A meta-analysis on the treatment of acute bacterial sinusitis showed that there was no significant difference in the successful treatment rate between short term

therapy (3-7 days) and long-term therapy (6-10 days) [119]. There was a study with similar results on lower respiratory tract infections from another meta-analysis [120]. Another meta-analysis on bacteraemia in critical care settings also showed that there was no difference between the effect of the long and short course on the clinical cure rate, microbiology cure rate as well as survival rate [121]. Regarding post-operative antibiotic treatment, a meta-analysis showed that the duration of antibiotic treatment is not associated with the risk of intra-abdominal infection after appendicectomy among adults [122]; whereas another meta-analysis showed no difference in preventing endometritis and fever between short-term and long term antibiotic prophylaxis for women having cesarean section [123]. But a meta-analysis regarding the treatment of acute pyelonephritis and septic urinary tract infections found that, despite no difference in treatment success rates between short course and long course antibiotic treatment in the overall analysis, a significantly higher risk of microbiological failure after short course treatment was found among subgroups who had urogenital abnormalities [124], suggesting the need for considering patients' underlying health conditions.

1.1.4.2 Opportunistic infection

Selective pressure caused by antibiotic use can change patients' microbiome and trigger the overgrowth of opportunistic organisms and subsequent infections [125]. One of the most important antibiotic-associated opportunistic infections is *Clostridium difficile* infection. The risk of *Clostridium difficile* infection in high-risk healthcare settings, e.g., hospital and nursing homes, is highly associated with previous antibiotic exposure, especially among patients above 65 years old or using corticosteroids [70, 126-128]. Exposure to almost all common antibiotic classes, including fluoroquinolones, macrolides, cephalosporins, penicillins and beta-lactamase inhibitor combinations, have been reportedly associated with an increased risk of developing *Clostridium difficile* infection [129]. However, the use of rifampicin can protect patients from *Clostridium difficile* infection due to its bioactivity against *Clostridium difficile* [130]. A time-series

study found that there was a lag between the association between antibiotic use and *Clostridium difficile* infection, which can be up to 5 months [131].

1.1.4.3 Antibiotic hypersensitivity

Almost all antibiotic classes can cause hypersensitivity reactions or allergic reactions. According to a large-scale population survey in 2009, 7.9% of US populations were reportedly allergic to penicillins, which was the leading cause of antibiotic hypersensitivity, followed by sulfonamides (4.3%), macrolides (1.2%), and cephalosporins (1.1%) [132]. However, when a patient is labelled with "antibiotic allergy" in clinical practice, it may not mean the patients are truly allergic to the antibiotic. A cross-sectional study in Australia found that nearly 20% of patients labelled "antibiotic hypersensitive" actually had a non-allergic reaction to antibiotics and should be de-labelled [133]. Interestingly, a previous study showed that patients with penicillin allergy received 65% more antibiotic prescriptions than patients without penicillin allergy after controlling for patients' characteristics, which suggested that there is a dramatic increase in the use of other second-line antibiotics and a higher risk of antibiotic resistance among these patients [134].

1.1.4.4 Other potential adverse outcomes

There is a concern regarding the association between previous exposure to antibiotics and the risk of non-communicable diseases. Previous studies have reported that early life exposure to antibiotics is associated with many types of allergic diseases, including asthma, atopic dermatitis, and allergic rhinitis [135-137], which might be attributed to the alteration of children's microbiomes after antibiotic exposure [135]. This theory was also considered as the potential explanation for the association of previous antibiotic use with obesity, diabetes, and inflammatory bowel diseases identified in previous epidemiological studies [138-140]. However, these associations currently cannot be verified as causal

relations due to the limitations of designs and data collection in these observational studies. For example, there is a lack of studies that collected the dose and duration of previous antibiotic treatment and examine the dose-response relationship. Another challenge is how to determine the direction of causal relationship between antibiotic exposure and chronic diseases. These studies were mainly based on administrative medical records to identify the development of diseases and previous antibiotic exposure. Since chronic diseases usually have a long development period, patients may have already developed the diseases before the date of diagnosis recorded in the database, and their high antibiotic prescribing rates could be the result rather than the cause of the diseases.

1.1.5 Methods applied in previous literature

Numerous studies have been performed to analyse the trends in antibiotic use, identify the determinants of antibiotic use, understand the potential adverse consequences, and explore strategies for improving antibiotic use. The most frequently used study designs in this area are ecological or cross-sectional studies using administrative data, e.g. European Surveillance of Antimicrobial Consumption Project [141] and the United States Medicare database [142]. Cohort studies have also been used to identify risk factors for antibiotic overuse [129, 143]. Some researchers used randomised trials to examine the effectiveness of interventions on optimising antibiotic use [97, 144] and used a meta-analysis for pooled data [119]. Mathematical epidemiological models were used to simulate the impact of antibiotic use on antibiotic resistance [145]. In addition to quantitative analysis, researchers also use qualitative methods to assess the validity of antibiotic prescribing quality indicators in healthcare settings [29]. Surveillance data and administrative data have been preferred because of the good accessibility for researchers, large sample size, and sound representativeness; but the lack of important individual variables, e.g., details of clinical presentations, chronic health conditions, and frequency of GP visits, is a barrier to generating high-quality epidemiological evidence in these

administrative data-based studies. By contrast, survey data and experimental studies are often single-centre studies with limited sample sizes. Large-scale cohort studies linking to administrative data may be able to fill the research gap of antibiotic use.

1.1.6 Knowledge gaps and rationales for my research projects

Although national antibiotic surveillance reports such as the AURA report [12] and DUSC report on antibiotic dispensing in the Pharmaceutical Benefits Scheme (PBS) [43] can provide an overall picture of antibiotic use in Australian communities and enable researchers to examine the trends, there is still insufficient granularity regarding antibiotic prescribing patterns by antibiotic classes, patient groups, and indications. Few studies have ever linked antibiotic prescribing data to patient-level data, e.g., demographics, socioeconomic status, health conditions, and health service records. The individual-level information might provide an opportunity to better understand antibiotic prescribing for key patient groups and certain conditions where there is a high prescribing rate in general practice.

My literature review in the Section 1.1.3.1 showed that one of the high-risk patient groups for antibiotic use is the aged population [46, 47]. However, there are few studies measuring the incidence rate of broad-spectrum antibiotic dispensing and related microbiology testing among older Australians, especially those with major chronic diseases who are particularly susceptible to bacterial infections. This is also the rationale for my first PhD project (Chapter 2), which examined the rate of antibiotic dispensing and microbiology testing in older adults by their comorbidities.

A better understanding of adherence to guidelines in antibiotic treatment for specific infections is also needed, as the feature of different infections may require different antibiotic stewardship. Some antibiotic prescribing patterns for common infections, e.g., respiratory tract infections and urinary tract infections in the community are not adherent to clinical guidelines and still not fully investigated. This is the rationale for my research in Chapter 3, 4 and 5. As discussed in Section 1.1.3.8, the rate of antibiotic prescribing

for upper respiratory tract infections in Australia was reportedly four times higher than what is recommended in guidelines [67], but it is still not known which factors are influencing these prescribing patterns in general practice. Assessing adherence to antibiotic treatment guidelines in urinary tract infections is even more complex, as there are different recommendations for treating patients with a low and high risk of complicated urinary tract infections. For example, a urine culture is not necessary for non-pregnant women but is needed to guide more appropriate and targeted antibiotic use among pregnant women, men and children [11]. To the best of my knowledge, no previous study has investigated the quality of antibiotic treatment for urinary tract infections among different patient groups in Australian general practice. Apart from this, the current knowledge on antibiotic-associated adverse events is limited (Section 1.1.4). My search of the literature revealed that no study on this issue considered both the patient individual level antibiotic exposure and aggregate-level (e.g., district-level, hospital-level, or general practice-level) factors. The independent effect of aggregate-level antibiotic use and individual patient-level antibiotic use on the likelihood of antibiotic resistance or non-response and their interaction has not been fully examined.

Overall, investigating the prevalence, determinants, and influence of antibiotic use with individual patient-level data might fill these research gaps. Additionally, a better understanding of antibiotic use among vulnerable patient groups (e.g., children, older adults, and patients with underlying chronic diseases) and the driving factors could be the basis of better targeted antibiotic stewardship programmes.

1.1.7 Description of general practices in Australia

The primary care system in Australia consists of general practice, pharmacy, dentistry, health promotion and other services [146]. General practice service is regarded as the cornerstone of the primary healthcare system as well as the gateway to

the secondary and tertiary healthcare system in Australia [147]. When people are seeking healthcare services, general practice is usually the first place people visit. If there are complicated medical problems and specialist service is required, general practitioners are responsible to refer the patients to hospitals or other specialist medical services. In Australia, people are not required to register in fixed general practices but it is estimated that 90% of patients will choose to visit a regular practice when they need primary healthcare services [148]. Traditionally, the normal working hours in general practice include 8 am to 6 pm on weekdays which are not public holidays and for some practices 8 am and 12 pm on Saturdays; it may vary among different practices [149].

Approximately 85% of the cost generated in the general practice service is reimbursed by the Australian government [146]. Australian citizens only pay for a small proportion of medical costs in the general practice whereas most fees are paid by the Medicare Benefits Schedule, a national healthcare service subsidy program funded by the Australian government [150]. And general practitioners can get paid when there is a public or private billing generated in the primary healthcare service [151]. In addition, general practitioners may receive extra payment when they are undertaking certain services such as after-hours consultations [152].

1.1.8 Summary

Antibiotic prescribing in clinical practice is one of the most important drivers for the emergence of antibiotic resistance, which is a major threat to human health. Antibiotic overuse is common in clinical practice, therefore monitoring and reducing unnecessary antibiotic prescribing in healthcare facilities is essential for controlling antibiotic resistance. Several determinants for antibiotic use at patient-, practice-, and health system-level were recognised by previous studies, most of which included limited patient individual-level information and insufficient granularity of antibiotic prescribing patterns. This knowledge gap may restrict the development of targeted antibiotic stewardship

programs in the community.

1.2 Thesis objectives

The overall aim of the thesis is to fill in those knowledge gaps of antibiotic prescribing patterns in the community and provide implications for controlling antibiotic overuse. Specifically, the objectives of the four studies in my thesis are as follows:

1) To estimate the community dispensing rate of antibiotics with high potential of resistance in the older Australian population who are particularly susceptible to antibiotic-resistant infections and compare it with the rate of microbiology testing among the study populations.

2) To examine the adherence to the recommendations in clinical guidelines regarding routine urine testing and antibiotic treatment for patients at low or high risk of complicated urinary tract infections in general practice.

3) To examine the association between after-hours consultations and the likelihood of antibiotic prescribing for self-limiting upper respiratory tract infections in general practice.

4) To quantify the independent contributions of general practice- and patient individual-level antibiotic prescribing to subsequent antibiotic treatment non-response in respiratory tract infections.

1.3 Methods

Two large-scale population-based databases in Australia, the 45 and Up Study [153] and the MedicineInsight programme [148] were used in my thesis. The Study in Chapter 2 was based on the 45 and Up study. The Studies in Chapter 3, 4 and 5 were based on the MedicineInsight programme. This section will introduce the data sources and

general methods used in the four studies included in the thesis. A summary of the methods for these four studies can be found in Table 1.3.

1.3.1 Data sources

1.3.1.1 The 45 and Up Study

The 45 and Up study is a large-scale longitudinal cohort study in Australia, which is developed and managed by the Sax Institute [153]. The Sax Institute is a non-profitable organisation funded by the government of New South Wales, with the aim of improving healthcare quality, health service, and health policy in New South Wales and Australia. The study recruited cohort participants aged over 45 years in New South Wales between 2006 and 2009. The participants are Australian citizens or permanent residents randomly sampled from the Medicare database, a universal health insurance scheme in Australia. The Sax Institute sent consent forms for participation and baseline questionnaires to the randomly sampled population. All participants were required to complete the questionnaire when they were recruited. The questionnaire contained questions regarding participants' demographic characteristics, socioeconomic status, personal health behaviours, chronic health conditions and medical history. By the end of 2009, a total of 267000 participants were recruited and the overall response rate was 18%, making the 45 and Up Study one of the largest cohort studies in the Southern Hemisphere [153].

Participants' information collected in the baseline questionnaires can be linked to routinely collected data in relation to their use of healthcare service and medications from a series of electronic health databases, e.g., the PBS database, Medicare Benefits Schedule (MBS) database, the NSW Admitted Patient Data Collection (APDC) database, and the NSW Registry of Births, Deaths and Marriages (RBDM) database. While the PBS database records subsidised pharmaceuticals for Australian citizens, MBS is a national healthcare service subsidy program for Australian citizens supported

by the Australian government, covering general practice consultations, pathology testing and diagnostic imaging [150]. The APDC is a dataset that contains electronic health records of inpatient hospital admissions in New South Wales [154]. The RBDM is a registry database containing records of births, marriages and deaths registered in New South Wales [154]. A unique and anonymized ID provided by the Department of Human Services in Australia was assigned to each participant by the Sax Institute so that researchers can use the ID to extract and link participants' records in PBS and MBS databases. Participant's records were linked to the APDC and RBDM database by the NSW Centre for Health Record Linkage (CHeReL) using probabilistic matching of patients' identifying characteristics such as age, sex, and medical history. The detailed data profile of the 45 and Up study has been published [153]. The cohort data linked to other datasets were obtained by my primary supervisor for a large program of work on infectious diseases within the cohort of which the work for my thesis is one component.

In the study in Chapter 2, I extracted participants' information from the following databases in the 45 and Up study:

1) The baseline questionnaire database, which contains the patients' demographics, socioeconomic status, lifestyle behaviours, and health conditions at baseline. The questionnaires used in the 45 and Up Study are available at https://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/.
2) The PBS database, which contains the records of medications dispensed in the community for participants under the universal healthcare system subsidised by the Australian government [155]. Data collected in the PBS database include the generic names of medications, date of dispensing, and the Anatomical Therapeutic Chemical (ATC) codes [18] for the medications.
3) The MBS database, which contains participants' records of GP visits and healthcare services under the universal healthcare system subsidised by the Australian government [150]. Data collected in the MBS database include the categories of health care services (e.g., laboratory tests, radiographic

examinations, and therapeutic procedures), the MBS item numbers assigned to each service category, the healthcare facilities where the services were provided (community or hospital), the date of service provided, and the charge of service.

4) The NSW APDC database, which contains participants' detailed records of hospital admissions in New South Wales. Data collected in the APDC database include the dates of admission and discharge, the diagnoses and the International Classification of Diseases and Related Health Problems, Australian modification (10^{th} version, ICD-10-AM) codes [156], the length of stay and other hospital admission-related information.
5) The NSW Registry of Births, Deaths and Marriages (RBDM) database, which contains participants' death information. The death dates of cohort participants were extracted from this database.

1.3.1.2 MedicineInsight Program

MedicineInsight is a large-scale longitudinal database of national primary care records in Australia which was established by NPS MedicineWise [148]. NPS MedicineWise is a non-profitable organisation funded by the Australian Government Department of Health. The purpose of the MedicineInsight program is to improve the quality of healthcare service in Australian general practice. From 2011, MedicineInsight collected de-identified patients' electronic health records from general practices in Australia that consented to participate in the programme [157]. Patients in the participating general practices were informed and can opt out if they do not want their de-identified data accessed by NPS MedicineWise. After a general practice agrees to participate in the program, NPS MedicineWise will regularly extract patients' records from the general practice using third-party data extraction tools (i.e., GRHANITE and cdmNet) [157]. Currently, the MedicineInsight program has collected longitudinal health records of 3.6 million patients from more than 600 general practices across Australia, representing 8% of all Australian general practices [148].

MedicineInsight provides comprehensive patients' healthcare information and general practices' characteristics in several datasets. Patients' records in different datasets can be linked by a unique and anonymised identifying number created for each patient. A detailed data profile of MedicineInsight has been published [148]. My studies in Chapter 3 to 5 in the thesis used a random sample of 25% of patients in the programme which was made available for researchers in the UNSW School of Population Health under a collaborative agreement with NPS MedicineWise.

In these studies, I extracted participants' information from the following databases in MedicineInsight:

1) the Encounter dataset, which contains the date and the detailed reasons for the GP encounters recorded in free text. In MedicineInsight, the encounter is defined as "an interaction between a patient and a healthcare professional" in general practice [148].
2) the Diagnosis dataset, which contains the diagnoses that the GP made in the encounters (free text) as well as the date of diagnosis.
3) the Script Item and Prescriptions datasets containing information regarding prescriptions in the GP encounters, e.g., the generic name and active ingredient of the medications (free text), the date of prescribing, the reason for prescribing (free text), routes, and the number of repeats.
4) the Requested Test dataset, which contains the records of laboratory tests requested in general practice, including the type of tests (free-text), the reasons for the test (free-text), and the date of tests.
5) the Patient dataset, which contains the demographics of patients, e.g., sex, year of birth, smoking and alcohol consumption status, and indigenous status.
6) the Conditions dataset, which contained a patient's medical records of major chronic diseases, e.g., cardiovascular diseases, diabetes, cancers, chronic kidney diseases, as well as the index dates. Those records in the Condition dataset were derived from fields in the Encounter, Diagnosis, the Script Item

and Prescriptions datasets by NPS MedicineWise.

7) the Immunisation dataset, which contains the records of patients' immunisation history, including the vaccination name (free text) and vaccination date.
8) the Site dataset, which contains the geographical characteristics of general practices, including the state, the regional remoteness index, and the regional socioeconomic status index of the sites.

1.3.2 The comparison of 45 and Up Study and MedicineInsight data

The participants in the 45 and Up Study were randomly sampled from residents aged over 45 years old in New South Wales at the recruitment stage. Therefore, the cohort data are suitable for estimating the incidence of antibiotic dispensing among older Australian populations. Compared with the 45 and Up Study, the advantages of the MedicineInsight program include its national coverage, its inclusion of patients of all age groups, and more detailed information regarding the diagnoses in the GP encounters and reasons for pharmaceutical prescribing. However, unlike those datasets linked to 45 and Up Study, one disadvantage of the MedicineInsight data is that it does not provide standardised coding such as ATC codes or ICD-10-AM codes to identify specific diagnoses, types of health services, and prescriptions. Therefore, researchers must develop methods to identify specific conditions or prescriptions. MedicineInsight does not use a random sampling method to recruit general practices or patients. However, the prevalence of several common diseases among Australians estimated in MedicineInsight is similar to the results from other data sources, suggesting there is good validity of MedicineInsight data [158-160]. A comparison of 45 and Up Study and MedicineInsight data is shown in Table 1.4.

1.3.3 Ethical approval

My study based on the 45 and Up Study was approved by the University of New

South Wales Human Research Ethics Committee (number 10186) and the NSW Population and Health Services Research Ethics Committee (HREC/10/CIPHS/97). The ethics approval was obtained by my primary PhD supervisor A/Prof. Bette Liu as a part of a larger research program.

My studies based on MedicineInsight were approved by the University of New South Wales Human Research Ethics Committee (number HC180900). I applied for and obtained the ethics approvals.

Table 1.3 Summary of studies in the thesis

	Chapter 2	**Chapter 3**	**Chapter 4**	**Chapter 5**
Design and population	Cross-sectional study: analysis of older populations in the 45 and Up Study.	Cross-sectional study: analysis of urinary tract infection episodes where antibiotics were prescribed recorded in the MedicineInsight data.	Cross-sectional study: analysis of upper respiratory tract infection episodes recorded in the MedicineInsight data.	Longitudinal study: analysis of respiratory tract infection episodes with antibiotics prescribed recorded in the MedicineInsight data.
Outcome	Incidence rate of community antibiotic dispensing and microbiology testing in 2015.	Proportion of urinary tract infection encounters with antibiotics prescribed that had accompanying urine microbiology testing between Jan 2013 and July 2018.	Proportion of upper respiratory tract infection episodes where antibiotics were prescribed between Feb 2016 and Jan 2019.	Proportion of respiratory tract infection antibiotic treatment non-response in 2018
Factor of interest	Comorbidities including COPD, asthma, cancer, diabetes, chronic kidney diseases, and cardiovascular	Patients' characteristics associated with complicated urinary tract infections: male, children, pregnancy, aged	The after-hour GP visits at weekends and public holidays.	General practice- and patient individual-level antibiotic prescribing in the past year.

	diseases; residence in aged care homes.	care home residents, with recurrent urinary tract infections, diabetes, and chronic kidney diseases.		
Statistical analysis	Multivariable zero-inflated negative binomial regression	Generalised estimating equations	Generalised estimating equations	Generalised estimating equations

Table 1.4 Comparison of the 45 and Up Study and MedicineInsight data

	45 and Up Study	**MedicineInsight data**
Participants	Residents in New South Wales aged over 45 years old at the recruitment stage (2006 to 2009)	Patients attending general practices that consent to participate in the MedicineInsight program across Australia
Age group	Adults aged 45 years or older in 2006-2009	All ages
Sampling	Random sampling from Medicare database	Non-random sampling
Linked to routinely collected health data	Yes	No
Antibiotic prescription information	Linked antibiotic dispensing data	Antibiotic prescribing data
Reasons for GP encounters	Not included	Included in most records
ATC/ICD-10-AM codes	Included in the linked datasets	Not included

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Chapter 2 Microbiology testing associated with antibiotic dispensing in older community dwelling adults

Chapter 2 contains the original work:

Peng Z, Hayen A, Kirk MD, Pearson S, Cheng AC, Liu B. Microbiology testing associated with antibiotic dispensing in older community-dwelling adults. *BMC Infect Dis* 2020; **20**: 306.

The study I present in this chapter addresses Objective 1 of my thesis: to estimate the community dispensing rate of antibiotics with high potential of resistance in the older Australian population who are particularly susceptible to antibiotic-resistant infections and compare it with the rate of microbiology testing among the study populations.

The study filled in the current knowledge gap regarding the variation of antibiotic dispensing by patients' chronic health conditions in the community. The discord between a high dispensing rate of antibiotics with great potential of resistance and a relatively low rate of related microbiology testing among older Australians with chronic lower respiratory diseases suggest the potential for excessive antibiotic prescribing in these patient groups.

As the first author of the article, I developed the overall study aims and design in consultation with my supervisors, conducted the data analysis, wrote the first draft of the manuscript and revised it with feedback and revisions by my supervisors and other co-authors, and submitted it to the peer-reviewed journal.

The supplementary methods, tables, and figure of this study are shown in Appendix 1 (Page 124)

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RESEARCH ARTICLE Open Access

Microbiology testing associated with antibiotic dispensing in older community-dwelling adults

Zhuoxin Peng[1*], Andrew Hayen[2], Martyn D. Kirk[3], Sallie Pearson[4,5], Allen C. Cheng[6] and Bette Liu[1]

Abstract

Background: It is commonly recommended that microbiological assessment should accompany the use of antibiotics prone to resistance. We sought to estimate the rate of microbiology testing and compare this to dispensing of the World Health Organization classified "watch" group antibiotics in primary care.

Methods: Data from a cohort of older adults (mean age 69 years) were linked to Australian national health insurance (Pharmaceutical Benefits Scheme & Medicare Benefits Schedule) records of community-based antibiotic dispensing and microbiology testing in 2015. Participant characteristics associated with greater watch group antibiotic dispensing and microbiology testing were estimated using adjusted incidence rate ratios (aIRR) and 95% confidence intervals (CI) in multivariable zero-inflated negative binomial regression models.

Results: In 2015, among 244,299 participants, there were 63,306 watch group antibiotic prescriptions dispensed and 149,182 microbiology tests conducted; the incidence rate was 0.26 per person-year for watch group antibiotic dispensing and 0.62 for microbiology testing. Of those antibiotic prescriptions, only 19% were accompanied by microbiology testing within − 14 to + 7 days. After adjusting for socio-demographic factors and co-morbidities, individuals with chronic respiratory diseases were more likely to receive watch group antibiotics than those without, e.g. asthma (aIRR:1.59, 95%CI:1.52–1.66) and chronic obstructive pulmonary disease (COPD) (aIRR:2.71, 95%CI:2.48–2.95). However, the rate of microbiology testing was not comparably higher among them (with asthma aIRR:1.03, 95%CI:1.00–1.05; with COPD aIRR:1.00, 95%CI:0.94–1.06).

Conclusions: Priority antibiotics with high resistance risk are commonly dispensed among community-dwelling older adults. The discord between the rate of microbiology testing and antibiotic dispensing in adults with chronic respiratory diseases suggests the potential for excessive empirical prescribing.

Keywords: Watch group antibiotics, Microbiology testing, Community, Stewardship

* Correspondence: zhuoxin.peng@student.unsw.edu.au
[1]School of Public Health and Community Medicine, University of New South Wales (UNSW), Sydney, NSW 2052, Australia
Full list of author information is available at the end of the article

Background

Antibiotic resistance is a severe threat to global public health. It is estimated that each year infections caused by antibiotic-resistant pathogens result in 700,000 deaths worldwide; the number might reach 10 million in 2050 if there is no effective action to curb resistance [1]. The overuse of antibiotics is considered as an important contributor to antibiotic resistance, [2] which could be effectively reduced by appropriate antibiotic stewardship [3]. To guide the use of antibiotics, the World Health Organization (WHO) proposed a three-category antibiotic classification system in 2017 [4]: namely access, watch, and reserve group antibiotics. Access group antibiotics are the first-line choices for common infections; watch group antibiotics are those with greater potential for developing resistance; and reserve group antibiotics are those considered "last resort" antibiotics for infections. WHO recommends that antibiotics in the watch and reserve groups (see Supplementary Table 1) should be limited to particular conditions and need special stewardship and monitoring [4]. There are also restricted antibiotic lists proposed in several countries for limiting the use of those antibiotics with high resistance potential [5–7]. Clinical guidelines for antibiotic prescribing in these countries also do not recommend them as the first choice for empirical therapy for common conditions in the community, e.g. respiratory tract infections, skin/wound infections, and urinary tract infections [8–10].

Earlier epidemiological studies and surveillance programs, nationwide and worldwide, have reported the use of some classes of watch/reserve group antibiotics and their relationship with antibiotic resistance in the population, e.g. the use of macrolides and *Streptococcus pneumoniae* resistance [11, 12], and the use of fluoroquinolones and cephalosporins and *Escherichia coli* resistance [11–13]. Some emerging multidrug-resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococcus (VRE), were also reported to be associated with the use of quinolines and extended-spectrum cephalosporins [14, 15]. However, there are limited data describing the use of watch/reserve group antibiotics among different population subgroups, especially susceptible elderly people with major chronic diseases or living in Long-Term Care Facilities (LTCF), and comparing the rate of antibiotic dispensing with microbiology testing in primary care settings. Therefore, we examined the incidence rate of watch/reserve group antibiotic dispensing among community-dwelling older adults and compared it with the rate of microbiology testing for bacterial infections according to individual chronic health conditions in a large Australian cohort, in order to better understand the pattern of watch/reserve group antibiotic dispensing in general practice.

Methods

Study population and data sources

We used the Sax Institute's 45 and Up Study, a large-scale cohort which recruited 267,153 participants aged ≥45 years from 2006 to 2009 in the largest Australian state, New South Wales (NSW). Participants were randomly sampled from the Department of Human Services (DHS) enrolment database. Detailed information on the cohort has been published previously [16]. Approximately 10% of adults aged 45 years and over in the general population of NSW were recruited. Participants completed a questionnaire at baseline about their demographics, lifestyle, and health information (available at https://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/). They also agreed to have their questionnaire information linked to their health records. In this study, we linked the cohort to the Pharmaceutical Benefits Scheme (PBS), Medicare Benefits Schedule (MBS) based on a unique identifier provided by the DHS, and the NSW Admitted Patient Data Collection (APDC), and the NSW Registry of Births, Deaths and Marriages (RBDM) database through probabilistic linkage by the NSW Centre for Health Record Linkage (CHeReL).

The PBS database records medicines dispensed for outpatients subsidized by the Australian government pharmaceutical scheme; data include the dates of dispensing, medicine names, and WHO Anatomical Therapeutic Chemical (ATC) codes. About 98% of recorded antibiotic prescriptions in the PBS database were supplied from community pharmacies; others were supplied from private hospitals or other healthcare facilities [17]. The MBS database records general practitioner (GP) visits and other medical services provided to patients subsidized by the Australian government. The data include the types of service, the dates of service conducted, and the codes for service item (MBS item number). The APDC database records patient hospital admissions in NSW; data include the admission dates and diagnoses coded according to the International Classification of Diseases version 10 Australian Modification (ICD-10-AM). The RBDM database records registered death information, including the death dates of participants.

Ethics

The study was approved by the University of New South Wales Human Research Ethics Committee (number 10186), and the NSW Population and Health Services Research Ethics Committee (HREC/10/CIPHS/97).

Outcomes

Our primary outcome was the number of watch and reserve group systemic antibiotic prescriptions dispensed to each cohort participant recorded in the PBS database

from 1st January 2015 to 31st December 2015 (observation period). The list of antibiotics classified as watch/reserve group is shown in Supplementary Table 1. We identified the antibiotic classes by their ATC codes [18].

A secondary outcome was the number of microbiology tests for bacterial infections received by each participant during 2015 based on records in the MBS database (see Supplementary Table 2). Some serology tests which might be used for diagnosing bacterial infections were also included. We excluded those microbiology tests only for viral, parasitic or fungal pathogens, and those tests provided in hospitals. As another secondary outcome, we examined the number of prescriptions of amoxicillin-clavulanate (ATC code J01CR02), the main broad-spectrum beta-lactam antibiotic outside the watch/reserve group dispensed in Australia during 2015 from the PBS database, since for many conditions prescriptions of this antibiotic would also require accompanying microbiology testing [10].

Covariates

Socio-demographic factors for each participant were derived from the 45 and Up Study baseline questionnaire. We included sex (men or women), age-group in 2015 (45–59, 60–64, 65–69, 70–74, 75–79, and ≥ 80 years), education (university degree or higher, certificate or vocational education, no school certificate), annual household income at baseline in Australian dollars (low: <$30,000, middle: $30000- < $70,000, high: ≥$70,000), and residential area (major city, regional/remote area). Missing values in each covariate were included as a separate group.

The primary patient subgroups of interest in our study were those with major chronic diseases and those living in LTCF. We derived co-morbidities and other health service use from the MBS and APDC databases. For participants who were dispensed watch/reserve group antibiotics during 2015, an index date was defined as the first date of watch/reserve group antibiotic dispensing; for participants who were not provided watch/reserve group antibiotics, the index date would be 9th July 2015, the median date of watch/reserve group antibiotic dispensing among participants. Residence in a LTCF was ascertained if participants had an MBS record of a medical service in a LTCF (see Supplementary Table 2 for codes) in the year before the index date. A history of major chronic diseases was based on hospitalization records within 3 years before the index date in the NSW APDC database, defined by the primary diagnosis codes (ICD-10-AM): cancer (C00-C97), diabetes mellitus (E10-E14), chronic obstructive pulmonary disease (COPD, J40-J44), chronic kidney disease (N18), and cardiovascular diseases (i.e. ischemic heart diseases or stroke, I20-I25 or I60-I69). We also included self-reported asthma that was indicated in the baseline questionnaire. The number of GP consultations in the MBS database (see Supplementary Table 2 for codes) and the number of hospital admissions in the NSW APDC database in the year before the index date were included as covariates for each participant, as these factors were shown to be associated with antibiotic use in a previous study [19].

Data analysis

In this analysis, we included participants who were alive on 1January 2015 based on death records in the NSW RBDM. Person-time in the analysis was calculated from 1 January 2015 to 31 December 2015 or date of death whichever came first. We calculated the number and incidence rate of watch/reserve group antibiotic prescriptions dispensing, microbiology testing, and amoxicillin-clavulanate dispensing in 2015 among the study population overall and according to different individual characteristics. Using multivariable zero-inflated negative binomial regression, we estimated adjusted incidence rate ratios (aIRR) and calculated 95% confidence intervals (CI) to identify the associations of major co-morbidity and residence in LTCF with watch/reserve group antibiotic dispensing and microbiology testing. We also assessed risk factors for the dispensing of macrolides (in the WHO watch group but not in the Australian restricted antibiotics list [7]), other watch/reserve group antibiotics, and amoxicillin-clavulanate separately. To verify the potential effect of prior antibiotic use on watch/reserve group antibiotic dispensing, we performed a sensitivity analysis and only included those watch/reserve group antibiotics without antibiotic prescriptions in the 14 days prior. All the socio-demographic, co-morbidities, and health service-related covariates described above were included in the model.

We also examined the timing of microbiology tests in relation to the dispensing of watch/reserve group antibiotics. We calculated the proportion of watch/reserve group antibiotic prescriptions that had an accompanying microbiology test performed within 14 days prior to or 7 days after the dispensing date for study populations, considering that the tests performed around the day of dispensing are potentially related to the antibiotic treatment.

All analyses were conducted using Stata version 14.1. Two-sided P value< 0.05 was used as the threshold for statistical significance.

Results

After excluding people who died before 2015, we included 244,299 individuals (mean age 69 years) of whom 120,747 (49%) were dispensed ≥1 antibiotic prescription in 2015. Among those 120,747 participants, a total of 403,492 antibiotic prescriptions were dispensed, of

which 63,306 (16%) were watch/reserve group antibiotics. There were 29,917 (12%) participants who were dispensed at least one watch/reserve group antibiotic prescription: 13,914 (5.7%) were dispensed one; 10,102 (4.1%) were dispensed two; and 5901 (2.4%) were dispensed three or more prescriptions. There were fewer than five reserve group antibiotic prescriptions; thus, they were included in the watch group analyses; and in the following text, we simply refer to the group as watch group. As shown in Table 1, the most commonly dispensed watch group antibiotics were macrolides (53,336 prescriptions), followed by quinolones and fluoroquinolones (8519 prescriptions). Among non-watch group antibiotics, amoxicillin-clavulanate was dispensed in 67,735 (17%) prescriptions. Over the observation period, there were 149,182 microbiology tests for bacterial infections conducted in the study population. The distribution of the intervals between a dispensed watch group antibiotic prescription and its closest microbiology test is shown in Supplementary Figure 1, 69% of which were in the − 14 days to + 7 days window.

In 2015, the incidence rate was 0.26 per person-year for watch group antibiotic dispensing and 0.62 per person-year for microbiology testing (Table 2). Overall, 11,993 (19%) watch group antibiotic prescriptions had a microbiology test within − 14/+ 7 days and were regarded as watch group prescriptions with a related microbiology test. Most patients with major chronic diseases or living in a LTCF had a higher incidence rate of watch group antibiotic dispensing, microbiology testing, and a higher proportion of antibiotic prescriptions with a related test when compared with other populations. However, patients with chronic respiratory diseases, i.e. COPD and asthma, were the exceptions, as only 17% of their prescriptions had a related microbiology test, lower than the rest of study populations.

Table 1 Number of dispensed antibiotic prescriptions and microbiology tests by types

Antibiotic	No. (%)
Total	**403,492 (100)**
By type	
Watch and reserve group [a, b]	**63,306 (16)**
Macrolides (ATC code: J01FA)	53,336 (13)
Quinolones and fluoroquinolones (ATC code: J01M)	8519 (2.1)
Others [c]	1451 (0.36)
Antibiotics not in watch or reserve group	**340,186 (84)**
Amoxicillin-clavulanate (ATC code: J01CR02)	67,735 (17)
Others	272,451 (68)
Microbiology test	No. (%)
Total	**149,182 (100)**
By type	
Urine examinations [d]	82,291 (55)
Microscopy & culture for specimens of sputum	4887 (3.3)
Microscopy & culture for other specimens	34,014 (23)
Microbial antigens, nucleic acid, or antibody testing	24,432 (16)
Others	3558 (2.4)

[a]. As defined by the WHO Model List of Essential Medicines in 2017
[b]. Included reserve group antibiotics ($N < 5$)
[c]. Included 3rd&4th-generation cephalosporins (ATC code: J01DD, J01DE), glycopeptides (ATC code: J01XA), ticarcillin and a beta-lactamase inhibitor (ATC code: J01CR03)
[d]. Included microscopy and culture

After adjustment in multivariable analysis (Fig. 1 and Supplementary Table 3), cancer, diabetes, and chronic kidney diseases were not associated with watch group antibiotic dispensing but associated with a higher likelihood of microbiology testing. Cardiovascular diseases were not associated with watch group antibiotic dispensing nor microbiology testing. The pattern of antibiotic dispensing and microbiology testing in COPD and asthma patients was different from patients with other chronic diseases. While both were strongly associated with greater use of watch group antibiotics, (COPD IRR: 2.71, 95%CI: 2.48–2.95, asthma IRR:1.59, 95%CI: 1.52–1.66), there was almost no increase in microbiology testing in COPD (aIRR:1.00, 95%CI: 0.94–1.06) and asthma (aIRR:1.03, 95%CI: 1.00–1.05) patients, if compared with people without COPD (asthma). Besides, in comparison with people not living in LTCF, those living in LTCF had a lower likelihood of receiving watch group prescriptions (aIRR: 0.91. 95%CI: 0.85–0.99) but a higher likelihood of microbiology testing (aIRR: 1.31 95%CI: 1.26–1.37).

Supplementary Table 4 shows that the incidence rate was 0.28 per person-year for amoxicillin-clavulanate dispensing. After adjustment, COPD, asthma, cancer, diabetes, and chronic kidney diseases, were all significantly associated with a higher likelihood of amoxicillin-clavulanate dispensing. When we restricted watch group antibiotic prescriptions to those without antibiotic prescriptions in the 14 days prior, we found that 39,088 (62%) prescriptions did not follow prior antibiotic use, and the association of chronic respiratory diseases with watch group antibiotic dispensing did not substantially change (see Supplementary Table 5). The incidence rate ratios for certain classes of watch group antibiotic dispensing and microbiology testing by type of test are shown in Supplementary Table 6 and 7, respectively.

Given the strong association of chronic respiratory diseases with watch group antibiotic dispensing, we further examined the relationships according to disease severity (Supplementary Table 8). We divided the population into four groups: 1) no asthma or COPD history; 2) only asthma; 3) less severe COPD (COPD hospitalization < 2 times in the past 3 years); and 4) more severe COPD (COPD hospitalization ≥2 times in the past 3 years). The

Table 2 Number and incidence of dispensed watch group antibiotic prescriptions and microbiology tests by participants' characteristics

Characteristic			Watch group antibiotic prescriptions			Microbiology tests	
	No. (%)	Person-years	No.	Incidence [a]	No. (%) related to a test [b]	No.	Incidence
Total	244,299 (100)	242,195	63,306	0.26	11,993 (19)	149,182	0.62
Sex							
Men	110,120 (45)	108,939	25,945	0.24	4908 (19)	58,787	0.54
Women	134,179 (55)	133,255	37,361	0.28	7085 (19)	90,395	0.68
Age (years)							
45–59	54,148 (22)	54,079	9874	0.18	1648 (17)	23,162	0.43
60–64	44,072 (18)	43,987	9824	0.22	1643 (17)	21,594	0.49
65–69	41,952 (17)	41,825	10,274	0.25	1794 (18)	22,786	0.55
70–74	35,584 (15)	35,394	10,423	0.29	2015 (19)	23,529	0.67
75–79	26,644 (11)	26,431	8657	0.33	1809 (21)	20,834	0.79
≥ 80	41,889 (17)	40,478	14,254	0.35	3084 (22)	37,277	0.92
Education							
University degree or higher	58,569 (24)	58,292	12,378	0.21	2395 (19)	31,232	0.54
Certificate or vocational education	155,309 (63)	153,930	40,426	0.26	7556 (19)	95,465	0.62
No certificate	26,824(11)	26,447	9424	0.36	1849 (20)	19,970	0.76
Missing	3597(1.5)	3527	1078	0.31	193 (18)	2515	0.71
Annual household Income [c]							
High	61,321 (25)	61,174	11,917	0.20	2252 (19)	28,887	0.47
Middle	64,662 (27)	64,297	14,739	0.23	2801 (19)	35,768	0.56
Low	67,170 (28)	66,197	21,235	0.32	4183 (20)	49,568	0.75
Unknown	51,146 (21)	50,526	15,415	0.31	2757 (18)	34,959	0.69
Area of residence							
Regional/remote area	113,290 (46)	112,373	25,942	0.23	5132 (20)	67,442	0.60
Major city	126,392 (52)	125,241	36,317	0.29	6679 (18)	79,168	0.63
Missing	4617 (1.9)	4581	1047	0.23	182 (17)	2572	0.56
History of chronic diseases							
Asthma	30,608 (13)	30,333	14,635	0.48	2522 (17)	21,914	0.72
COPD	3540 (1.5)	3272	4702	1.44	810 (17)	4034	1.23
Cancer	16,355 (6.7)	15,583	5511	0.35	1265 (23)	14,942	0.96
Diabetes Mellitus	18,730 (7.7)	18,277	7719	0.42	1716 (22)	19,430	1.06
Choric Kidney Diseases	4532 (1.9)	4127	2381	0.58	632 (27)	7683	1.86
Cardiovascular diseases [d]	13,213 (5.4)	12,671	5537	0.44	1182 (21)	12,902	1.02
Residence in LTCF [e]							
No	236,911 (97)	235,660	59,853	0.25	11,148 (19)	138,282	0.59
Yes	7388 (3.0)	6535	3453	0.53	845 (25)	10,900	1.68

[a]: per person-year
[b]: a watch/reserve prescription was defined as "related to a test" if there is microbiology testing within 14 days prior to or 7 days after the prescription (see methods)
[c]: It is household income at baseline. Low: < 30,000 AUD, middle: 30000- < 70,000 AUD, high: ≥70,000 AUD
[d]: Included ischemic heart diseases and stroke
[e]: LTCF: Long Term Care Facilities

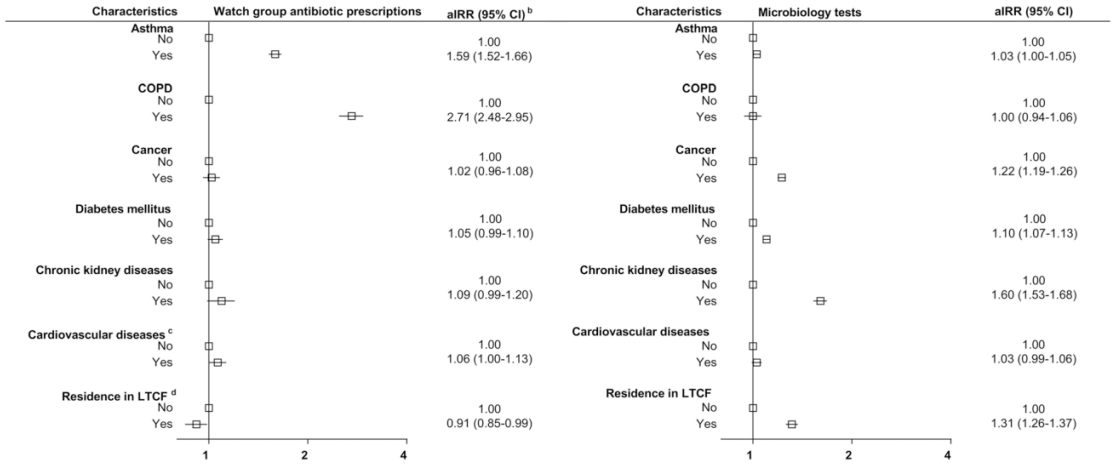

Fig. 1 Incidence rate ratio [a] for watch group antibiotic dispensing and microbiology testing by participants' characteristics. **a**: Zero-inflated negative binomial regression adjusted by sex, age, education level, income level, residential remoteness, residence in Long Term Care Facilities (LTCF), history of chronic diseases, number of GP visits in the year before the index date, number of hospital admissions in the year before the index date. **b**: aIRR: adjusted incidence rate ratio, CI: confidence intervals. **c**: Included ischemic heart diseases and stroke. **d**: LTCF: Long Term Care Facilities

test for linear trend showed a significant increase in the likelihood of watch group antibiotic dispensing by disease severity ($P < 0.001$), but no increase in microbiology testing ($P = 0.161$), which is consistent with the main analysis.

Discussion

We found that in a large community-based cohort of older people, there were 26 prescriptions of watch group antibiotics dispensed and 62 microbiology tests for bacterial infections performed per 100 people in 2015. Only 19% of watch group antibiotic prescriptions were accompanied by microbiology testing within − 14 to + 7 days. The patterns of antibiotic dispensing and microbiology testing varied in patients with different chronic health conditions after adjustment. Patients with cancer, diabetes, and chronic kidney diseases did not have a higher likelihood of receiving watch group antibiotics but had a higher likelihood of microbiology testing and receiving amoxicillin-clavulanate. We found people with chronic respiratory diseases, i.e. asthma and COPD, were significantly more likely to receive watch group antibiotics as well as amoxicillin-clavulanate; however, they did not have a comparably higher likelihood of receiving microbiology testing. People in LTCF were not dispensed more watch group antibiotics than those not in LTCF but were more likely to be tested.

Although surveillance programs for antibiotic resistance worldwide [20, 21] are constantly monitoring antibiotic consumption in the population, there are limited data on the appropriateness of antibiotic use. Simply looking at antibiotic consumption may not be enough for fully understanding the factors driving antibiotic resistance. The use of microbiology testing can be considered as a proxy for assessing the appropriateness of antibiotic use [22]. But few studies have examined the rate of microbiology testing in antibiotic treatment. It is only known that empirical antibiotic treatment for infections is quite common in primary care: a study in Europe found that the proportion of empirical antibiotics prescribed for urinary tract infection ranged from 59.4% in the Netherlands to 95.1% in England [23].

When we compared the likelihood of watch group antibiotic dispensing and microbiology testing in the study population, there was a unique pattern identified among people with asthma and COPD, i.e. the high likelihood of watch group antibiotics and amoxicillin-clavulanate dispensing did not accompany a comparably high likelihood of microbiology testing. Meanwhile, these people had a lower proportion of antibiotic prescriptions related to testing. Since the discord was not observed in other patients with chronic diseases, we cannot simply interpret it as the result of susceptibility to infections or a higher likelihood of GP visits. A possible explanation is that the discord might be the result of excessive watch group antibiotic use for exacerbation of chronic respiratory diseases. On the one hand, routine use of antibiotics for asthma exacerbation is not supported by sufficient evidence [24] but is common in clinical practice according to studies in the US and Europe [25–27]. On the other hand, although long-term macrolide use can effectively reduce the exacerbation of COPD

due to its anti-inflammatory effect [28], it will significantly increase the emergence of macrolide resistance [29]. Currently, there is no agreement on the use of long-term macrolides or clear suggestions about the monitoring of antibiotic resistance in COPD guidelines [10, 30, 31]. A previous study found that 38% of antibiotic use for COPD in hospitals might be inappropriate [32], which was in line with our results in the community setting. Taken together, our findings support more comprehensive guidelines and stewardship among those with chronic respiratory diseases, which requires identification of barriers to appropriate prescribing and potential mechanisms for monitoring of antibiotic use in these populations. Future strategies may also include the establishment of clear and detailed criteria for selecting patients who are suitable for macrolide prophylaxis in COPD guidelines, [33] introduction of point-of-care testing of C-reactive protein, which has been shown to reduce antibiotic use among patients with COPD exacerbations by identifying those unlikely to benefit from antibiotic therapy [34], and the use of novel macrolides with anti-inflammatory effects but no antibiotic effects which could reduce COPD exacerbations but not lead to increases in antibiotic resistance [35].

Earlier studies reported that inappropriate antibiotic prescribing was common among those living in LTCF [36, 37]. Our study demonstrated that after adjusting for age and comorbidities, the use of watch group antibiotics and amoxicillin-clavulanate was not significantly elevated in this group compared to those living outside of LTCF; however, the likelihood of microbiology testing was higher. The high likelihood of microbiology testing may be the result of over-investigation for asymptomatic bacteriuria, which frequently occurs in LTCF residents [38].

A major strength of our study is the use of data linkage of routinely collected administrative health data. To our knowledge, this approach is underused in studies investigating antimicrobial stewardship. A limitation of our study was the lack of clinical information to determine indications for antibiotic use and the results of microbiology testing. Thus, we were unable to assess the actual appropriateness of each prescription, and whether its temporally related microbiology test was truly in the same episode. Our comparison between rates of antibiotic dispensing and microbiology testing is a crude measure of antibiotic stewardship and should be considered alongside other measures of appropriate antibiotic prescribing. Besides, the MBS database only records the three most expensive pathology items for one patient if there are more than three tests during the one episode (1 day) [39]. This issue will inevitably result in potential under-ascertainment of testing in those episodes with three or more testing records. We used a previously published method [40] to estimate the scale of under-ascertainment from potential incomplete records and found that it would only affect about 11% of all episodes. Therefore, this is unlikely to have a major impact on our findings.

Conclusions

Watch group antibiotics are commonly dispensed among older adults in the community. This is particularly true for patients with asthma and COPD; however, their likelihood of receiving microbiology testing is not comparably high, indicating the potential for excessive empirical watch group antibiotic use. Since watch group antibiotics have high resistance potential, focusing antibiotic stewardship efforts might be needed among older populations with chronic respiratory diseases in the primary care setting.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12879-020-05029-z.

Additional File 1 Table S1. Classification for watch group and reserve group according to the WHO Model List of Essential Medicines

Additional File 2 Table S2. Medicare Benefits Schedule (MBS) codes used for GP consultations, aged care facilities (or Long-Term Care Facilities, LTCF) attendance and microbiology testing

Additional File 3 Table S3. Incidence rate ratio for watch group antibiotic dispensing and microbiology testing by participants' characteristics

Additional File 4 Table S4. Incidence and incidence rate ratio for dispensed amoxicillin-clavulanate prescriptions by participants' characteristics

Additional File 5 Table S5. Incidence and incidence rate ratio for dispensed watch group antibiotic prescriptions without antibiotic use in the 14 days prior to dispensing by participants' characteristics

Additional File 6 Table S6. Incidence rate ratio for dispensed macrolides and other watch group antibiotics prescriptions by participants' characteristics

Additional File 7 Table S7. Incidence rate ratio for certain types of microbiology testing among 244,299 participants by participants' characteristics

Additional File 8 Table S8. Incidence of dispensed antibiotic prescriptions and microbiology tests and their association between chronic lower respiratory tract diseases

Additional File 9 Figure S1. The distribution of the intervals between dispensed script of watch group antibiotics and its closest microbiology test (only include intervals ≤30 days).

Abbreviations

WHO: World Health Organization; LTCF: Long-Term Care Facilities; NSW: New South Wales; DHS: Department of Human Services; PBS: Pharmaceutical Benefits Scheme; MBS: Medicare Benefits Schedule; APDC: NSW Admitted Patient Data Collection; RBDM: The NSW Registry of Births, Deaths and Marriages; CHeReL: Centre for Health Record Linkage; ATC: Anatomical Therapeutic Chemical; GP: General practitioner; ICD-10-AM: International Classification of Diseases version 10 Australian Modification; COPD: Chronic obstructive pulmonary disease; aIRR: Adjusted incidence rate ratios; CI: Confidence intervals

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Authors' contributions
Development of overall study aims and design - ZP, BL, & AH. Data analyses – ZP assisted by AH. Wrote the first draft of the manuscript -ZP. Revision of subsequent drafts of the manuscript and approval of the final manuscript – ZP, AH, MK, SP, AC, & BL. The author(s) read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the Sax Institute but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Sax Institute.

Ethics approval and consent to participate
The study was approved by the University of New South Wales Human Research Ethics Committee (number 10186), and the NSW Population and Health Services Research Ethics Committee (HREC/10/CIPHS/97). Sax Institute granted the administrative permission to access the raw data.

Consent for publication
Not applicable.

Competing interests
AC serves on the editorial board of BMC Infectious Diseases. No other author has reported a potential conflict of interest relevant to this manuscript.

Author details
[1]School of Public Health and Community Medicine, University of New South Wales (UNSW), Sydney, NSW 2052, Australia. [2]School of Public Health, Faculty of Health, University of Technology Sydney, Sydney, NSW, Australia. [3]National Centre for Epidemiology and Population Health, Australian National University, Canberra, ACT, Australia. [4]Medicines Policy Research Unit, Centre for Big Data Research in Health, University of New South Wales, Sydney, NSW, Australia. [5]Menzies Centre for Health Policy, School of Public Health, The University of Sydney, Sydney, NSW, Australia. [6]Department of Epidemiology and Infectious Diseases, Monash University and Alfred Health, Melbourne, VIC, Australia.

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Publisher's Note

Chapter 3 Microbiology testing and antibiotic treatment for urinary tract infections in general practice

Chapter 3 contains the original work:

Peng Z, Hayen A, Hall J, Liu B. Microbiology testing and antibiotic treatment for urinary tract infections in general practice: a nationwide observational study. *Infection* 2021; **49**: 249-55

The study I present in this chapter addresses Objective 2 of my thesis: to examine the adherence to the recommendations in clinical guidelines regarding routine urine testing and antibiotic treatment for patients at low or high risk of complicated urinary tract infections (UTIs) in general practice.

The study found that there was potential underuse of urine culture among some high-risk patient groups who had episodes of UTIs, including patients under five years old, those with recurrent UTIs, and residents of aged care homes. Targeted antibiotic stewardship might be needed to improve antibiotic prescribing guided by urine culture among those patients who are at high risk of complicated UTIs.

As the first author of the article, I developed the overall study aims and design in consultation with my supervisors, conducted the data analysis, wrote the first draft of the manuscript and revised it with feedback and revisions by my supervisors and other co-authors, and submitted it to the peer-reviewed journal.

The supplementary methods, tables, and figure of this study are shown in Appendix 2 (Page 139)

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ORIGINAL PAPER

Microbiology testing and antibiotic treatment for urinary tract infections in general practice: a nationwide observational study

Zhuoxin Peng[1] · Andrew Hayen[2] · John Hall[1] · Bette Liu[1]

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Abstract

Purpose Routine urine testing is recommended prior to antibiotic treatment for urinary tract infections (UTIs) among high-risk groups for complicated UTIs. This study aims to examine whether the proportion of UTI encounters where antibiotics are prescribed that have accompanying urine testing differs by patient groups.

Methods A retrospective analysis was conducted using records of general practice encounters for UTIs occurring between January 2013 and July 2018 in an Australian national database. We calculated the proportion of UTI encounters with antibiotics prescribed that had accompanying urine microbiology testing and the odds ratios for the likelihood of testing by patient groups using generalised estimating equations.

Results Of 132,688 UTI encounters with antibiotics prescribed, 95,800 (72.2%) were accompanied by urine testing. Among high-risk groups for complicated UTIs and expected to have a high likelihood of testing, we found pregnant women [82.6% vs. non-pregnant 72.3%, adjusted odds ratio (aOR) 1.82, 95% confidence intervals (CI) 1.55–2.12] and children aged 5–9 years (77.6% vs. 20–44 years 72.0%, aOR 1.33, 95% CI 1.22–1.45) had relatively high odds of testing. However, children aged < 5 years (68.7% vs. 20–44 years 72.0%, aOR 0.83, 95% CI 0.76–0.90), patients with recurrent UTIs (69.0% compared to first-onset UTIs 73.6%, aOR 0.81, 95% CI 0.79–0.83), and patients in residential aged care facilities (67.3% vs. not 72.3%, aOR 0.80, 95% CI 0.72–0.90) had relatively low odds of testing.

Conclusion Our results suggest inconsistencies and potential underuse of urine testing when antibiotics were prescribed for high-risk groups in UTI management. Further antibiotic stewardship is needed to improve guideline-based antibiotic prescribing for UTIs.

Keywords Urinary tract infections · Urine microbiology testing · General practice · Guideline adherence · Antibiotics

Introduction

Urinary tract infections (UTIs) cause a large burden of disease. Approximately 150 million people worldwide are affected every year [1] and half of the women will experience at least one UTI episode throughout their lifetime [2]. UTI is one of the top indications for antibiotic prescribing [3–6]. An important issue in UTI treatment is the emergence of antibiotic resistance. The resistance rates in UTI causative pathogens around the world range from 14% to 45% for first-line antibiotics such as trimethoprim and from 0.5% to 13% for second-line antibiotics such as ciprofloxacin [7]. Urine microbiology testing plays an important role in guiding treatment decisions and preventing inappropriate antibiotic use for UTIs. International clinical guidelines [8–13] recommend that urine microbiology testing should be routinely performed when starting antibiotic treatment for UTIs in specific populations, including men, pregnant women, children, older adults in residential aged care facilities (RACF) or nursing homes, those with recurrent UTIs, and others at high risk of complicated UTIs. Pregnant women, male, patients with recurrent UTIs, diabetes, and renal insufficiency are associated with increased risk of complicated

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✉ Zhuoxin Peng
zhuoxin.peng@student.unsw.edu.au

[1] School of Public Health and Community Medicine, University of New South Wales, Sydney, NSW 2052, Australia

[2] School of Public Health, Faculty of Health, University of Technology Sydney, Sydney, NSW, Australia

UTIs [10]. Older people in RACF face a high risk of UTIs caused by multidrug-resistant organisms [14, 15]. UTIs in children may lead to additional adverse outcomes such as impaired renal growth and early hypertension [16]. Conversely, clinical guidelines [8–11] do not support routine urine testing for patients suspected of having uncomplicated UTIs due to the limited impact on treatment outcome [17] and unnecessary expense and burden on health systems [18]. Thus, the variation in urine testing between patient groups with and without complicating factors can provide useful insight into the adherence to guidelines and the quality of UTI management in clinical practice.

However, little is known about what proportion of clinical encounters for UTIs have accompanying urine microbiology testing when antibiotics are prescribed, and whether the variation in urine testing is consistent with the recommendations on who should routinely be tested in clinical practice. We, therefore, examined to what extent the variation of microbiological testing in UTI antibiotic treatment matched guidelines using a large national repository of electronic records from Australian general practices (MedicineInsight database).

Methods

Data sources

MedicineInsight is a database developed by NPS MedicineWise in Australia [19]. It contains national records of clinical encounters from more than 650 general practices, 3300 general practitioners (GPs), and 3.6 million patients across Australia from the 1990s [20]. De-identified information on patients' demographics, history of general practice encounters, prescriptions, and pathology test requests are available. In this database, the Encounter dataset contains records of each general practice encounter for patients, including encounter dates, de-identified practice site numbers, and reasons for encounter in free text. Similarly, the Diagnosis dataset contains diagnosis records including diagnosis dates and diagnosis reasons (free text). The Prescription dataset contains records of all prescriptions given to patients, including prescription dates and generic drug names (free text). The Requested Test dataset contains records of pathology tests requested by a practice, including request dates and test names (free text). The general characteristics of patients, e.g., sex, year of birth, are available in the Patient dataset; and common chronic conditions as well as the onset dates are included in the Conditions dataset (derived by NPS MedicineWise). Geographical information on general practice sites are available in the Site dataset. Records for each participant can be identified by a unique individual number. More detailed information on Medicineinsight has been published [19]. This study is based on a simple random sample of 25% of all patients in MedicineInsight and their records which are available for analysis by independent researchers.

Population and definitions

We extracted all general practice encounters for UTIs between January 2013 and July 2018 from patients in our Medicineinsight random sample. The UTI encounters were identified by search terms (e.g., "UTI", "cystitis") in the "encounter reason" field from the Encounter dataset or "diagnosis reason" from the Diagnosis dataset; we excluded all "suspected" cases and only included confirmed UTIs (see details in Supplementary Methods). We defined two types of UTI, first-onset UTIs and recurrent UTIs, according to the established criteria in guidelines [9, 10]. UTI encounters were classified as first-onset if, for the same patient, there was no UTI encounter (diagnosis) record within 6 months prior and no more than one UTI record within 1 year prior. Recurrent UTIs were classified if either there were one or more UTI encounter (diagnosis) records for that individual within 6 months prior, or two or more UTI records 1 year prior; or if the term "recurrent" was in the encounter (diagnosis) reason field. UTI encounters with a UTI encounter 28 days prior were excluded from the analysis, as they were considered part of the same episode.

Antibiotic prescriptions and urine microbiology tests were identified from the Prescription dataset and the Requested Test dataset using the search terms outlined in the Supplementary Methods. To determine whether a patient was prescribed an antibiotic or had a urine microbiology test related to a UTI encounter, we linked the UTI encounters to Prescription and Pathology datasets using a match on both the patient's unique identifying number and the date of the UTI encounter. Patients with a UTI encounter were classified as having an antibiotic if there was a record of an antibiotic prescription on the same day. They were classified as having a urine test if there was a record of a requested test on the same day or within 14 days prior to the UTI encounter, as urine tests might be requested in the previous encounters for distinguishing between UTIs and other conditions with similar symptoms.

Statistical analysis

As the main outcome, we calculated the proportion of UTI encounters where antibiotics were prescribed that had an accompanying urine microbiology test. We compared the percentage of UTI encounters where microbiology testing was requested by patients' characteristics related to the risk of developing complicated UTI, including the type of UTIs (first-onset or recurrent), sex, age at encounter (0–4, 5–9,

10–19, 20–44, 45–74, and ≥ 75 years), pregnancy status, residence in RACF, and chronic comorbidities known to increase the risk of complicated UTIs (chronic kidney diseases and diabetes). We used search terms and algorithms to identify whether a woman was pregnant at the time of her UTI encounter and whether the encounter occurred for someone living in a RACF, having diabetes or chronic kidney diseases (see Supplementary Methods). We also examined the classes of antibiotics prescribed in the UTI encounters. First-onset and recurrent UTI encounters were examined separately.

To determine the association of patients' characteristics with microbiology testing in UTI encounters and adjust for clustering by patient and practice, we performed logistic generalised estimating equations (GEE) models. We adjusted for the covariates described above and practice site remoteness based on the Accessibility and Remoteness Index of Australia (in three categories: major cities; inner regional areas; outer regional and remote areas) [21] and socioeconomic level based on the Index of Relative Socio-economic Advantage and Disadvantage (in five quantiles) [22]. First we used all encounters in the base model. Then analyses for pregnancy were restricted to women aged 10–44 years old (reproductive age) and for RACF to adults aged over 75 years. We ran a sensitivity analysis using different windows to define whether a test was related to the UTI encounter (7 and 21 days).

Statistical analysis was performed using SAS statistical software, version 9.4, (SAS Institute, Cary, NC).

Results

Our analysis included a total of 158, 770 UTI encounters from 1 January 2013 to 31 July 2018, of which 107,626 (67.8%) were classified as first-onset and 51,144 (32.2%) were classified as recurrent UTIs (Table 1). Antibiotics were prescribed in 132,688 (83.6%) encounters [first-onset: 92,260 (85.7%); recurrent: 40,428 (79.0%)]. Of those UTI encounters with antibiotics prescribed, 95,800 (72.2%) had an accompanying urine microbiology test recorded [first-onset: 67,909 (73.6%); recurrent: 27,891 (69.0%)]. The proportion of UTI encounters with antibiotics prescribed and accompanying microbiology testing by patients' sex and age is shown in Supplementary Fig. 1.

The antibiotic classes prescribed in the UTI encounters are shown in Table 1. Two first-line antibiotics for UTI encounters, trimethoprim and cefalexin [8], made up the majority of antibiotic prescriptions for both first-onset (82.1%) and recurrent UTI encounters (69.7%). Proportions of encounters with amoxicillin and amoxicillin-clavulanate did not differ much between first-onset and recurrent UTIs. Quinolones, a second-line antibiotic with special restrictions on prescribing in Australia [8], made up a higher percentage of antibiotics prescribed for recurrent UTIs (6.8%) than first-onset UTIs (2.2%). There was also a higher percentage of nitrofurantoin prescriptions in recurrent UTIs (7.0%) than first-onset UTIs (2.2%).

Table 1 Total number of antibiotic prescriptions for first-onset and recurrent urinary tract infections (UTIs) by class, Medicineinsight database, January 2013 to July 2018

	First-onset UTIs *N* (%)	Recurrent UTIs *N* (%)
All classes	98,325 (100)	45,294 (100)
Trimethoprim	41,260 (42.0)	14,724 (32.5)
Cefalexin	39,408 (40.1)	16,836 (37.2)
Amoxicillin-clavulanate	6865 (7.0)	4136 (9.1)
Amoxicillin	4135 (4.2)	1729 (3.8)
Quinolones	2211 (2.2)	3097 (6.8)
Nitrofurantoin	2126 (2.2)	3174 (7.0)
Others	2230 (2.3)	1598 (3.5)

Table 2 gives the proportion of UTI encounters with accompanying microbiology testing when antibiotics were prescribed, according to patients' characteristics. Variation in urine testing was identified among patients at a high risk of complicated UTIs. Males received slightly more testing than females [73.0% vs. 72.1%, adjusted OR (aOR) 1.08 (95% Confidence Intervals (CI) 1.04–1.13)]. Compared to adults aged 20–44 years, children under 5 years with UTIs who received antibiotic prescriptions were significantly less likely to be tested [68.7% vs. 72.0%, aOR 0.83 (95% CI 0.76–0.90)]; whereas children aged between 5 and 9 years [77.6% vs. 72.0%, aOR 1.33 (95% CI 1.22–1.45)] were more likely to be tested. Compared to patients with a UTI and antibiotic treatment seen in major cities, those in inner regional practices were more likely to have testing [74.1% vs. 72.4%, aOR 1.18 (95% CI 1.14–1.23)] whilst those seen in more remote practices were less likely [68.3%, aOR 0.92 (95% CI 0.88–0.96)]. Patients with recurrent UTIs were also less likely to be tested than those with first-onset UTIs [69.0% vs. 73.6%, aOR 0.81 (95% CI 0.79–0.83)]. Patients with diabetes and chronic kidney diseases had similar levels of testing compared to those without. Pregnant women were more likely to be tested compared to other women of a similar age [82.6% vs. 72.3%, aOR 1.82 (95% CI 1.55–2.12)]. In adults aged over 75 years, people living in RACF were less likely to be tested than those not living in RACF [67.3% vs. 72.3%, aOR 0.80 (95% CI 0.72–0.90)].

Findings were mostly similar in analyses stratified by first-onset or recurrent UTI encounters (shown in Supplementary Tables 1, 2) and sensitivity analysis using two different windows to ascertain testing (7 and 21 days, shown in Supplementary Tables 3, 4), except for recurrent UTI

Table 2 General practice encounters for urinary tract infections (UTIs), the proportion of encounters with antibiotics prescribed that had accompanying urine microbiology testing, and adjusted odds ratios for the likelihood of urine microbiological testing, Medicineinsight database, January 2013 to July 2018

Characteristics	Total encounters for UTIs	Encounters for UTIs with antibiotics	Encounters for UTIs with antibiotics and tests	Likelihood of testing in encounters for UTIs with antibiotics		
	N	*N*	*N*	Proportion (%)[a]	Adjusted OR (95% CI)[b]	*P*
Total population[c]	158,770	132,688	95,800	72.2		
Sex						
Female	138,140	117,398	84,632	72.1	1.00	< 0.001
Male	20,630	15,290	11,168	73.0	1.08 (1.04–1.13)	
Age (years)						< 0.001
0–4	4399	3081	2117	68.7	0.83 (0.76–0.90)	< 0.001
5–9	4701	3860	2996	77.6	1.33 (1.22–1.45)	< 0.001
10–19	8463	7317	5542	75.7	1.23 (1.16–1.31)	< 0.001
20–44	43,663	38,252	27,535	72.0	1.00	
45–74	60,595	51,353	36,876	71.8	1.03 (0.99–1.06)	0.14
≥ 75	36,948	28,825	20,734	71.9	1.03 (0.99–1.08)	0.16
Area remoteness						< 0.001
Major cities	100,030	83,153	60,178	72.4	1.00	
Inner regional areas	37,785	31,138	23,064	74.1	1.18 (1.14–1.23)	< 0.001
Outer regional/remote areas	20,953	18,396	12,557	68.3	0.92 (0.88–0.96)	< 0.001
Type of UTIs						
First-onset UTIs	107,626	92,260	67,909	73.6	1.00	< 0.001
Recurrent UTIs	51,144	40,428	27,891	69.0	0.81 (0.79–0.83)	
Diabetes						
No	141,564	118,756	85,907	72.3	1.00	0.34
Yes	17,206	13,932	9893	71.0	0.98 (0.93–1.03)	
Chronic kidney diseases						
No	156,265	130,690	94,345	72.2	1.00	0.19
Yes	2505	1998	1455	72.8	1.08 (0.96–1.22)	
Female at 10–44 years old[d]	48,855	43,042	31,242	72.6		
Pregnancy						
No	47,473	41,829	30,240	72.3	1.00	< 0.001
Yes	1382	1213	1002	82.6	1.82 (1.55–2.12)	
People aged over 75 years old[e]	36,948	28,825	20,734	71.9		
Living in RACF[f]						
No	33,154	26,461	19,144	72.3	1.00	< 0.001
Yes	3794	2364	1590	67.3	0.80 (0.72–0.90)	

[a]Proportion = No. of encounters for UTIs with antibiotics and tests/No. of encounters for UTIs with antibiotics

[b]*OR* odds ratio, *CI* confidence intervals. Base model included sex, age group, remoteness and socioeconomic index of general practice sites, the types of UTI (first-onset or recurrent), patients' diabetes and chronic kidney diseases history, and clustering of encounters by patient and general practice site

[c]*N* = 132,688 for multivariable analyses

[d]*N* = 43,042 for multivariable analyses

[e]*N* = 28,825 for multivariable analyses

[f]*RACF* residential aged care facilities

encounters where antibiotics were prescribed for patient groups under 5 years or living in RACF, as their odds of testing were not found significantly different from comparable populations without the risk factor in these encounters.

Discussion

In our national sample of general practice records in Australia, 72.2% of UTI encounters where antibiotics were

prescribed had accompanying microbiology tests. First-line antibiotics accounted for approximately 80% of antibiotics prescribed for first-onset UTIs and 70% for recurrent UTIs. Among populations at high risk of complicated UTIs and therefore recommended by clinical guidelines [8–13] to receive routine urine microbiology testing, we did not find the likelihood of testing was significantly higher when antibiotics were prescribed among patients with diabetes (71.0%) or chronic kidney diseases (72.8%); while for children under 5 years old (68.7%), those living in RACF (67.3%), and those with recurrent UTIs (69.0%), the likelihood of testing appeared to be even lower than comparable populations without these risk factors. Reassuringly, among pregnant women (82.6%) and children aged between 5 and 9 years (77.6%) the likelihood was significantly higher.

Similar to international guidelines, Australian national guidelines for UTI management [8] recommend urine culture for pregnant women, men, children, patients with recurrent UTIs, residents in RACF, and patients with other risk factors for complicated UTIs prior to starting antibiotic treatment. However unlike some international guidelines, during the observation period for this report (2013–2018), the first-line antibiotics for UTIs were trimethoprim or cefalexin; and second-line options included nitrofurantoin, amoxicillin, amoxicillin-clavulanate, fosfomycin, norfloxacin, or ciprofloxacin. The current guidelines have changed to trimethoprim or nitrofurantoin as first-line antibiotics but our findings regarding the type of antibiotic prescribed were generally consistent with the recommendations at the time.

Regarding testing for UTIs, it is known that complicated UTIs have a much broader range of causative pathogens than uncomplicated UTIs. Besides *E. coli*, the dominant causative pathogen, other pathogens with high potential for resistance, such as *Klebsiella* spp, and *Pseudomonas* spp, are more frequently identified in patients with complicated UTIs [23]. The underuse of urine testing among these patients can be a potential driving factor for inappropriate antibiotic prescribing in UTI management. Therefore, unlike in the antibiotic treatment for uncomplicated UTIs where microbiology testing is not necessary, microbiology tests have greater significance in directing therapy for complicated UTIs and are routinely recommended for patients susceptible to complicated UTIs in guidelines [8–13]. A previous Canadian study reported that 77% of adult females suspected of uncomplicated cystitis received urine microbiology testing in general practice [24], which was similar to our findings in adult females, but comparable large-scale data on urine testing among high-risk groups for complicated UTIs are scant.

There are concerns in RACF regarding the overuse of urine testing for asymptomatic bacteriuria [25], as positive urine culture results without other indications have limited clinical significance and might lead to unnecessary antibiotic use in this setting [26]. However, those concerns do not contradict the recommendation regarding routine urine testing for symptomatic UTIs in RACF from local Australian and international guidelines [8, 12, 13]. Our results suggest there may be underuse of urine culture in RACF, as we found that when antibiotics were prescribed for UTIs for older patients in RACF, only 67.3% had a test recorded, even significantly less than similar-aged adults living outside of RACF. An Australian survey reported that only 64% of antibiotic prescriptions for urinary tract symptoms in RACF were accompanied by microbiology testing (including other microbiology tests), which was in line with our findings [27].

We also found that inconsistent with local and international guidelines [8, 10], patients with recurrent UTIs were slightly less likely to have a test (69.0%) than those with first-onset UTIs (73.6%) when antibiotics were prescribed. A possible explanation is that some clinicians may hold the view that urine culture is unnecessary when patients respond well to previous empiric therapy [28]. But it is important to note that urine culture is necessary for the differential diagnosis of recurrent UTIs, as many non-infectious urinary tract conditions, e.g. overactive bladder or vulvodynia, may have shared symptoms overlapping with recurrent UTIs [29]. Our findings reflected the need for improving the awareness of the importance of urine culture in guiding antibiotic treatment for recurrent UTIs in general practice.

The proportion of encounters with testing in children aged 5–9 years old was higher (77.6%) than adults; whereas in children aged less than 5 years old (68.7%) the proportion was lower. This difference in practice may relate to the difficulty of collecting urine samples from young children who have not been toilet trained [30]. Clinical guidelines in the UK and Canada recommend special "clean-catch" methods for very young children, but most countries still do not provide clear recommendations on this issue [30].

Potential factors influencing urine testing and culture may include a lack of awareness among clinicians regarding the indications for urine culture and concerns regarding urine culture contamination among specific populations such as residents in RACF [31, 32]. Interventions in general practice, e.g., education programs regarding guideline updates for front-line clinicians, routine audit and feedback on urine culture use, and computerized decision support system for guiding diagnosis may help improve the awareness of appropriate microbiology testing among general practitioners [32]. Potential measures to improve the sensitivity of urine testing include specimen refrigeration and providing instructions on sampling collection for patients [33].

It is reassuring to find in this study that first-line antibiotics (trimethoprim and cefalexin) accounted for most antibiotic prescriptions for UTIs, while quinolones and other second-line antibiotics only accounted for a small proportion, suggesting good practice in antibiotic choice for UTIs. Besides, pregnant women with UTIs were found more likely

to be tested than other similar-aged women who were not pregnant. This could be due to the clinical guidelines for pregnancy care that strongly recommend routine screening for UTIs and asymptomatic bacteriuria as a part of antenatal care [34, 35]. We also observed that men were more likely to receive urine testing than women in UTI management. Clinicians may be more cautious with UTIs in men because they are uncommon and abnormalities of the urinary tract often play an important role in the etiology [8]. Also, there are fewer studies on UTIs and antibiotic recommendations for men [36]. Therefore, clinicians may also be more likely to perform urine testing to help guide antibiotic treatment for male patients. In addition, we note that the proportion of those tested was relatively lower in the outer regional and remote areas compared with major cities, but higher in inner regional areas. Accessibility to testing may differ between regions although it is unclear why patients seen in inner regional areas were more likely to be tested than those in major cities.

The major strengths of our study include the large and representative study population from a national general practice database and the consideration of important patient characteristics associated with complicated UTIs. There are also limitations. First, patients may have had UTI encounters or microbiology tests for UTIs with a health practitioner not providing data to the MedicineInsight database and we would therefore not have a record for this. However, this would only bias our results if this differed between patient groups. Second, we used free text searches to identify microbiological testing, pregnancy, and residence in RACF, which may lead to misclassification. Third, we lack information about the actual urine culture results to determine how appropriate the prescribed antibiotics were, although this was not the primary aim of the study.

Conclusion

In this population-based analysis of UTI encounters with antibiotics prescribed in general practice, we found potential underuse of urine testing in antibiotic treatment among patient groups at high risk of complicated UTIs, especially children under 5 years old, patients with recurrent UTIs, and older adults living in RACF, which can be an important driving factor for inappropriate antibiotic use in UTI management. Given increasing concerns about antibiotic resistance, particularly among common causative pathogens for UTIs, our findings highlight the need for increasing clinicians' awareness of the importance of urine testing for these high-risk patient groups when they start antibiotic treatment for UTIs. Although the recommendation has been included in current guidelines, further antibiotic stewardship is needed to improve guideline-based antibiotic prescribing for UTIs in clinical practice.

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Author contributions Development of overall study aims and design—ZP, BL, and AH. Data analyses—ZP assisted by AH. Wrote the first draft of the manuscript—ZP. Revision of subsequent drafts of the manuscript and approval of the final manuscript—all authors.

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Data availability The data that support the findings of this study are available from the NPS MedicineWise but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the NPS MedicineWise.

Compliance with ethical standards

Conflict of interests Not applicable.

Ethical approval The study was approved by the University of New South Wales Human Research Ethics Committee (number HC180900).

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Chapter 4 After-hours consultations and antibiotic prescribing for self-limiting upper respiratory tract infections in general practice

4.1 Summary

Co-author information: Zhuoxin Peng[1], Wen-Qiang He[1], Andrew Hayen[2], John Hall[1], Bette Liu[1]

1. School of Population Health, University of New South Wales, Sydney, New South Wales, Australia
2. School of Public Health, Faculty of Health, University of Technology Sydney, Sydney, New South Wales, Australia

As the first author of the article, I developed the overall study aims and design in consultation with my supervisors, conducted the data analysis, wrote the first draft of the manuscript and revised it with feedback and revisions by my supervisors and co-authors. The manuscript has been submitted to a peer-reviewed journal.

Objectives: To determine the association between after-hours consultations and the likelihood of antibiotic prescribing for self-limiting upper respiratory tract infections (URTIs) in general practice.

Design: A cross-sectional analysis using Australian national general practice data (MedicineInsight).

Setting and participants: We analysed records of general practice encounters for URTIs between 1 February 2016 and 31 January 2019 in MedicineInsight.

Main outcome measures: The proportion of first-time URTI episodes where antibiotic prescribing occurred on the same day (immediate prescribing); the adjusted odds ratios (ORs) and 95% confidence intervals (CI) for the likelihood of antibiotic prescribing obtained by using generalised estimating equations.

Results: Among 357287 URTI episodes included in the analysis, antibiotics were recorded as being prescribed in 172605 episodes (48.3%). After adjusting for patients'

demographics, practice characteristics and seasons, consultations on weekends (versus weekdays, OR=1.42, 95%CI=1.39-1.45) and national public holidays (versus not holidays, OR=1.23, 95%CI=1.17-1.29) were associated with a higher likelihood of immediate antibiotic prescribing. Adjustment for patients' presentations and diagnoses at the time of episodes changed the association strength but the effect of weekends (versus weekdays, OR=1.37, 95%CI=1.33-1.41) and holidays (versus not holidays, OR= 1.10, 95%CI= 1.03-1.18) remained significant.

Conclusions: General practice consultations on weekends and public holidays were associated with a higher likelihood of immediate antibiotic prescribing for self-limiting URTIs in general practice. Studies to better understand the reasons underlying the high antibiotic prescribing behaviour are needed.

The supplementary methods and tables of this study are shown in Appendix 3 (Page 158)

4.2 Introduction

Upper respiratory tract infections (URTIs) are the most common reasons for general practice consultations in primary care.[1] Most URTIs are self-limiting viral infections for which antibiotics are not indicated.[2-4] Therefore, Australian and international guidelines do not recommend immediate antibiotic prescribing in first-time acute URTI presentations unless patients are considered at high risk of complications.[2-4] However, antibiotics are commonly overprescribed for URTIs in general practice. A previous Australian study found that antibiotic prescribing rates were up to 40% for rhinosinusitis & unspecified URTIs and more than 80% for otitis media, exceeding guideline recommendations (0.5%-8% for rhinosinusitis & unspecified URTIs and 20%-30% for otitis media) in general practice.[5] Therefore, there is an urgent need to better understand factors that trigger antibiotic overuse in URTI episodes and improve antibiotic prescribing in primary care.

An ecological study in the UK analysed the proportion of consultations in which antibiotics were prescribed and found that compared to regular daytime general practitioners, practitioners in after-hours primary care clinics were more likely to prescribe antibiotics for patients.[6] However it is unclear whether the after-hours effect reflects excessive antibiotic prescribing on weekends or holidays or just a difference in the patients' presentations at those times. Although there is evidence of differences in the quality of healthcare provided at night or weekends,[7] the higher antibiotic volume in after-hours consultations might also be attributed to sicker patients that doctors encounter. Using an Australian national general practice database, we conducted a cross-sectional study to answer two questions: 1) is there an association between after-hours consultations and a greater proportion of antibiotic prescribing in self-limiting URTIs; and 2) to what extent the association is mediated through characteristics of the patients' presentation at the encounter.

4.3 Methods

4.3.1 Data sources

We used electronic medical records of patients' general practitioner (GP) visits between 1 February 2016 and 31 January 2019 (36 months) from MedicineInsight, an Australian national database of electronic primary care records which includes data from more than 650 general practices and 3.6 million patients managed by NPS MedicineWise.[8] MedicineInsight consists of a number of datasets, separately recording patients' demographic characteristics, chronic health conditions, details of GP encounters including consultation reasons, diagnoses, prescriptions, medical examinations, and practice geographical information. A unique and anonymised identification number is assigned to each patient and practice so that the information pertaining to a patient or practice in different datasets can be linked. We used a 25% random sample of patients in the de-identified MedicineInsight data which was available for research purposes.

4.3.2 Ethical approval

The Human Research Ethics Committee at the University of New South Wales approved this study (number HC180900).

4.3.3 URTI episodes and immediate antibiotic prescribing

We included "first-time" URTI episodes in MedicineInsight during the 36-month study period in our analyses. We used search terms (see Appendix 3 Supplementary Table 1) based on earlier studies[9, 10] to identify URTI episodes from the encounter reason, diagnosis reason and prescription reason fields in the MedicineInsight database. If a search term was found in any one of these three fields from a patient's record, we defined that there was a URTI episode on that day for the patient. We excluded URTI episodes which routinely require antibiotic treatment e.g., pertussis and epiglottitis, URTI episodes where there were other reasons listed for the patient encounter on the same day, and URTI

episodes among patients with significant comorbidities i.e., cancers, diabetes, heart failure, chronic obstructive pulmonary disease, chronic renal failure, and other immune deficiencies (see Appendix 3 supplementary Table 2 for the identification of immune deficiencies) who might be at high risk of complications. URTI episodes that occurred in outer regional and remote areas in Australia were also excluded, as antibiotic prescribing for URTIs in those settings might be influenced by other factors, including limited access to healthcare and a high incidence of rheumatic fever.[2] We included only "first-time" URTI encounters which were defined if for the same patient there was no other URTI presentation in the 30 days prior.

Our study outcome was whether there was immediate antibiotic prescribing for patients in their URTI episodes. This was ascertained if there was a record of a systemic antibiotic prescription (see Appendix 3 Supplementary Table 3 for the identification of antibiotic prescriptions) on the same day as the "first-time" URTI episode.

4.3.4 Temporal variables and covariates

Our main factor of interest was the difference in prescribing on weekends and public holidays. We defined weekends as Saturday and Sunday. We selected four national public holiday periods in Australia: Christmas & New Year holiday (23 December to 5 January), Australia Day (26 January), Easter weekend (Good Friday to Easter Monday, for which the dates differ by year), and Anzac Day (25 April). The potential effect modification by seasons in Australia was also considered (summer: December to February; autumn: March to May; winter: June to August; spring: September to November).

We extracted patients' demographic factors and details of their clinical presentation reported at the time of the URTI episodes. Demographic characteristics included sex and age. Clinical characteristics of the presentation included patients' body temperature records (normal, fever [≥38°C], or not recorded), suspected aetiology as labelled by the GPs (viral, bacterial, or unspecified), and specific diagnoses (tonsillitis, pharyngitis, sinusitis, otitis media, or unspecified URTIs). We estimated the patients' prior use of

antibiotics by calculating the number of antibiotic prescriptions the patient had in the past year before the URTI episode as a continuous variable. The general practice location (major cities or inner regional area)[11] and the Index of Relative Socio-economic Advantage and Disadvantage (in 5 quintiles)[12] were also considered.

4.3.5 Statistical analysis

We calculated the proportion of URTI episodes where immediate antibiotic prescribing was recorded for all URTI episodes and by temporal factors and other covariates. Then multivariable logistic regression with generalised estimating equations was performed to test the association between URTI episodes on weekends, public holidays or seasons and the likelihood of immediate antibiotic prescribing, adjusting for those covariates and the clustering of patients and practices. To better understand to what extent the weekend, holiday, and seasonal effects were mediated through characteristics of the patients' presentation and diagnosis at the time of URTI episodes, we used two models: Model 1 only adjusted for patients' demographic factors, previous antibiotic use and practices' characteristics while Model 2 additionally adjusted for patients' body temperature, aetiology as determined in the patient records, and specific diagnoses. In addition, we performed sensitivity analyses to examine the association by age groups, fever or not, aetiology labels and URTI diagnosis types. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

4.4 Results

After excluding 62699 URTI episodes not considered as "first-time" encounters, 46538 URTI episodes in outer regional or remote areas, and 45222 URTI episodes among patients with significant comorbidities, our analyses included 357287 first-time URTI episodes during February 2016 and January 2019 (Table 1). Approximately 45% of

episodes were among children under 18 years old, and 50% were among adults aged between 18 and 64 years old. Fever was reported in 3% of all episodes and the proportion of URTIs labelled as bacterial origin was 4%. Of all episodes, 34% were assigned a diagnosis of tonsillitis, pharyngitis, sinusitis, or otitis media and 66% as unspecified URTIs. Antibiotics were prescribed on the same day in 172605 episodes (48.3%), with a higher proportion prescribed for episodes occurring on weekends (versus weekdays, 55.7% vs 47.5%) and public holidays (versus not holidays, 57.0% vs 48.1%). Seasonally, URTI episodes in summer were more likely to be prescribed antibiotics (52.4%) while the proportion in winter was lower (46.4%). We also observed that adults, patients with fever, URTIs labelled as bacterial, or URTIs with specific diagnoses had a relatively higher likelihood of immediate antibiotic prescribing. The proportion of episodes where antibiotics were prescribed at weekends vs. weekdays broken down by diagnoses is shown in Appendix 3 supplementary Table 4.

After adjusting for patients' demographics and practice characteristics in Model 1, weekends (versus weekdays, OR=1.42, 95%CI=1.39-1.45), public holidays (versus not holidays, odds ratio [OR]=1.23, 95% confidence intervals [CI]=1.17-1.29), and summer (versus winter, OR=1.21, 95%CI=1.19-1.24) were significantly associated with a higher likelihood of immediate antibiotic prescribing (Table 2). After additionally adjusting for characteristics of the patients' clinical presentation in Model 2, the OR (95% CI) for weekends relative to weekdays was 1.37 (1.33-1.41); the OR (95% CI) for holidays relative to not holidays was 1.10 (1.03-1.18); and the seasonal difference became very small (summer versus winter, OR=1.04, 95%CI=1.01-1.06).

In the sensitivity analyses by different age groups (Appendix 3 supplementary Table 5), weekends were significantly associated with a higher likelihood of antibiotic prescribing across all ages, but holidays were only significantly associated with a higher likelihood of antibiotic prescribing among adults. When we only considered those without fever nor a "bacterial origin" label and those without specific diagnoses (Appendix 3 Supplementary Table 6), the weekend and public holiday effects remained significant.

Table 4.1. Proportion of first-time upper respiratory tract infections (URTI) episodes with immediate antibiotics prescribed.

	URTI episode, No. (%)	Proportion with antibiotics prescribed, %
Total	357287 (100)	48.3
Demographical factors		
Sex		
Male	157210 (44)	46.8
Female	200077 (56)	49.5
Age (years)		
0-2	50586 (14)	33.9
3-5	41879 (12)	42.1
6-11	44180 (12)	44.3
12-17	26739 (7)	49.6
18-44	126929 (36)	54.0
45-64	50164 (14)	54.2
≥65	16180 (5)	55.2
Socioeconomic index level		
1 (most disadvantaged)	37367 (11)	48.0
2	45935 (13)	47.0
3	84847 (24)	48.6
4	71613 (20)	48.2
5 (most advantaged)	115905 (33)	48.9
Area Remoteness		
Major cities	289618 (81)	48.2
Inner Regional areas	67651 (19)	48.7
Clinical characteristics		
Body temperature		
Not recorded	234836 (66)	49.1
Without fever (<38°C)	111662 (31)	45.1
With fever (≥38°C)	10789 (3)	64.4
Aetiology labels		
Unspecified origins	248504 (70)	61.6
Viral	93766 (26)	5.4
Bacterial	15017 (4)	96.0
Diagnosis of URTIs		

Tonsillitis	33588 (9)	89.9
Pharyngitis	18579 (5)	71.7
Sinusitis	37208 (10)	84.6
Otitis media	33731 (9)	88.4
Unspecified URTIs	234181 (66)	29.0
Temporal factors		
Day of a week		
Weekdays	321071 (90)	47.5
Weekends	36216 (10)	55.7
Seasons		
Winter	119886 (34)	46.4
Spring	94318 (26)	49.5
Summer	58984 (17)	52.4
Autumn	84099 (24)	46.8
Public Holidays		
No	349243 (98)	48.1
Yes	8044 (2)	57.0

Table 4.2 Multivariable analysis evaluating the association between temporal factors and the proportion of immediate antibiotic prescribing in upper respiratory tract infection (URTI) episodes.

	Model 1 [a]		Model 2 [b]	
	OR (95% CI) [c]	P value	OR (95% CI)	P value
Day of a week				
Weekdays	1.00		1.00	
Weekends	1.42 (1.39-1.45)	<0.001	1.37 (1.33-1.41)	<0.001
Seasons		<0.001		0.024
Winter	1.00		1.00	
Spring	1.13 (1.11-1.15)	<0.001	1.03 (1.00-1.05)	0.021
Summer	1.21 (1.19-1.24)	<0.001	1.04 (1.01-1.06)	0.013
Autumn	1.02 (1.00-1.03)	0.087	1.01 (0.98-1.03)	0.614
Public Holidays				
No	1.00		1.00	
Yes	1.23 (1.17-1.29)	<0.001	1.10 (1.03-1.18)	0.003

a. Model 1: Logistic Generalised Estimating Equation model adjusting for sex, age groups,

the socio-economic index, the remoteness of areas, the number of antibiotic prescriptions for a patient in the previous year, and clustering in patients and practices

b. Model 2: Model 1 + clinical characteristics (body temperature, aetiology labels and the diagnosis of URTIs)

c. OR: odds ratio; CI: confidence intervals

4.5 Discussion

In this study of antibiotic prescribing for URTIs in Australian general practice between February 2016 and January 2019, we found immediate antibiotic prescribing appeared to be high (almost 50%) and comparable to that found in the Australian study conducted in earlier years.[5] We observed that there was a higher likelihood of immediate antibiotic prescribing at weekends, public holidays and during summer. Adjustment for patients' presentations such as fever and the type of URTIs explained some of the variation associated with weekends and public holidays but did not fully explain the effects, suggesting the existence of other factors driving antibiotic prescribing behaviours at weekends and holidays.

Our study population mainly consisted of relatively young and healthy patients, as due to our exclusion of people with significant comorbidities, 95% of patients were under 65 years old. However, we still observed a very high antibiotic prescribing rate overall (48.3%) and this was substantially higher for diagnoses including tonsillitis (89.9%), pharyngitis (71.7%), sinusitis (84.6%) and otitis media (88.4%). Worldwide, antibiotic overuse for URTIs is a long-standing concern in clinical practice[13]. Our findings did not differ substantially from previous reports from Australia which showed that 89% of otitis media and 94% of tonsilitis or pharyngitis episodes received antibiotics between 2010 and 2015 [5] and in the US 72% of sinusitis and 80% of otitis media episodes received antibiotics between 2010 and 2011 [14].

A German study showed that the overall antibiotic prescribing rate on Friday was higher than other working days of a week in general practice.[15] An ecological study in

the UK reported a higher likelihood of overall antibiotic prescribing in after-hours clinics if compared with daytime general practices.[6] Previous studies have suggested that doctors might see more severe conditions on weekends or holidays compared with weekdays.[16, 17] Our results in the main analysis showed that adjusting for factors that might be related to the severity of the presentation, e.g., fever, presumed causes, or prominent localising features, can explain some but not all of the excess antibiotic prescribing on weekends and holidays. In sensitivity analyses, the weekend effect remained significant across all subgroups, which supports that there might be other important factors that determine whether antibiotics are prescribed for URTIs. Several issues at both the health system and practice level may explain the higher prescribing that we observed. Clinicians often have a higher workload, more limited time and access to laboratory diagnostics for decision-making in after-hours service[18]. They are also more likely to encounter unfamiliar patients or demanding patients asking for quick solutions.[18, 19] All these challenges may contribute to greater antibiotic prescribing in after-hours care.

While the weekend effect remained strong in all subgroups, we found that the public holiday effect was not significant among children, patients with fever or labelled with an infection of “bacterial origin” and patients with localising features in subgroup analysis. To our knowledge, no studies have ever examined the heterogeneity of after-hours effects in different patient groups. Further studies are needed to understand the underlying reasons which were not captured in our study.

Overall there were more antibiotics prescribed to people with URTI in winter compared to the summer. However, the proportion of individuals with URTI who were prescribed antibiotics in summer compared to winter was higher; in the multivariable analysis, the difference is just marginally significant. The lower proportion of antibiotic prescribing for upper respiratory tract infections in winter might be the result of the high incidence of influenza and other viral respiratory tract infections in winter.

The major strength of our study is the use of large and representative national

general practice datasets. Limitations include our use of records of prescriptions of antibiotics rather than the actual use of antibiotics. It is possible that GPs prescribed the antibiotics immediately but asked patients to only take them if the URTI symptoms did not improve (i.e. delayed treatment strategy).[2, 4] Also, although we had some details on the patients' presentations, the actual disease severity may not be conveyed through these measures and a high proportion of encounters lacked records of body temperature or aetiology. Because we did not have the time stamp of the consultations, consultations on the weekday night were misclassified as in the normal working times. We also lacked detailed information regarding GP's characteristics, such as their ages or levels of experience which might influence antibiotic prescribing.[20] Additionally, the method of linking GP encounter records to prescription records on the same day cannot guarantee that the URTIs were the real reasons for antibiotic prescribing; and the use of free text to identify both URTIs and antibiotic prescriptions may lead to some misclassification. However, since the proportions we estimated resembled those described in an earlier study in Australia,[5] the misclassification was probably not significant.

4.6 Conclusion

Weekends and public holidays were associated with a higher likelihood of immediate antibiotic prescribing for self-limiting URTIs in general practice. Future multi-centre studies with detailed and accurate clinical information of patients' clinical presentations and medical examination results will help validate my findings and add to the knowledge of reasons underlying this higher prescribing behaviour.

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Chapter 5 Practice- and individual-level antibiotic prescribing associated with antibiotic treatment non-response in respiratory tract infections

Chapter 5 contains the original work

Peng Z, Hayen A, Liu B. Practice- and individual-level antibiotic prescribing associated with antibiotic treatment non-response in respiratory tract infections: a national retrospective observational study. *J Antimicrob Chemother* 2021; **76**: 804-12.

The study I present in this chapter addresses Objective 4 of my thesis: to quantify the independent contributions of general practice- and patient individual-level antibiotic prescribing to subsequent antibiotic treatment non-response in respiratory tract infections.

The study found that general practice-level broad- to narrow-spectrum antibiotic ratio was a predictor for the likelihood of patients' antibiotic treatment non-response (defined as re-prescribing a different antibiotic within 30 days of initial prescribing) in respiratory tract infection episodes, even if the patients themselves had no direct individual-level antibiotic exposure. The findings provide a deeper understanding of the significance of reducing broad-spectrum antibiotic prescribing in general practice.

As the first author of the article, I developed the overall study aims and design in consultation with my supervisors, conducted the data analysis, wrote the first draft of the manuscript and revised it with feedback and revisions by my supervisors and other co-authors, and submitted it to the peer-reviewed journal.

The supplementary methods and tables of this study are shown in Appendix 4 (Page 166)

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Practice- and individual-level antibiotic prescribing associated with antibiotic treatment non-response in respiratory tract infections: a national retrospective observational study

Zhuoxin Peng [1]*, Andrew Hayen[2] and Bette Liu[1]

[1]*School of Public Health and Community Medicine, University of New South Wales, Sydney, New South Wales, Australia;* [2]*School of Public Health, Faculty of Health, University of Technology Sydney, Sydney, New South Wales, Australia*

*Corresponding author. E-mail: zhuoxin.peng@student.unsw.edu.au

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Objectives: Antibiotic overuse results in adverse clinical outcomes. This study quantified the independent contributions of practice- and individual patient-level antibiotic prescribing to antibiotic treatment non-response in respiratory tract infections (RTIs) in primary care.

Methods: RTI episodes with antibiotic prescribed in 2018 were extracted from an Australian national general practice database. Practices were classified into tertiles by total antibiotic prescriptions per patient and ratios of broad- to narrow-spectrum antibiotic prescriptions. The association between practice- and individual patient-level antibiotic prescribing in the previous year and antibiotic treatment non-response (defined as prescription of a different antibiotic) ≤30 days after the initial RTI episode was quantified using generalized estimating equations.

Results: Of 84 597 RTI episodes with antibiotics prescribed in 558 practices, 5570 (6.6%) episodes of treatment non-response were identified. Patients with high individual-level antibiotic prescribing (≥4 prescriptions/year) had an increased risk of treatment non-response (versus no prescriptions/year: OR = 1.64, 95% CI = 1.52–1.77). At the practice level, there was no significant association between total antibiotic prescriptions per patient and treatment non-response (high versus low: OR = 0.99, 95% CI = 0.92–1.06). RTI episodes in practices with high broad- to narrow-spectrum antibiotic ratios had an increased risk of treatment non-response (versus low-ratio practices: OR = 1.14, 95% CI = 1.05–1.23); this association was only observed among patients with <4 antibiotic prescriptions/year.

Conclusions: The general practice-level broad- to narrow-spectrum antibiotic ratio was a predictor of RTI antibiotic treatment non-response in patients with lower individual-level antibiotic use. The measure of practice-level antibiotic prescribing could potentially guide the improvement of antibiotic treatment.

Introduction

Respiratory tract infection (RTI) is the most common indication for antibiotic prescribing in clinical practice.[1] A major concern arising from this is excessive antibiotic use and subsequent adverse outcomes, including antibiotic resistance, treatment non-response, opportunistic infections and mortality in RTI episodes.[2] Measuring antibiotic use in healthcare settings is considered a critical element in antibiotic stewardship, given its important role in informing effective strategies to reduce antibiotic overuse.[3] There is high variability of antibiotic prescribing among different regions, medical practices and clinicians, which cannot be simply explained by epidemics or patient-illness severity.[4–7] In fact, a large proportion of the variation should be ascribed to the appropriateness of clinicians' prescribing behaviours.[4,7]

Several ecological studies at national, district and hospital levels have identified the association between the variation of antibiotic use in healthcare facilities and antibiotic-associated adverse events.[8–11] Other studies based on patient-level data have reported the association between individual patient-level antibiotic exposure and subsequent antibiotic resistance or treatment non-response in RTI management.[11–13] To date, however, we know of no studies considering antibiotic use at both individual and healthcare-facility levels to determine their independent contribution to patients' antibiotic treatment outcomes. We hypothesized that high antibiotic use at the general-practice level may exert selection pressure[14] on local bacterial pathogens and subsequently contribute to high antibiotic resistance and treatment non-response rate among regular patients within the practice

(or the surrounding area), even when patients had no previous individual antibiotic exposure. Accordingly, the measure of antibiotic prescribing at general-practice level should be able to serve as a predictor of RTI antibiotic treatment non-response in the practice, independent of individual-level antibiotic exposure. Quantifying the independent effect of practice-level antibiotic use may help identify new opportunities to improve antibiotic prescribing and prevent adverse outcomes of RTIs and other infectious diseases in clinical practice. Therefore, the objective of this retrospective cross-sectional study was to examine the association of general practice- and individual-level antibiotic prescribing with antibiotic treatment outcomes in RTIs among the Australian population in primary care.

Methods

Data source

For this study we used MedicineInsight, a longitudinal research database derived from national electronic health records of over 3.6 million patients in approximately 600 general practices across Australia, which is managed by NPS MedicineWise.[15] MedicineInsight includes a number of datasets relating to fields in the practice clinical information system. In this study we used: (i) the Encounter dataset, which contains the reasons for general practice encounters in free-text; (ii) the Diagnosis dataset, recording free-text information on the diagnosis made during the encounters; (iii) the Script Item & Prescription dataset, including prescription information; (iv) the Patient dataset, containing patient demographic information; (v) the Conditions dataset, recording patients' chronic health conditions; (vi) the Immunization dataset, containing patients' vaccination history; and (vii) the Site dataset, containing geographical information on practices. All patients and practices have their own unique and anonymized identifying numbers by which their records in different datasets can be linked. A detailed description of MedicineInsight has been published.[15] This study used a simple random sample of 25% of all patients in MedicineInsight, which is available for analysis by researchers.

Ethics

The study was approved by the University of New South Wales Human Research Ethics Committee (number HC180900).

Selection criteria for practices and patients

Our study included RTI episodes where antibiotics were prescribed to 'regular patients' between January and December 2018 (the most recent and complete calendar year of MedicineInsight data available at the time of study commencement). All the practices included were required to meet data quality criteria, which were, in the year 2017: (i) ≥250 encounter records; (ii) ≥300 prescription records; (iii) ≥100 unique patients who visited the practice; and (iv) <15% of prescription records with missing medicine names. We defined, as specified in the Royal Australian College of General Practitioners standards,[16] a 'regular patient' in a practice as a patient who had ≥3 encounter records between January 2016 and December 2017 at that practice.

Identification of RTI episodes with antibiotics prescribed

We extracted records from the Encounter, Diagnosis and Prescription datasets in 2018 and used a search-term list based on an earlier study[17] to identify episodes related to RTIs [see terms in the Supplementary Methods (available as Supplementary data at *JAC* Online)]. An RTI episode of a regular patient was included in analyses if the Encounter, Diagnosis or Prescription reason field contained a term to indicate an RTI and there was also a prescription record of a systemic antibiotic on the same day for that patient (see the Supplementary Methods for the identification of systemic antibiotics). Only RTI episodes with one antibiotic prescribed on the day (i.e. monotherapy) were included. An RTI episode was considered as part of the same episode and excluded from analyses if it occurred within 30 days of an earlier episode and the same antibiotic was prescribed. Records with missing information on patient demographic variables were excluded from analyses. Figure 1 shows a flow chart of these exclusions.

Outcomes

The primary outcome was antibiotic treatment non-response in the RTI episodes. Treatment non-response was defined when a different type of antibiotic was prescribed for RTIs within 30 days after the initial episode. This definition has been used in previous studies to determine RTI antibiotic treatment failure or non-response.[18,19] A sensitivity analysis was conducted to include records of referral to a specialist or an emergency department after the original RTI episode in the definition of treatment non-response. As we did not have detailed reasons for referrals recorded in the database, a shorter window (14 days) was used to increase the likelihood that the referral records were related to the original RTI episodes.

Practice- and individual-level antibiotic prescribing

The primary exposure of interest was practice-level systemic antibiotic prescribing in 2017. The whole year prior to the observation period was used to control for seasonal and annual variations in practices. We calculated two aggregate-level antibiotic prescribing indicators, which were commonly used in primary care settings.[17,20,21] The first indicator was the quantity of antibiotics prescribed in a practice, calculated as the total number of systemic antibiotic prescriptions per patient who made one or more visits to the practice in 2017. The second was the ratio of broad- to narrow-spectrum antibiotic prescriptions at the practice in 2017. We classified broad- and narrow-spectrum antibiotics in accordance with the US CDC.[21] Penicillin and β-lactamase inhibitor combinations (e.g. amoxicillin/clavulanate), second- and third-generation cephalosporins, macrolides (except erythromycin), lincosamides and fluoroquinolones were classified as broad-spectrum antibiotics. Other penicillins (e.g. penicillin, amoxicillin and ampicillin), first-generation cephalosporins and erythromycin were classified as narrow-spectrum antibiotics. Practices were categorized into tertiles by these two indicators with those classified as 'low' including the bottom third, 'medium' the middle third and 'high' the top third.

We also estimated individual patient-level antibiotic exposure in 2017. This was calculated as the total number of systemic antibiotic prescriptions for each patient in 2017 and categorized into three levels: no prescriptions, 1–3 prescriptions/year (low) and ≥4 prescriptions/year (high).

Covariates

Demographic information extracted from the MedicineInsight database included patients' sex and age group (0–4, 5–9, 10–19, 20–44, 45–64 and ≥65 years) at the time of RTI episodes, the remoteness of practices based on the Accessibility and Remoteness Index of Australia (in three categories: major cities, inner regional areas and outer regional and remote areas)[22] and the regional socioeconomic levels of practices (in five quintiles) based on the Index of Relative Socio-economic Advantage and Disadvantage in Australia.[23] We also extracted patients' clinical characteristics, including RTI types (upper RTIs, lower RTIs and unknown types; see details in the Supplementary Methods), types of antibiotics initially prescribed in the RTI episodes (narrow-spectrum β-lactam antibiotics, including narrow-spectrum penicillins and first-generation cephalosporins; broad-spectrum β-lactam antibiotics, including broad-spectrum penicillins and second/third-generation cephalosporins; doxycycline; macrolides and

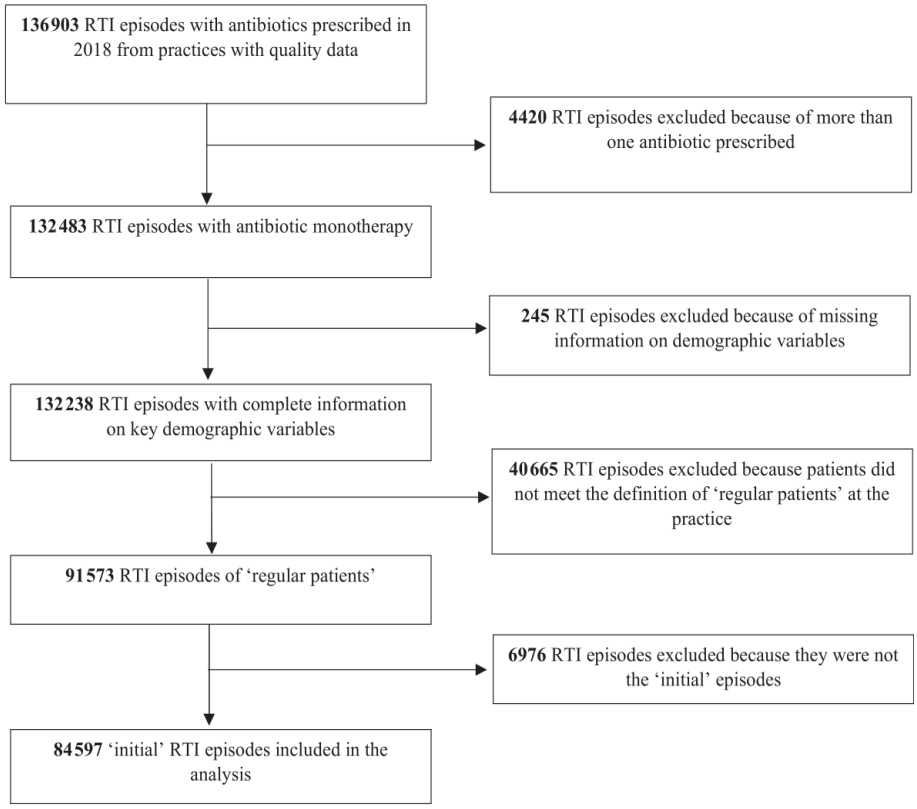

Figure 1. Flow chart showing the inclusion of RTI episodes in the analysis.

lincosamides; and other antibiotics), chronic respiratory comorbidities (asthma and COPD), other major comorbidities (i.e. cancers, diabetes, chronic kidney diseases, coronary heart diseases, stroke, heart failure, dementia and chronic liver diseases) and history of pneumococcal vaccination in the past 10 years. The number of general practice consultations and RTI treatment non-response for each patient in 2017 were also extracted as continuous variables.

Statistical analysis

The unit of analysis was an RTI episode with antibiotics prescribed in 2018. A descriptive analysis was performed to examine the proportion of RTI episodes where treatment non-response occurred overall and according to practice-level tertiles of antibiotic prescribing, individual-level antibiotic prescribing, demographic characteristics and clinical characteristics.

Logistic generalized estimating equation models were performed to assess the association between practice- and individual-level antibiotic prescribing and treatment non-response in RTI episodes, accounting for clustering due to multiple RTI episodes in the same patient and practice, and the covariates described above. Initially the model only examined the association between two measures of practice-level antibiotic prescribing and treatment non-response, accounting for clustering, demographic characteristics of patients (sex and age) and geographical information on practices. Then we added the individual-level antibiotic prescribing into the model and then patients' clinical characteristics. This enabled us to examine how these characteristics impacted the likelihood of treatment non-response. We also performed stratified analyses by patient individual-level antibiotic prescribing and explored the interaction between practice- and individual-level antibiotic prescribing.

Sensitivity analyses were conducted to examine the association: (i) when referrals within 14 days were additionally considered in the definition of treatment non-response; (ii) using different time intervals (7, 14 and 21 days) as the window of treatment non-response; and (iii) including re-prescription of the same antibiotic in the definition of treatment non-response.

We used the GENMOD Procedure in SAS version 9.4 (SAS Institute, Cary, NC, USA) for the statistical analysis.

Results

After excluding 14 practices, our analyses included 558 practices that met the quality criteria. In 2017, the median number of total antibiotic prescriptions per patient in the included practices was 0.92 (IQR = 0.78–1.12) and the median ratio of broad- to narrow-spectrum antibiotic prescriptions was 0.67 (IQR = 0.52–0.89). Descriptive statistics for practices in each tertile of antibiotic prescribing are shown in Table 1.

Among regular patients in the included practices in 2018, a total of 84 597 RTI episodes with an antibiotic prescribed and 5570 episodes of treatment non-response were identified, giving a

Table 1. Characteristics of general practices by tertiles of practice-level antibiotic prescribing in 2017

	Tertiles of antibiotic prescriptions per patient		
	low	medium	high
Total no.	186	186	186
Antibiotic prescriptions per patient, median (IQR) [range]	0.68 (0.60–0.78) [0.01–0.82]	0.92 (0.88–0.98) [0.82–1.03]	1.24 (1.12–1.45) [1.03–2.40]
Area remoteness, no. (%)			
major cities	112 (60)	118 (63)	113 (61)
inner regional areas	39 (21)	42 (23)	47 (25)
outer regional/remote areas	35 (19)	26 (14)	26 (14)
Socioeconomic index level, no. (%)			
1 (most disadvantaged)	31 (17)	31 (17)	34 (18)
2	30 (16)	28 (15)	33 (18)
3	49 (26)	46 (25)	36 (19)
4	41 (22)	23 (12)	37 (20)
5 (most advantaged)	32 (17)	55 (30)	45 (24)
	Tertiles of ratio of broad- to narrow-spectrum antibiotics[a]		
	low	medium	high
Total no.	186	186	186
Ratio of broad- to narrow-spectrum antibiotic prescriptions, median (IQR) [range]	0.47 (0.39–0.52) [0.10–0.57]	0.67 (0.62–0.74) [0.57–0.81]	1.04 (0.89–1.26) [0.81–3.79]
Area remoteness, no. (%)			
major cities	100 (54)	119 (64)	124 (67)
inner regional areas	52 (28)	42 (23)	34 (18)
outer regional/remote areas	34 (18)	25 (13)	28 (15)
Socioeconomic index level, no. (%)			
1 (most disadvantaged)	49 (26)	27 (15)	20 (11)
2	26 (14)	36 (19)	29 (16)
3	47 (25)	42 (23)	42 (23)
4	29 (16)	33 (18)	39 (21)
5 (most advantaged)	34 (18)	48 (26)	50 (27)

[a]Broad-spectrum antibiotics included penicillin and β-lactamase inhibitor combinations, second- and third-generation cephalosporins, macrolides (except erythromycin), lincosamides and fluoroquinolones; narrow-spectrum antibiotics included narrow-spectrum penicillins (e.g. penicillin, amoxicillin and ampicillin), first-generation cephalosporins and erythromycin.

treatment non-response rate of 6.6% (Table 2). Antibiotic treatment non-response was more common among female patients, the oldest patient group (≥65 years), patients with lower RTIs, those with broader-spectrum antibiotics prescribed in the initial RTI episodes and those having chronic comorbidities or history of pneumococcal vaccination. Patients in practices with high antibiotic prescriptions per patient in the past year had a higher proportion of treatment non-response (6.9%) than those in practices with medium (6.7%) and low (6.2%) levels. A similar trend was found in practices with high broad- to narrow-spectrum antibiotic ratios in the past year (7.1%) versus practices with medium (6.6%) and low (6.1%) ratios and among patients with high individual-level antibiotic exposure in the past year (9.0%) versus those with low (6.4%) and no (5.4%) exposure.

In the multivariable model adjusting for patient and practice characteristics (Table 3), practices with high per-patient antibiotic prescriptions were not associated with antibiotic treatment non-response when compared with practices with low per-patient antibiotic prescriptions (OR = 1.05, 95% CI = 0.97–1.13). Practices with a high ratio of broad- to narrow-spectrum antibiotics were significantly associated with an increased risk of antibiotic treatment non-response when compared with practices with a low ratio (OR = 1.15, 95% CI = 1.06–1.24). Adjustment for the individual-level antibiotic exposure in the past year, which was a strong predictor of treatment non-response (high versus no prescription: OR = 1.64, 95% CI = 1.52–1.77), made little difference to the associations of practice-level per-patient antibiotic prescriptions (high versus low: OR = 0.99, 95% CI = 0.92–1.06) and broad- to narrow-spectrum antibiotic ratio (high versus low: OR = 1.14, 95% CI = 1.05–1.23) with treatment outcomes. Additional adjustment for patient clinical characteristics did not affect the identified associations.

Effect modification was observed in the analyses stratified by individual-level antibiotic prescribing (Table 4). We found that the

Table 2. Antibiotic treatment non-response in RTI episodes in 2018 by characteristics of patients and practices

	RTI episode, no. (%)	Proportion with treatment non-response, %
Total	84 597 (100)	6.6
By patient-level factors		
patient demographics		
sex		
male	33 046 (39)	6.0
female	51 551 (61)	6.9
age (years)		
0–4	10 622 (13)	6.7
5–9	5911 (7)	4.5
10–19	7288 (9)	4.9
20–44	24 066 (28)	6.0
45–64	20 443 (24)	7.0
≥65	16 265 (19)	8.3
patient clinical characteristics		
type of RTIs		
upper respiratory tract infections	57 741 (68)	6.0
lower respiratory tract infections	17 679 (21)	8.2
unknown	9177 (11)	7.0
antibiotic classes prescribed in the RTI episode[a]		
narrow-spectrum β-lactam antibiotics	45 839 (54)	6.0
broad-spectrum β-lactam antibiotics	17 174 (20)	6.9
doxycycline	7023 (8)	7.1
macrolides or lincosamides	11 078 (13)	7.8
others	3483 (4)	8.2
respiratory comorbidities[b]		
no	65 072 (77)	6.3
yes	19 525 (23)	7.4
other comorbidities[c]		
no	66 139 (78)	6.2
yes	18 458 (22)	8.0
pneumococcal vaccination record in the past 10 years		
no	74 622 (88)	6.3
yes	9975 (12)	8.6
patient individual-level antibiotic prescriptions in the past year		
0	32 741 (39)	5.4
low (1–3)	33 353 (39)	6.4
high (≥4)	18 503 (22)	9.0
By practice-level factors		
practice-level geographical factors		
area remoteness		
major cities	60 270 (71)	6.7
inner regional areas	15 640 (18)	6.5
outer regional/remote areas	8687 (10)	5.7
socioeconomic index level		
1 (most disadvantaged)	12 493 (15)	6.1
2	12 229 (15)	6.4
3	18 716 (22)	6.5
4	17 025 (20)	6.9
5 (most advantaged)	23 842 (28)	6.8
practice-level antibiotic prescribing in the past year		
antibiotic prescriptions per patient		
low	23 318 (28)	6.2
medium	30 762 (36)	6.7
high	30 517 (36)	6.9

Continued

Table 2. *Continued*

	RTI episode, no. (%)	Proportion with treatment non-response, %
ratio of broad- to narrow-spectrum antibiotic prescriptions[d]		
low	28 872 (34)	6.1
medium	30 691 (36)	6.6
high	25 034 (30)	7.1

[a]Narrow-spectrum β-lactam antibiotics included narrow-spectrum penicillins (e.g. penicillin, amoxicillin and ampicillin) and first-generation cephalosporins; broad-spectrum β-lactam antibiotics included penicillin and β-lactamase inhibitor combinations and second- and third-generation cephalosporins.
[b]Respiratory comorbidities included asthma and COPD.
[c]Other comorbidities included cancers, diabetes, chronic kidney diseases, coronary heart diseases, stroke, heart failure, dementia and chronic liver diseases.
[d]Broad-spectrum antibiotics included penicillin and β-lactamase inhibitor combinations, second- and third-generation cephalosporins, macrolides (except erythromycin), lincosamides and fluoroquinolones; narrow-spectrum antibiotics included narrow-spectrum penicillins (e.g. penicillin, amoxicillin and ampicillin), first-generation cephalosporins and erythromycin.

Table 3. Multivariable analysis evaluating the association between prior practice- and individual-level antibiotic prescribing and antibiotic treatment non-response in RTI episodes in 2018

	Model 1[a]		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Practice-level antibiotic prescribing in the past year						
antibiotic prescriptions per patient		0.239		0.331		0.412
low	1.00		1.00		1.00	
medium	1.06 (0.99–1.15)	0.097	1.04 (0.97–1.12)	0.301	1.04 (0.97–1.12)	0.301
high	1.05 (0.97–1.13)	0.248	0.99 (0.92–1.06)	0.744	0.99 (0.92–1.07)	0.893
ratio of broad- to narrow-spectrum antibiotic prescriptions[b]		0.002		0.005		<0.001
low	1.00		1.00		1.00	
medium	1.08 (1.00–1.16)	0.047	1.07 (1.00–1.15)	0.064	1.09 (1.01–1.17)	0.025
high	1.15 (1.06–1.24)	<0.001	1.14 (1.05–1.23)	0.001	1.18 (1.09–1.27)	<0.001
Patient individual-level antibiotic prescriptions in the past year				<0.001		<0.001
0	–	–	1.00		1.00	
low (1–3)	–	–	1.22 (1.14–1.31)	<0.001	1.22 (1.14–1.31)	<0.001
high (≥4)	–	–	1.64 (1.52–1.77)	<0.001	1.65 (1.53–1.78)	<0.001

[a]Model 1: logistic generalized estimating equation model adjusting for demographic information (sex, age), practice-level remoteness of areas, socio-economic index of areas and clustering in patients and practices. Model 2: Model 1 + individual-level antibiotic prescriptions in the past year. Model 3: Model 2 + patient clinical characteristics (types of RTIs in the episodes, antibiotic classes prescribed in the RTI episodes, respiratory comorbidities, other comorbidities and history of pneumococcal vaccination).
[b]Broad-spectrum antibiotics included penicillin and β-lactamase inhibitor combinations, second- and third-generation cephalosporins, macrolides (except erythromycin), lincosamides and fluoroquinolones; narrow-spectrum antibiotics included narrow-spectrum penicillins (e.g. penicillin, amoxicillin and ampicillin), first-generation cephalosporins and erythromycin.

practice-level broad- to narrow-spectrum antibiotic ratio was significantly associated with a higher risk of treatment non-response among patients with no and low individual antibiotic prescribing, but not among patients with high individual-level antibiotic prescribing. When patients with no and low individual antibiotic use were grouped together, a significant interaction was identified between the practice-level broad- to narrow-spectrum antibiotic ratio and individual-level antibiotic prescribing [*P* interaction = 0.023; Table S1 (available as Supplementary data at *JAC* Online)].

When referrals were included in the definition of treatment non-response in the sensitivity analysis, there were an additional 405 RTI episodes that met the definition of treatment non-response, increasing the estimated proportion of treatment non-response from 6.6% to 7.1%. However, the associations between practice- and individual-level antibiotic prescribing and treatment non-response remained unchanged (Table S2). Using different time windows did not change the association identified in the main analysis (Table S3), but the associations between both practice-level antibiotic prescribing measures and RTI treatment

Table 4. Multivariable analysis evaluating the association between prior practice-level antibiotic prescribing and antibiotic treatment non-response in RTI episodes in 2018, stratified by patient individual-level antibiotic prescriptions in the past year

	Patient individual-level antibiotic prescriptions in the past year					
	0		low (1–3)		high (≥4)	
	OR (95% CI)[a]	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Practice-level antibiotic prescribing in the past year						
antibiotic prescriptions per patient		0.993		0.607		0.122
low	1.00		1.00		1.00	
medium	0.99 (0.88–1.13)	0.918	1.01 (0.90–1.14)	0.852	1.15 (0.99–1.34)	0.068
high	1.00 (0.88–1.14)	0.999	0.96 (0.85–1.08)	0.469	1.03 (0.89–1.20)	0.682
ratio of broad- to narrow-spectrum antibiotic prescriptions[b]		0.007		0.013		0.576
low	1.00		1.00		1.00	
medium	1.20 (1.06–1.36)	0.005	1.06 (0.95–1.18)	0.325	0.94 (0.82–1.08)	0.358
high	1.20 (1.05–1.38)	0.008	1.19 (1.06–1.35)	0.003	0.99 (0.85–1.15)	0.885

[a]Logistic generalized estimating equation models were used, adjusting for patient demographic information (sex, age), practice-level remoteness of areas, socioeconomic index of areas and clustering in patients and practices.
[b]Broad-spectrum antibiotics included penicillin and β-lactamase inhibitor combinations, second- and third-generation cephalosporins, macrolides (except erythromycin), lincosamides and fluoroquinolones; narrow-spectrum antibiotics included narrow-spectrum penicillins (e.g. penicillin, amoxicillin and ampicillin), first-generation cephalosporins and erythromycin.

outcomes were not significant when re-prescription of the same antibiotic was included in the definition of treatment non-response (Table S3). After adjusting for the number of previous general practice visits and RTI treatment non-response, the strength of association between individual-level antibiotic prescribing and RTI treatment outcomes became weaker, while the association of practice-level antibiotic prescribing was similar to the main analyses (Table S4).

Discussion

This study was novel in that it assessed the effect of both practice- and individual patient-level antibiotic prescribing on RTI antibiotic treatment non-response in Australian general practices. Our findings confirmed that high individual patient-level antibiotic prescribing was associated with an increased risk of treatment non-response. After adjusting for this strong individual-level predictor, a high broad- to narrow-spectrum antibiotic ratio within a general practice was a significant risk factor for RTI treatment non-response, whereas the total number of antibiotic prescriptions per patient at practice-level was not associated with RTI treatment non-response. We also identified heterogeneity in effects, whereby the significant association between practice-level broad- to narrow-spectrum antibiotic ratio and risk of treatment non-response was only observed among patients with no or low individual antibiotic exposure.

Similar to our findings, a Norwegian outpatient study on RTI antibiotic treatment reported prescribing of a new antibiotic within 28 days of 5.5%.[24] A US study on RTI antibiotic treatment among children, which defined treatment non-response as re-prescriptions of any antibiotics after initial episodes, reported a 30 day non-response rate of 8.2%,[25] which was also similar to our results if we used a similar definition. However, a UK longitudinal study of all ages with a similar definition of treatment non-response, i.e. change in antibiotic within 30 days (accounting for 94% of all events), reported treatment non-response in RTIs of over 10%[18] and another UK study on childhood RTI antibiotic treatment reported an antibiotic 'non-response' rate within 14 days of only 1.2%.[12] The variability in treatment non-response rates in different studies may be due to differences in study populations, clinical management or treatment non-response definitions.

Previous studies have identified an association between antibiotic use and antibiotic resistance in RTIs.[11] A meta-analysis found a significant association between individual antibiotic use in primary care settings and the development of antibiotic resistance in RTIs, with a lag effect of 0–12 months.[26] Another cross-national ecological study among 26 European countries found that countries with higher outpatient consumption of penicillin had a higher rate of penicillin-resistant *Streptococcus pneumoniae*.[27] Our study builds on these earlier reports as, in addition to examining aggregate-level antibiotic prescribing, we were also able to take into consideration individual-level antibiotic exposure, demographics and clinical characteristics.

Our findings, that practice-level antibiotic prescribing to patients with low or no direct antibiotic exposure could increase the risk of RTI treatment non-response, potentially support our hypothesis that selection pressure for antibiotic resistance can affect patients who directly received the antibiotics and other regular patients without direct antibiotic exposure in the practice. Although the majority of RTI episodes are likely to be viral in aetiology, changing antibiotic in an RTI episode could represent worsening symptoms after initial treatment and suggest a higher likelihood of bacterial coinfection.[28] Therefore, antibiotic resistance could be a plausible mechanism linking practice-level antibiotic prescribing with these relatively more severe RTI episodes.

However, as we used the outcome of prescribing of a second antibiotic as a proxy for treatment non-response, the association identified in our study could be mediated through mechanisms other than antibiotic resistance. For example, if antibiotics are prescribed for RTIs of viral origin, antibiotic treatment 'non-response' would naturally occur and could be an indicator of greater diagnostic error or antibiotic misuse rather than the emergence of antibiotic resistance. Another possibility is that patients with frequent consultations may also have a higher expectation of recovery or a lower tolerance of symptoms and such patients or their doctors may be more likely to change antibiotics.

Our sensitivity analyses support the existence of multiple mechanisms for the associations observed in this study. After adjusting for consultation behaviours, i.e. the number of patient general practice visits and treatment non-response in the past year, the strength of association between antibiotic prescribing and treatment outcomes became weaker at the individual level, but remained unchanged at practice level, suggesting that the mechanism linking RTI antibiotic non-response with individual-level antibiotic prescribing may be partly due to prescribing behaviours. In contrast, if the definition of antibiotic 'non-response' included re-prescription of the same antibiotic, the association for practice-level broad- to narrow-spectrum ratio was no longer significant, but this did not substantially change the individual-level associations. If RTI episodes where the same antibiotic was prescribed were more mild than ones where the antibiotic was changed, then this effect could be due to these events being less likely to be bacterial in aetiology and influenced by previous antibiotic use.

Furthermore, patients with low individual antibiotic exposure were more likely to be affected by practice-level antibiotic prescribing than patients with high individual exposure. The exact mechanisms for this stratified effect remain to be investigated. A possible explanation is that patients with high individual antibiotic exposure already had a substantially higher risk of antibiotic treatment non-response and, therefore, practice-level exposure did not contribute much to furthering their risk.

Study limitations include that the measurement of treatment outcomes could be incomplete due to free-text records and a lack of information regarding mortality, hospital admissions, detailed referral reasons and visits to a practice outside of the MedicineInsight network. There were also potential uncontrolled confounders, such as practitioner characteristics. However, these issues with measurement would only lead to bias if they differed between exposure categories. Each patient recorded in this database can only be linked to a single general practice. However, a patient in Australia can attend multiple general practices and, therefore, there was the potential for duplicated patient information. The patient duplication rate in MedicineInsight was estimated at 4%.[15] We did not have information about the actual antibiotic consumption and therefore used the information on antibiotic prescribing as a proxy. We used a fixed exposure period (the whole year of 2017) rather than a time-varying exposure period (e.g. 12 months before an RTI episode) to measure antibiotic exposures before RTI episodes. The advantage of using the fixed period was controlling for seasonal and annual variations of disease epidemics, whereas the disadvantage was the potential of introducing exposure misclassification. The 12 month exposure period also means we cannot measure the short-term effect of previous antibiotic use on RTI treatment outcomes (e.g. a lag of 0–3 months), which could be stronger than the long-term effect quantified in our study.[26] In this study we did not quantify antibiotic use as DDDs. This may not largely influence our results, as a previous study on antibiotic use in the Australian population found that the number of prescriptions generally correlated well with DDDs for quantifying antibiotic prescribing.[29]

Current clinical guidelines recommend reducing broad-spectrum antibiotic use whenever possible for preventing antibiotic resistance and *Clostridioides difficile* infection.[30–32] Our results support these recommendations and suggest that, compared with the total antibiotic prescriptions per patient in a practice, the proportion of broad-spectrum antibiotics is a better practice-level predictor as it has a stronger association with non-effective antibiotic prescribing in RTI management. However, future studies are needed to examine whether these associations identified among patients in general practices can be generalizable to other populations or healthcare facilities.

In conclusion, the broad- to narrow-spectrum antibiotic ratio at general-practice level was a significant predictor of RTI antibiotic treatment non-response in the community, whereas the general practice-level total antibiotic prescriptions per patient were not associated with RTI treatment outcomes. Our findings suggest that a measure of practice-level broad-spectrum antibiotic prescribing could potentially act as an important indicator of potential for antibiotic resistance in clinical practice.

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Transparency declarations

None to declare.

Supplementary data

Supplementary Methods and Tables S1 to S4 are available as Supplementary data at *JAC* Online.

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Chapter 6 Discussion and Conclusions

6.1 Major findings in the thesis

Using two large population-based electronic health datasets, the 45 and Up Study and the MedicineInsight program, the four studies included in my thesis provide a better understanding of the pattern of antibiotic use and related microbiology testing in the Australian community.

In Chapter 2, I estimated the community dispensing rate of important broad-spectrum antibiotics and the variation in antibiotic dispensing by their chronic health conditions among an older adult population in 2015. The dispensing rate of World Health Organization watch group antibiotic classes (macrolides, quinolones, and third-generation cephalosporins), which have a high potential of antibiotic resistance and often serve as the second-line choice for common infections [1], was 0.26 prescriptions per person-year among older Australians in 2015. When I investigated the variation in antibiotic dispensing by patients' chronic health conditions, I found that the watch group antibiotic dispensing rates among patients with asthma and chronic obstructive pulmonary disease were 59% to 171% higher than comparable populations without chronic respiratory diseases. Only 19% of watch group antibiotic prescriptions were accompanied by microbiology testing. Patients with chronic lower respiratory diseases did not have a high rate of microbiology testing and even had a lower proportion of testing-related watch group antibiotic dispensing than the comparable patient group without chronic respiratory diseases. The discord between watch group antibiotic dispensing and microbiology testing in patients with chronic lower respiratory diseases suggests a potential lack of antimicrobial susceptibility monitoring among these patient groups. With a better understanding of which groups use antibiotics with high resistance potential, we can identify populations who can particularly benefit from antibiotic stewardship and design targeted antibiotic stewardship for those populations.

Chapter 3 and Chapter 4 investigated the determinants of adherence to clinical guidelines in antibiotic treatment for common infections in general practice. Chapter 3

focused on antibiotic use and urine culture in urinary tract infection episodes. According to current clinical guidelines in Australia [2], urine culture is not recommended for non-pregnant women with uncomplicated urinary tract infections before they receive antibiotic treatment, but it should be routinely performed for patients at high risk of complicated urinary tract infections, including children, men, pregnant women, patients with recurrent urinary tract infections, chronic kidney diseases, diabetes, and those living in aged care homes. In this study, I found that the overall proportion of urinary tract infection episodes with antibiotics prescribed in Australian general practice between January 2013 and July 2018 was 72.2%. In more than 97% of episodes, antibiotics that are recommended in the UTI clinical guidelines were prescribed for patients. And first-line antibiotics were prescribed in more than 80% of first-onset UTIs. But several high-risk groups had a relatively lower likelihood of urine culture than comparable patient groups, including children under five years old, patients with recurrent urinary tract infections, and residents in aged care homes, suggesting that the management of urinary tract infections among these patient groups should be a target for future antibiotic stewardship. Chapter 4 focused on the determinants of immediate antibiotic prescribing for upper respiratory tract infections in general practice, which is not necessary for 80% to 90% of episodes according to clinical guidelines [2]. In this Chapter, I analysed the impact of temporal factors on the likelihood of immediate antibiotic prescribing for self-limiting upper respiratory tract infections. I found that, compared with GP consultations on typical weekdays, GP consultations on weekends or public holidays were associated with a higher likelihood of immediate antibiotic prescribing for self-limiting upper respiratory tract infections, which was not fully explained by the mediating effect of the patients' diagnosis and some characteristics of their presentation.

Chapter 5 investigated the effect of general practice-level and patient individual-level antibiotic prescribing on antibiotic treatment non-response (defined as re-prescribing a different antibiotic within 30 days of initial prescribing) in respiratory tract infection episodes. The number of previous antibiotic scripts prescribed for each patient

was identified as a strong predictor of antibiotic treatment non-response. After controlling for the individual-level antibiotic exposure, the ratio of broad- to narrow-spectrum antibiotic prescriptions in a practice was another significant predictor for antibiotic non-response among patients within the practice, whereas the total number of antibiotic scripts per patient prescribed in a practice was not associated with antibiotic treatment non-response. The association between practice-level broad-spectrum antibiotic prescribing and treatment non-response can be observed among patients with no or low individual-level antibiotic exposure, suggesting that antibiotic use in general practice may change the resistance of the bacteria in the environment so that there is more likelihood of antibiotic non-response among patients without direct antibiotic exposure.

6.2 The original contribution in the context of existing literature

Clinical guidelines make various recommendations regarding management of infectious diseases and antibiotic use among certain groups of people, e.g., children, older people, pregnant women, patients with major chronic diseases, and residents in aged care homes, due to their high risk of developing complicated infections or antibiotic-associated adverse events.[2-6] However, there is limited knowledge about the gap between guideline recommendations and actual antibiotic prescribing patterns in Australian community settings where the majority of antibiotic prescribing in Australia occurs [7]. Chapter 2 and Chapter 3 provided insights into the adherence to antibiotic treatment guidelines, in particular the accompanying use of microbiological testing in real-world settings. To my knowledge, the study in Chapter 2 is the first investigation of the community antibiotic dispensing rates and microbiology testing rates by different patients' major chronic diseases in Australia. These data are useful for identifying the potential target population for antibiotic stewardship. The study in Chapter 3 is the first Australian report on the antibiotic treatment for urinary tract infections among high-risk groups for complicated urinary tract infections based in the community. The unexpected lower

proportion of urine testing among children under five years old, patients with recurrent urinary tract infections and residents in aged care homes reflected the need for increasing GP's awareness of the importance of urine testing among the high-risk groups.

Apart from those patient-level characteristics, previous studies reported other practice or health system factors that may influence antibiotic prescribing behaviours or antibiotic treatment outcomes (e.g. antibiotic resistance or non-response), including after-hours consultations [8] and healthcare facility-level antibiotic usage [9, 10]. But these studies are limited by a lack of patient-level information (e.g., comorbidities, frequency of GP visits, clinical presentations in the episodes) and therefore they can only examine these associations at an ecologic level. Chapter 4 and Chapter 5 extended knowledge by quantifying the independent contribution of after-hour effects and practice-level antibiotic use to antibiotic prescribing behaviours and antibiotic treatment non-response. Verifying these factors may provide a better understanding of the underlying drivers for antibiotic overprescribing and antibiotic non-response in clinical practice in the community.

6.3 Implications for practice and future research

The results of my thesis have broad implications for quality antibiotic prescribing in the community as well as future research.

6.3.1 Improving general practitioners' awareness of guideline-based antibiotic prescribing in certain circumstances

The results of my thesis suggest that there is a need for developing educational programs for GPs to improve guideline-based antibiotic prescribing in general practice，targeting the following areas:

1) The use of quinolones and 3rd generation cephalosporins for patients with chronic obstructive pulmonary diseases and asthma. These antibiotics are neither the recommended choice for chronic lower respiratory diseases nor the first-line choice for

respiratory tract infections that may trigger the exacerbation of chronic obstructive pulmonary diseases.

2) The importance of urine testing in urinary tract infection episodes among children under 5 years old, patients with recurrent urinary tract infections and residents living in aged care homes, as they are at high risk of complicated urinary tract infections and routine urine testing is recommended for them. Although there is a delay in receiving the urine culture results and clinicians often need to give initial therapy before getting the results, high-risk patients will still benefit from the urine culture as they usually do not have an adequate response to first-line antibiotics [2].

3) The use of delayed antibiotic prescribing strategy for first-onset upper respiratory tract infection encounters, particularly in after-hours consultations. The delayed prescribing strategy means in the first presentation for an upper respiratory tract infection, GPs are suggested to reserve antibiotics and just provide symptomatic therapy; if patients' symptoms do not improve in the next 3 to 7 days then GPs start to consider antibiotic treatment [2]. It is highly recommended in Australian and international guidelines, as upper respiratory tract infections are usually of viral origin and self-limiting [2, 11] and delayed antibiotic prescribing has been proved both safe for patients and effective for reducing unnecessary antibiotic use in clinical practice [12].

6.3.2 Increasing organisation-level support for quality antibiotic prescribing

Besides GP's awareness of guideline-based antibiotic prescribing, healthcare resource issues may be another essential driver for inappropriate antibiotic prescribing. The higher proportion of immediate antibiotic prescribing for upper respiratory tract infections in after-hour consultations (Chapter 4) might be attributed to high workload, limited time and access to laboratory diagnostics for decision-making [13]. Therefore, organisation-level support such as providing decision support systems, i.e., computer programs for GPs which can offer antibiotic prescribing recommendations according to

patients' health conditions [14], increasing staff recruitment [15], and improving laboratory capacity (e.g. rapid point of care pathology testing) in general practice [13] may be needed to support better decision-making for antibiotic use in primary care.

6.3.3 Using validated quality indicators to monitor antibiotic use and assess the effectiveness of antibiotic stewardship programs

A valid measure for antibiotic prescribing in antibiotic stewardship programs should be directly associated with clinical outcomes of interest [16]. Chapter 5 examined the association between antibiotic treatment non-response and two commonly used measures for antibiotic use at the practice-level: total antibiotic prescriptions per patient and ratio of broad- to narrow-spectrum antibiotic prescriptions. I found only the broad- to narrow-spectrum antibiotic ratio was associated with antibiotic treatment non-response. Therefore, the practice-level broad- to narrow-spectrum antibiotic ratio can serve as an indicator of significant potential for resistance and could be used for monitoring antibiotic use in antibiotic stewardship programs in general practice.

6.3.4 Antibiotic stewardship in the era of COVID-19

The study periods of the four projects were before the COVID-19 outbreak. Although my results do not directly inform the influence of COVID-19 on antibiotic prescribing behaviours, Chapter 2 and 4 have suggested that antibiotic overuse for non-bacterial infections is common in general practice. Literature has shown that there is a decreasing trend in overall outpatient antibiotic prescribing during the COVID-19 pandemic in Australia and other countries [17-19]. It might be mainly due to lockdowns that reduced the transmission of respiratory tract infections [19]. The reduction may be also because people are only seeing the doctor for really serious illnesses in this period. However, a meta-analysis showed that 58% of hospitalised patients with COVID are reported to consume antibiotics during their episodes in high-income countries, although antibiotics

have no efficacy in treating this viral infection [20]. These data suggest that reducing antibiotic overuse when there is no indication is still important for antibiotic stewardship in the era of pandemics.

6.3.5 Recommendations for future research

In Chapter 2, I found that patients with chronic obstructive pulmonary diseases have a higher dispensing rate of watch group antibiotics than populations without chronic obstructive pulmonary diseases. It was also higher than patient subgroups with other major chronic diseases. This could be due to current recommendations on long term macrolide use for the prevention of exacerbations of chronic obstructive pulmonary diseases.[21] However, approximately 50% of chronic obstructive pulmonary disease exacerbations are caused by bacterial infections, whereas the remaining 50% are caused by viral infections and non-infectious factors [22]. Currently, there are no detailed recommendations about defining suitable patient groups for long term macrolide treatment and antibiotic resistance monitoring among the long term macrolide user in clinical guidelines, as sputum culture has limited clinical significance for these patients [2]. The discord between the high antibiotic dispensing rate and low microbiology testing rate identified in Chapter 2 likely reflects the lack of diagnostic methods to guide macrolide use among patients with chronic obstructive pulmonary diseases in clinical practice. This could be a direction of future research on introducing new diagnosis methods and reducing unnecessary antibiotic prescribing in the population with known high antibiotic use.

The factors underlying some of the antibiotic prescribing patterns identified in my studies need to be better understood. In Chapter 4, I found that there was a difference between children and adults in the likelihood of immediate antibiotic prescribing in holiday versus non-holiday periods; in Chapter 5, I found heterogeneity of practice-level antibiotic prescribing effect on antibiotic non-response among patients with low and high individual-level antibiotic exposure. Future research may explore the potential

mechanisms behind these associations and provide a better understanding of antibiotic prescribing behaviours in general practice.

6.4 Strengths and limitations

The major strength of the studies in the thesis is the use of two large electronic health datasets, both of which capture a wide range of information regarding patient demographic characteristics, socio-economic information, medical history and healthcare service records. The large sample size in these two databases can provide sufficient statistical power for analysing some less common and understudied conditions, such as urinary tract infection episodes among patients at risk of complicated urinary tract infections, after-hour GP consultations, and the occurrence of antibiotic treatment non-response. In addition, the longitudinal records of patients' interactions with the healthcare service in these two databases allowed me to sort out the temporal sequence between determinants of interest and study outcomes.

There are also limitations in my work. A major issue is the potential for misclassification. In each of the four studies, I had to use a match on the patient IDs and the dates of records to link the antibiotic prescription records to microbiology testing, GP encounter reasons, or microbiology testing to determine the test-guided antibiotic prescribing or the reasons for antibiotic prescribing. This is because there is no prescribing reason information for all the antibiotic records in the 45 and Up Study and most antibiotic prescriptions in the MedicineInsight database do not include a prescription reason. I assumed that a prescription was related to a diagnosis (or a laboratory testing) of the same patient if they occurred on the same day. But if there was mismatching on prescriptions and diagnosis (or testing), it might result in misclassification for exposure and outcome measures. In the 45 and Up Study, chronic diseases were defined by hospital admission, because we do not have chronic disease information from the primary care database and we can only get that information from the hospital admission dataset. We

did have self-reported chronic disease information in the 45 and Up Study questionnaires but they might not be reliable, whilst hospitalisations, based on coded medical records are likely to be more reliable. This means patients with mild chronic diseases who did not require hospital admission were not be identified in the study. For the studies using MedicineInsight data, a specific challenge was that there was no standardised coding to identify specific antibiotic classes, encounter reasons, diagnoses, and the types of laboratory testing in the database. I used a series of search algorithms for identification in free-text records, but this can be potential source of misclassification. Another issue is that I cannot be certain I have all the episodes of a patient in the MedicineInsight data.

I also did not have the exact timing of general practice consultations in the MedicineInsight database. Therefore, in Chapter 4, I could not identify consultations in the weekday evenings and nights and misclassified those after-hours consultations into the reference groups. This may lead to an underestimate of the after-hours effect on antibiotic prescribing behaviours. Additionally, GPs used both specific diagnoses (e.g. tonsillitis, otitis media) and non-specific diagnoses (e.g. URTI). Different GPs may have different habits regarding recording using specific and non-specific diagnoses. And therefore in Chapter 4, the estimation of antibiotic prescribing rate for specific diagnoses could be biased due to the different GP preferences of recording diagnoses. All these limitations above may lead to potential misclassification.

The findings of my projects are based on the fact that in the Australian healthcare system, general practice is the first and main site where people are seeking primary health care services. But in the real world, people can choose private hospitals or healthcare facilities that are not included in the databases of 45 and Up Study and MedicineInsight. These will lead to limitations in my projects. When I calculated the community antibiotic dispensing rate in Chapter 2, I did not include antibiotic dispensing in the private hospitals and other healthcare facilities, and this will underestimate the dispensing rate. In Chapter 4, When I identified first-time episodes or episodes when re-prescriptions occurred, it was possible that patients went to practices not included in the MedicineInsight program, or

attended an emergency department, or were admitted to a hospital, before or after the episodes, but it is not possible to consider those factors in my study.

The lack of detailed indication information of antibiotic prescribing limited the assessment of the appropriateness of antibiotic prescribing. There is no actual antibiotic consumption data in the databases I used for my studies, so I had to use antibiotic dispensing (Chapter 2) or antibiotic prescribing (Chapter 3, 4, and 5) data as a proxy, and this may lead to the overestimate of actual antibiotic use among patients. The overall rate of patients not taking the medication dispensed in high-income countries is around 15% [23], but there are no data specific to antibiotics. For the study which used 45 and Up Study data, a specific limitation is that the MBS dataset only recorded the three most expensive pathology testing services in an episode (one day for a patient). It was estimated that about 11% of episodes might be influenced by this issue and pathology testing records might not be completely captured in these episodes [24]. In Chapter 3, I can only exclude "suspected UTIs" by searching free-text variables as there is no detailed documentation of clinical presentations in the dataset. But some GPs may not directly enter "suspected UTIs" into the encounter reason field; instead, they will choose to conduct urine microscopy, culture and sensitivity when there are suspected cases. And as I mentioned in Chapter 5, due to the lack of detail on clinical presentation, I cannot distinguish between genuine bacterial infection treatment failure and patient high expectations around the duration of viral illness when there was antibiotic re-prescribing, which may lead to an overestimated effect that I observed in the study. Future studies with more comprehensive documentation of patient clinical presentations and medical examination results may help validate the results of Chapter 5.

There may be selection bias which influences the generalisability of the findings based on these two databases. The participants in the 45 and Up Study were recruited by unsolicited invitation and were required to send their questionnaires back to the Study coordinating centre, and the cohort has been shown to have higher education level and socioeconomic status than the general population of the same age groups; the study also

oversampled those participants in rural areas or aged over 80 years old [25, 26]. The study populations in MedicineInsight are patients in the participating general practices, therefore it may underrepresent those populations who are healthy, who do not usually attend GPs, who are more likely to visit multiple doctors, or have limited access to healthcare facilities [27].

However, the limitations listed above are likely to only have a slight influence on my results. The estimates of disease prevalence from these two databases were similar to the results based on other population-based studies in Australia [28-30]. And in my studies, the estimated proportion of antibiotic prescribing in respiratory tract infection episodes (Chapter 4) and the proportion of microbiology testing in urinary tract infection episodes (Chapter 3) were comparable to earlier studies in Australia and other high-income countries [31-33].

As the studies in this thesis were observational, there were unmeasured factors that might lead to confounding, including clinicians' characteristics (e.g., age and experience), patients' detailed clinical presentations, and medical examination results such as urine dipstick test. Some results may not have a substantial impact on the results. For example, a lack of documentation of urine dipstick results in Chapter 3 might mitigate the failure to send a urine culture. But urine dipsticks have low sensitivity and limited clinical significance in guidelines for UTI diagnosis, so it may not be an important limitation of the study [34]. On the other hand, I still cannot exclude the possibility that some unmeasured confounders may be important alternative explanations for the associations observed in my studies. For example, the effect of previous practice-level antibiotic prescribing on patients' antibiotic treatment non-response observed in Chapter 5 could be attributed to unmeasured differences such as the GP's clinical experience level.

6.5 Overall conclusion

My thesis demonstrates that antibiotics are commonly dispensed in the community and there might be potential for excessive broad-spectrum antibiotic use among older

Australians. Additionally, antibiotic prescriptions in general practice for common presentations such as respiratory and urinary tract infections may not always be adherent to current recommendations in clinical guidelines. My findings suggest that there is a need to improve GP's awareness of guideline-based antibiotic prescribing and related microbiology testing when prescribing antibiotics for older adults with chronic lower respiratory tract diseases, when treating urinary tract infections for patients at high risk of complicated urinary tract infections, and when GP consultations occur on weekends and holidays. My study also provides a better understanding of the indirect influence of high broad-spectrum antibiotic prescribing on patients in general practice. The thesis contributes to a deeper insight into the patterns and determinants of community antibiotic prescribing in Australia and offers evidence for more targeted antibiotic stewardship programs in the community.

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Appendix 1. Supplementary methods, tables and figure for Chapter 2

Supplementary Table 1. Classification for watch group and reserve group according to the WHO Model List of Essential Medicines

Watch group antibiotics	
Antibiotic class	**ATC code**
Macrolides	J01FA
Quinolones and fluoroquinolones	J01M
3rd-generation cephalosporins	J01DD
Glycopeptides	J01XA
Antipseudomonal penicillins + beta-lactamase inhibitor	J01CR03, J01CR05
Carbapenems	J01DH
Penems	J01DI03
Reserve group antibiotics	
Antibiotic class	**ATC code**
Aztreonam	J01DF01
4th & 5th generation cephalosporins	J01DE, J01DI01, J01DI02, J01DI54
Polymyxins	J01XB
Fosfomycins	J01XX01
Oxazolidinones	J01XX08, J01XX11
Tigecycline	J01AA12
Daptomycin	J01XX09

Supplementary Table 2. Medicare Benefits Schedule (MBS) codes used for GP consultations, aged care facilities (or Long-Term Care Facilities, LTCF) attendance and microbiology testing

GP consultations	
MBS item number	**Description**
3 to 51	Attendances by General Practitioners
193,195,197,199, 597, 599	Attendances by General Practitioners
2497 to 2559	Attendances by General Practitioners
5000-5067	Attendances by General Practitioners
Participants aged care facility attendance	
MBS item number	**Description**
20, 35, 43, 51, 92, 93, 95, 96, 5010, 5028, 5049, 5067, 5260, 5263, 5265, 5267	Residential Aged Care Facility Attendances
731	Contribution to a Multidisciplinary Care Plan, or to a review of a multidisciplinary care plan, for a resident in an aged care facility
903	Residential Medication Management Review
2125, 2138, 2179, 2220	Medical practitioner telehealth attendances at a residential aged care facility
10947, 10948,	At the time of the attendance, is located at a residential aged care facility
73934, 73935,	Approved pathology authority from in a residential aged care home or institution
10984	A care recipient receiving care in a residential aged care service
82223, 82224, 82225	Telehealth attendance at a residential aged care facility
Microbiology testing	
MBS item number	**Description**
69300	Microscopy of wet film material other than blood, from 1 or more sites, obtained directly from a patient (not cultures)
69303	Culture and (if performed) microscopy to detect pathogenic micro-organisms from nasal swabs, throat swabs, eye swabs and ear swabs (excluding swabs taken for epidemiological surveillance)

69306	Microscopy and culture to detect pathogenic micro-organisms from skin or other superficial sites
69312	Microscopy and culture to detect pathogenic micro-organisms from urethra, vagina, cervix or rectum (except for faecal pathogens)
69316, 69317,	Detection of Chlamydia trachomatis by any method
69318, 69319,	Microscopy and culture to detect pathogenic micro-organisms from specimens of sputum (except when part of items 69324, 69327 and 69330)
69321	Microscopy and culture of post-operative wounds, aspirates of body cavities, synovial fluid, CSF or operative or biopsy specimens, for the presence of pathogenic micro-organisms involving aerobic and anaerobic cultures and the use of different culture media
69324, 69325, 69327, 69328, 69330, 69331	Microscopy (with appropriate stains) and culture for mycobacteria - 1 specimen of sputum, urine, or other body fluid or 1 operative or biopsy specimen
69333	Urine examination (including serial examination) by any means other than simple culture by dip slide
69345	Culture and (if performed) microscopy without concentration techniques of faeces for faecal pathogens, using at least 2 selective or enrichment media and culture in at least 2 different atmospheres
69354, 69357, 69360,	Blood culture for pathogenic micro-organisms (other than viruses)
69363	Detection of Clostridium difficile or Clostridium difficile toxin (except if a service described in item 69345 has been performed)
69384, 69387, 69390, 69393, 69396, 69400, 69401	Quantitation of 1 antibody to microbial antigens not elsewhere described in the Schedule
69471	Test of cell-mediated immune response in blood for the detection of latent tuberculosis by interferon gamma release assay (IGRA) in the following people

69494, 69495, 69496, 69497, 69498	Detection of a virus or microbial antigen or microbial nucleic acid (not elsewhere specified)

Supplementary Table 3. Incidence rate ratio [a] for watch group antibiotic dispensing and microbiology testing by participants' characteristics

Variable	Watch group antibiotic prescriptions		Microbiology tests	
	aIRR (95%CI) [b]	P	aIRR (95%CI)	P
Asthma				
No	1.00		1.00	
Yes	1.59 (1.52-1.66)	<0.001	1.03 (1.00-1.05)	0.048
COPD				
No	1.00		1.00	
Yes	2.71 (2.48-2.95)	<0.001	1.00 (0.94-1.06)	0.950
Cancer				
No	1.00		1.00	
Yes	1.02 (0.96-1.08)	0.541	1.22 (1.19-1.26)	<0.001
Diabetes Mellitus				
No	1.00		1.00	
Yes	1.05 (0.99-1.10)	0.105	1.10 (1.07-1.13)	<0.001
Chronic kidney diseases				
No	1.00		1.00	
Yes	1.09 (0.99-1.20)	0.071	1.60 (1.53-1.68)	<0.001
Cardiovascular diseases [c]				
No	1.00		1.00	
Yes	1.06 (1.00-1.13)	0.061	1.03 (0.99-1.06)	0.126
Residence in LTCF [d]				
No	1.00		1.00	
Yes	0.91 (0.85-0.99)	0.019	1.31 (1.26-1.37)	<0.001

a: Zero-inflated negative binomial regression adjusted by sex, age, education level, income level, residential remoteness, residence in LTCF, history of chronic diseases, number of GP visits in the year before the index date, number of hospital admissions in the year before the index date

b: aIRR: adjusted incidence rate ratio CI: confidence intervals

c: Included ischemic heart diseases and stroke

d: LTCF: Long Term Care Facilities

Supplementary Table 4. Incidence and incidence rate ratio [a] for dispensed amoxicillin-clavulanate prescriptions by participants' characteristics

Variable	Amoxicillin-clavulanate prescriptions			
	No.	Incidence	aIRR (95%CI) [b]	P
Total	67,735	0.28		
Asthma				
No	53,584	0.25	1.00	
Yes	14,151	0.47	1.42 (1.36-1.48)	<0.001
COPD				
No	64,011	0.27	1.00	
Yes	3724	1.14	2.13 (1.95-2.32)	<0.001
Cancer				
No	61,521	0.27	1.00	
Yes	6214	0.40	1.10 (1.04-1.16)	<0.001
Diabetes Mellitus				
No	59,143	0.26	1.00	
Yes	8592	0.47	1.10 (1.05-1.16)	<0.001
Chronic kidney diseases				
No	65,048	0.27	1.00	
Yes	2687	0.65	1.25 (1.14-1.38)	<0.001
Cardiovascular diseases [c]				
No	62,007	0.27	1.00	
Yes	5728	0.45	1.03 (0.97-1.09)	0.399
Residence in LTCF [d]				
No	64,389	0.27	1.00	
Yes	3346	0.51	1.06 (0.98-1.14)	0.148

a: Zero-inflated negative binomial regression adjusted by sex, age, education level, income level, residential remoteness, residence in LTCF, history of chronic diseases, number of GP visits in the year before the index date, number of hospital admissions in the year before the index date

b: aIRR: adjusted incidence rate ratio CI: confidence intervals

c: Included ischemic heart diseases and stroke

d: LTCF: Long Term Care Facilities

Supplementary Table 5. Incidence and incidence rate ratio [a] for dispensed watch group antibiotic prescriptions without antibiotic use in the 14 days prior to dispensing by part by participants' characteristics

Variable	Watch group antibiotic prescriptions without antibiotic use in the 14 days prior			
	No.	Incidence	aIRR (95%CI) [b]	P
Total	39,088	0.16	-	-
Asthma				
No	30,177	0.14	1.00	
Yes	8911	0.29	1.71 (1.64-1.79)	<0.001
COPD				
No	36,504	0.15	1.00	
Yes	2584	0.79	2.75 (2.53-2.99)	<0.001
Cancer				
No	35,869	0.16	1.00	
Yes	3219	0.21	1.02 (0.96-1.09)	0.513
Diabetes Mellitus				
No	34,609	0.15	1.00	
Yes	4479	0.25	1.04 (0.98-1.09)	0.205
Chronic kidney diseases				
No	37,708	0.16	1.00	
Yes	1380	0.33	1.15 (1.04-1.26)	0.005
Cardiovascular diseases [c]				
No	35,964	0.16	1.00	
Yes	3124	0.25	1.02 (0.96-1.09)	0.450
Residence in LTCF [d]				
No	37,067	0.16	1.00	
Yes	2021	0.31	1.00 (0.92-1.07)	0.904

a: Zero-inflated negative binomial regression adjusted by sex, age, education level, income level, residential remoteness, residence in LTCF, history of chronic diseases, number of GP visits in the year before the index date, number of hospital admissions in

the year before the index date

b: aIRR: adjusted incidence rate ratio CI: confidence intervals

c: Included ischemic heart diseases and stroke

d: LTCF: Long Term Care Facilities

Supplementary Table 6. Incidence rate ratio [a] for dispensed macrolides and other watch group antibiotics prescriptions by participants' characteristics

Variable		Macrolides		Other Watch group antibiotics	
		aIRR (95%CI) [b]	P value	aIRR (95%CI)	P value
Asthma					
	No	1.00		1.00	
	Yes	1.66 (1.58-1.73)	<0.001	1.15 (1.01-1.31)	0.033
COPD					
	No	1.00		1.00	
	Yes	2.85 (2.59-3.12)	<0.001	1.86 (1.54-2.26)	<0.001
Cancer					
	No	1.00		1.00	
	Yes	0.92 (0.86-0.98)	0.014	1.28 (1.11-1.47)	0.001
Diabetes Mellitus					
	No	1.00		1.00	
	Yes	1.05 (0.99-1.12)	0.083	0.96 (0.84-1.10)	0.585
Chronic kidney diseases					
	No	1.00		1.00	
	Yes	0.91 (0.82-1.02)	0.102	1.39 (1.15-1.68)	0.001
Cardiovascular diseases [c]					
	No	1.00		1.00	
	Yes	1.07 (0.99-1.14)	0.071	1.01 (0.87-1.17)	0.902
Residence in LTCF [d]					
	No	1.00		1.00	
	Yes	0.88 (0.81-0.96)	0.003	0.97 (0.81-1.15)	0.702

a: Zero-inflated negative binomial regression, adjusted by sex, age, education level, income level, residential remoteness, residence in LTCF, history of chronic diseases, number of GP visits in the year before the index date, number of hospital admissions in the year before the index date

b: aIRR: adjusted incidence relative risk; CI: confidence intervals

c: Included ischemic heart diseases and stroke

d: LTCF: Long Term Care Facilities

Supplementary Table 7. Incidence rate ratio [a] for certain types of microbiology testing among 244,299 participants by participants' characteristics

Variable	aIRR (95%CI) [b]			
	Urine examinations	Microbiology & culture for sputum specimens	Microbiology & culture for other specimens	Microbial antigens, nucleic acid, or antibody testing
Asthma				
No	1.00	1.00	1.00	1.00
Yes	0.96 (0.92-0.99)	2.09 (1.86-2.34)	1.02 (0.96-1.08)	1.08 (1.02-1.15)
COPD				
No	1.00	1.00	1.00	1.00
Yes	0.81 (0.75-0.87)	3.65 (3.10-4.31)	0.93 (0.83-1.04)	1.06 (0.92-1.22)
Cancer				
No	1.00	1.00	1.00	1.00
Yes	1.30 (1.24-1.35)	1.27 (1.09-1.47)	1.19 (1.12-1.27)	1.06 (0.98-1.14)
Diabetes Mellitus				
No	1.00	1.00	1.00	1.00
Yes	1.16 (1.12-1.20)	0.80 (0.69-0.93)	1.09 (1.03-1.16)	0.95 (0.89-1.02)
Chronic kidney diseases				
No	1.00	1.00	1.00	1.00
Yes	1.85 (1.75-1.96)	1.10 (0.87-1.38)	1.38 (1.26-1.52)	1.22 (1.08-1.37)
Cardiovascular diseases [c]				
No	1.00	1.00	1.00	1.00
Yes	1.02 (0.97-1.06)	0.93 (0.79-1.08)	0.95 (0.89-1.02)	1.15 (1.06-1.24)

Residence in LTCF [d]				
No	1.00	1.00	1.00	1.00
Yes	1.41 (1.34-1.47)	0.88 (0.73-1.07)	1.36 (1.27-1.47)	0.85 (0.76-0.94)

a: Zero-inflated negative binomial regression adjusted by sex, age, education level, income level, residential remoteness, residence in LTCF, history of chronic diseases, number of GP visits in the year before the index date, number of hospital admissions in the year before the index date

b: aIRR: adjusted incidence rate ratio CI: confidence intervals

c: Included ischemic heart diseases and stroke

d: LTCF: Long Term Care Facilities

Supplementary Table 8. Incidence of dispensed antibiotic prescriptions and microbiology tests and their association [a] between chronic lower respiratory tract diseases

	No asthma /COPD	Asthma & No COPD		Less severe COPD [c]		More severe COPD [d]		
N (%)	211,343 (87)	29,416 (12)		2575 (1.1)		965 (0.4)		
Incidence (person-years)								
Watch group antibiotics	0.22	0.43		1.11		2.37		
Amoxicillin-clavulanate	0.57	0.67		1.14		1.37		
Microbiology tests	0.60	0.70		1.17		1.40		
Association	Reference	aIRR (95% CI) [b]	P value	aIRR (95%CI)	P value	aIRR (95%CI)	P value	P value for trend
Watch group antibiotics	1.00	1.59 (1.52-1.66)	<0.001	2.53 (2.29-2.81)	<0.001	5.15 (4.43-5.98)	<0.001	<0.001
Macrolides	1.00	1.66 (1.58-1.74)	<0.001	2.60 (2.33-2.91)	<0.001	5.83 (4.96-6.85)	<0.001	<0.001
Other watch group antibiotics	1.00	1.11 (0.97-1.28)	<0.001	1.97 (1.55-2.50)	<0.001	2.09 (1.55-2.82)	<0.001	<0.001
Amoxicillin-clavulanate	1.00	1.43 (1.36-1.49)	<0.001	2.11 (1.91-2.34)	<0.001	3.27 (2.81-3.81)	<0.001	<0.001
Microbiology tests	1.00	1.02 (1.00-1.05)	0.079	1.00 (0.94-1.07)	0.998	1.03 (0.93-1.14)	0.622	0.161

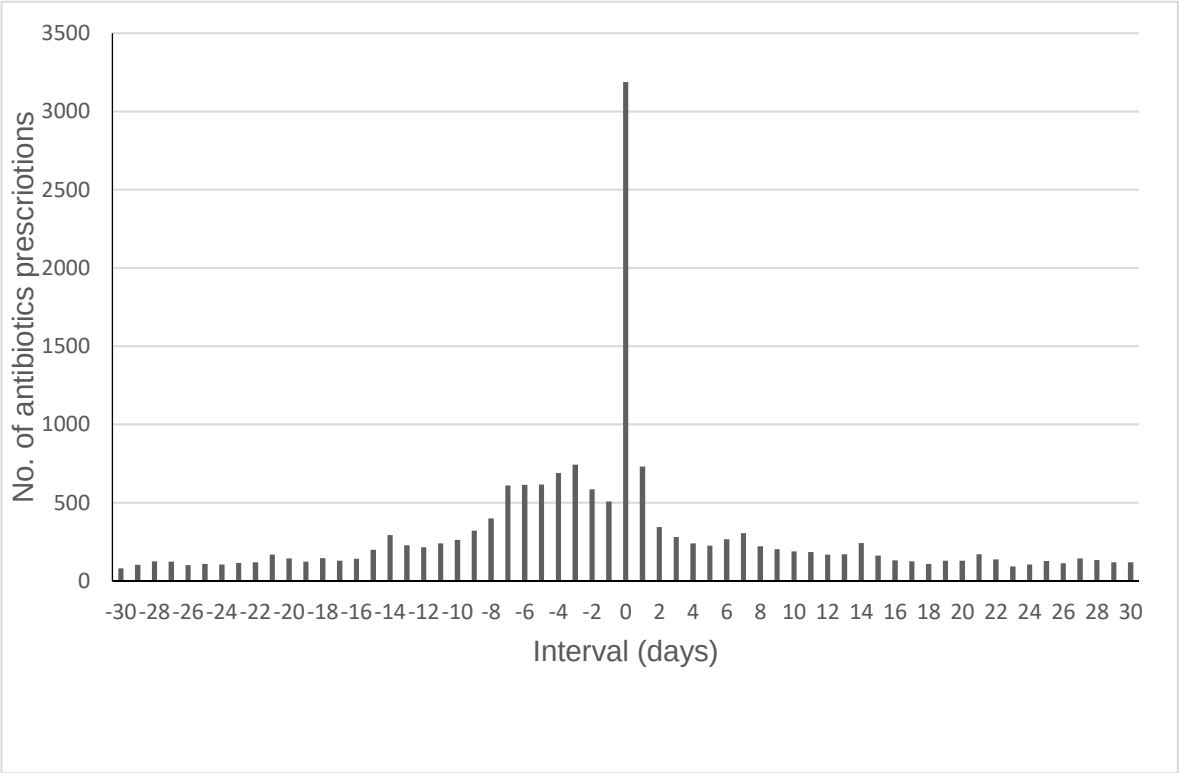
a: Zero-inflated negative binomial regression, adjusted by sex, age, education level, income level, residential remoteness, residence in Long Term Care Facilities (LTCF), history of chronic diseases, number of GP visits in the year before the index date, number of hospital admissions in the year before the index date

b: aIRR: adjusted incidence relative risk; CI: confidence intervals

c: hospitalization <2 times in the past three years

d: hospitalization ≥2 times in the past three years

Supplementary Figure 1. The distribution of the intervals between a dispensed script of watch group antibiotics and its closest microbiology test (only include intervals ≤ 30 days).



Appendix 2. Supplementary methods, tables and figure for Chapter 3

Supplementary Methods

Identification of encounters for UTIs

We searched the “encounter reason” field in the Encounter dataset or “diagnosis reason” in the Diagnosis dataset. Those records containing any one of the terms below were defined as encounters for UTIs. Records containing "?", "probable", "suspected", "possible" were excluded.

Search terms	Search terms
UTI	INFECTION, URINARY
URINARY TRACT INFECT	URINARY INFECTION
INFECTION - URINARY TRACT	INFECTIONS, URINARY
CYSTITIS	PYURIA
BLADDER INFECTION	UROSEPSIS
URINARY SEPSIS	PYELONEPHRITIS

Identification of antibiotic prescriptions

We searched the “medicine active ingredient” field in the Prescription dataset. Those records containing any one of the terms below were defined as antibiotic prescriptions.

Search terms	Search terms
DOXYCYCLINE	AMPICILLIN
CHLORTETRACYCLINE	AMOXICILLIN
TETRACYCLINE	AMOXYCILLIN
MINOCYCLINE	PIPERACILLIN
TIGECYCLINE	TICARCILLIN
CHLORAMPHENICOL	PENICILLIN
CLOXACILLIN	DICLOXACILLIN
TAZOBACTAM	MEROPENEM
CEFALEXIN	ERTAPENEM
CEPHALEXIN	IMIPENEM
CEFALOTIN	TRIMETHOPRIM
CEFAZOLIN	SULFAMETHIZOLE
CEFOXITIN	SULFATHIAZOLE
CEFUROXIME	SULFAMETHOXAZOLE
CEFACLOR	SULFADIAZINE
CEFOTAXIME	ERYTHROMYCIN
CEFTAZIDIME	ROXITHROMYCIN
CEFTRIAXONE	CLARITHROMYCIN
CEFEPIME	AZITHROMYCIN
AZTREONAM	CLINDAMYCIN
LINCOMYCIN	OFLOXACIN
TOBRAMYCIN	NORFLOXACIN
GENTAMICIN	MOXIFLOXACIN
NEOMYCIN	GATIFLOXACIN
AMIKACIN	NALIDIXIC
VANCOMYCIN	COLISTIN
TEICOPLANIN	POLYMYXIN
NITROFURANTOIN	METRONIDAZOLE
FOSFOMYCIN	TINIDAZOLE
SPECTINOMYCIN	DAPTOMYCIN
METHENAMINE	BACITRACIN
LINEZOLID	

Identification of urine microbiology tests

We searched the “result name” field in the Requested Test dataset. Those records below were defined as urine microbiology tests.

Search terms	Search terms
CULTURE - URINE	X URINE MICROBIOLOGY
(UM-0)URINE MICROBIO	C & S URINE
(UM-0)URINE MICROBIOLOGY	URINE (MSU,EMU ETC) MICRO
(UMC-0)URINE MICRO &	CULTURE - URINE (MDG)
(UMC-0)URINE MICRO & CULTURE	CULTURE URINE
(UMS-0)URINE MICRO C	CUMULATIVE URINE MICROSCOPY
(UMS-0)URINE MICRO CULTURE/SENS.	M/C/S URINE
.CULTURE URINE	MC&S URINE
2ND URINE FOR M&C	MIC/CULT/SEN URINE .
BACTERIOLOGY: CULTURE URINE	MICRO URINE
UIC-0 (URINE MICRO/CULTURE)	UMC-0 (URINE MICRO / CULTURE)
UM-0 (URINE MICROBIOLOGY)	UMC-0 (URINE MICRO& CULTU
UM-0 (URINE MICRO/CULTURE	UMC-0 (URINE MICRO& CULTURE)
UM-0 (URINE MICRO/CULTURE)	UMD-0 (URINE MICRO/DIPSTICK)
UM-0 (URINE MICROBIOLOGY)	UMM URINE MICROBIOLO
UM-0 (URINE MICROSCOPY)	UMM URINE MICROBIOLOGY
UMC-0 (URINE MICRO + CULTURE)	UMM-0 (URINE MICRO/CULTUR
UMC-0 (URINE MICRO CULTURE/SENS.)	UMM-0 (URINE MICRO/CULTURE)
UMC-0 (URINE MICRO & CULTURE)	UMM-1 (URINE MICRO/CULTURE)
UMC-0 (URINE MICRO + CULTURE)	UMS-0 (URINE MICRO CULTURE/SENS.)
URINE CULTURE 2	URINE M,C&S
MICRO-URINE	URINE CULTURE REPORT
MICROBIOLOGICAL EXAM - URINE	URINE ENTEROCOCCUS SENS (ORG1)
MICROBIOLOGY - URINE	URINE FOR M/C/S
MICROBIOLOGY URINE	URINE FOR M/C/S (NON-REPORTABLE)

MICROSCOPY URINE	URINE FOR M/C/S 1
MIDSTREAM URINE MC&S	URINE FOR MCS
MIDSTREAM URINE MICRO & CULTURE	SENS - URINE
MUC-0 (URINE MICRO & CULTURE)	SENS 1 - URINE
MURINE MICROBIOLOGY	SENS 2 - URINE
MYCOBACTERIAL CULT. URINE	SUB URINE MC&S
UMS-0 (URINE MICRO CULTURE/SENS.)	SUBMITTED URINE MC&S
UR URINE MICROBIOLOG	U- URINE MCS DHM
UR URINE MICROBIOLOGY	U-BACT AG URINE/CSF
URC-0 (URINE M+C)	U-URINE CULTURE 1
URC-0 (URINE MICROBIOLOGY)	U-URINE M,C&S
URC-0 (URINE MICROSCOPY)	U-URINE M,C&S2
URC-0 (URINE MICRO / CULTURE)	URINE - MICRO
MSU, MC&S	URINE - MICRO & CULT
URINE - CSU MC	URINE - MICRO & CULTURE
URINE - CSU MC&S	URINE - MICRO ONLY
URINE MICRO & CHEM	URINE - MICRO/CULT.
URINE RESULTS	URINE - MICROBIOLOGY
URINE M,C&S.	URINE - MICROSCOPY ONLY
URINE M,C&S2	URINE 2 CULTURE
URINE M,C+S X	URINE 2 MICROSCOPY
URINE M,C\T\S	URINE AFB CULTURE
URINE M/C/S	URINE MICRO CULTURE/SENS.
URINE MANUAL MICRO	URINE CULT & SENS
URINE MC	URINE CULT/URINALYSI
URINE MICRO & CULTUR	URINE CULTURE
URINE MICRO & CULTURE	URINE CULTURE (NEPEAN)
URINE MICRO & CULTURE (ARL)	URINE CULTURE 1
URINE MICRO & CULTURE (PPL)	URINE MICROBIOLOGY
URINE MICRO & CULTURE (YRP)	URINE MICROBIOLOGY: CULTURE URINE
URINE MICRO + CULTURE	URINE MICROBIOLOGY: MICROSCOPY URINE
U-URINE M,C\T\S	URINE MICROCULTURE
U-URINE M,C\T\S2	URINE MICROSCOPY
U-URINE MCS	URINE MICROSCOPY & CULTURE
U-URINE MCS DHM	URINE MICROSCOPY (UM-0)

U-URINE MCS1	URINE MICROSCOPY AND CULTURE
U-URINE MICRO/CULT1	URINE MICRO ONLY
U-URINE MICRO/CULT2	URINE MICRO \T\ CULTURE
U-URINE MICRO/CULT3	URINE MICRO& CULTURE
UCS-0 (URINE SENSITIVITY)	URINE MICRO.
UFO-0 (URINE FASTIDIOUS ORG+CULT)	URINE MICRO.\T\ CULT.
URINE AFB MICROSCOPY	URINE MICRO/CULT MAS
URINE C&S	URINE MICRO/CULT1
URINE CHEM/MICRO ONLY	URINE MICRO/CULT2
URINE COLIFORM SENS (ORG1)	URINE MICRO/CULT3
URINE COLIFORM SENS (ORG2)	URINE MICRO/CULTURE
URINE MICRO + CULTURE (UMC-0)	URINE MICRO/CULTURE (UBB-0)
URINE MICRO - LINK	URINE M C & S
URINE MICRO / CULTUR	URINE M C AND S
URINE MICRO / CULTURE	URINE M C \T\ S
URINE MICRO AND CHEMISTRY ONLY	URINE M \T\ C
MSU	URINE M&C
URINE MICRO AND CULTURE	URINE M&C UMC-0
URINE MICRO C/S	URINE M&CUMC-0
URINE MICRO CULTURE	URINE M+C
URINE MICRO CULTURE & SENSITIVIT	URINE M, C
URINE MICRO CULTURE & SENSITIVITY	URINE M, C \T\ S
URINE MC&S	URINE MICROSCOPY ONL
URINE MC&S UCS-0	URINE MICROSCOPY ONLY
URINE MC&S.	URINE MICROSCOPY/DIP
URINE MC&S1	URINE M\T\C
URINE MC+S	URINE SENS
URINE MCS	URINE SENSITIVITIES
URINE MCS DHM	URINE SENSITIVITY
URINE MICRO/CULTURE (UIC-0)	URINE(2) CULT
URINE MICRO/CULTURE (UIH-0)	URINE(2) MICRO
URINE MICRO/CULTURE (UM-0)	URINE MCS LISMORE
URINE MICRO/CULTURE (UM-1)	URINE MCS URM-0
URINE MICRO/CULTURE (UMM-0)	URINE MCS1

URINE MICRO/CULTURE (UMM-1)	URINE MC\T\S
URINE MICRO/CULTURE REPORT	URINE MICRO
URINE MICROAND CULTURE	_URINE MICROSCOPY
URINE M & C	URINE M,C
URINE(3)CULT	URINE M,C & S
URINE(3)MICRO	URINE-MICRO, CULTURE & SENSITIVI
URINE, MICRO & DIPSTIX	URINE-MICRO, CULTURE & SENSITIVITY
URINE MICRO AND CULT	_URINE CULTURE
MSU - M,C	UMCS
URINE MICRO CULTURE/	MSU, MC&S
URINE MICRO CULTURE/ SENS	URM-0 (URINE MICRO)
UMC MICRO & CULT	Umc Micro And Cult
U-UC	

Identification of encounters for UTIs in pregnant patients

Pregnant patients were identified if patients had any of records below: “pregnancy”, “pregnant”, “antenatal care”, or “antenatal visit”, in the “encounter (diagnosis) reason” field both prior to and after encounters for UTIs and the intervals between these two pregnancy records were fewer than 90 days. In addition, encounters for UTI containing “pregnancy”, “pregnant” or “antenatal” were also defined as encounters for UTIs during pregnancy.

Identification of encounters for UTIs in patients living in residential aged care facilities (RACF), having diabetes or chronic kidney diseases

Patients living in RACF were identified if they had any records containing “NURSING HOME” or “RACF”, or “Aged Care Facilit” in “encounter reason” field or “RACF”, “Nursing home”, or “NURSING HOME CONSULTATION” in “Encounter Type” field in Encounter dataset before the encounters for UTIs. Patients with diabetes or chronic kidney diseases were identified if they had any records of diabetes or chronic kidney diseases in the Conditions dataset before the encounters for UTIs.

Table S1. General practice encounters for first-onset urinary tract infections (UTIs), proportion of encounters with antibiotics prescribed that had accompanying urine microbiology testing, and odds ratios for likelihood of urine microbiological testing, Medicineinsight database, January 2013 to July 2018

Characteristics	**Total encounters for UTIs**	**Encounters for UTIs with antibiotics**	**Encounters for UTIs with antibiotics and tests**	**Likelihood of testing in encounters for UTIs with antibiotics**		
	N	**N**	**N**	**Proportion (%) [a]**	**Adjusted OR (95% CI) [b]**	**p**
Total population [c]	**107 626**	**92 260**	**67 909**	**73.6**		
Sex						
Female	93 274	81 595	59 952	73.5	1.00	
Male	14 352	10 665	7957	74.6	1.10 (1.05-1.16)	<0.001
Age (years)						**<0.001**
0-4	3544	2542	1756	69.1	0.81 (0.74-0.88)	<0.001
5-9	3613	3031	2366	78.1	1.31 (1.19-1.43)	<0.001
10-19	6646	5838	4469	76.6	1.23 (1.14-1.31)	<0.001
20-44	33 813	30 095	21 951	72.9	1.00	
45-74	40 478	35 102	25 852	73.6	1.04 (1.00-1.08)	0.03
≥75	19 532	15 652	11 515	73.6	1.02 (0.97-1.07)	0.36
Area remoteness						**<0.001**
Major cities	68 437	58 442	43 224	74.0	1.00	
Inner regional areas	25 005	21 205	15 999	75.5	1.20 (1.15-1.25)	<0.001
Outer regional/remote areas	14 182	12 612	8685	68.9	0.92 (0.87-0.96)	<0.001
Diabetes						
No	97 708	84 046	61 928	73.7	1.00	

Yes	9918	8214	5981	72.8	0.98 (0.93-1.04)	0.50
Chronic kidney diseases						
No	106 364	91 216	67 136	73.6	1.00	
Yes	1262	1044	773	74.0	1.07 (0.92-1.24)	0.40
Female at 10-44 years old [d]	**37 751**	**33 835**	**24 863**	**73.5**		
Pregnancy						
No	36 671	32 878	24 071	73.2	1.00	
Yes	1080	957	792	82.8	1.79 (1.50-2.12)	<0.001
People aged over 75 years old [e]	**19 532**	**15 652**	**11 515**	**73.6**		
Living in RACF [f]						
No	17 793	14 560	10 785	74.1	1.00	
Yes	1739	1092	730	66.8	0.72 (0.62-0.82)	<0.001

a. Proportion= No. of encounters for UTIs with antibiotics and tests / No. of encounters for UTIs with antibiotics

b. OR: odds ratio; CI: confidence intervals. Base model included sex, age group, remoteness and socioeconomic index of general practice sites, patients' diabetes and chronic kidney diseases history, and clustering of encounters by patient and general practice site

c. N=92 260 for multivariable analyses

d. N=33 835 for multivariable analyses

e. N=15 652 for multivariable analyses

f. RACF: residential aged care facilities

Table S2. General practice encounters for recurrent urinary tract infections (UTIs), proportion of encounters with antibiotics prescribed that had accompanying urine microbiology testing, and odds ratios for likelihood of urine microbiological testing, Medicineinsight database, January 2013 to July 2018

Characteristics	**Total encounters for UTIs**	**Encounters for UTIs with antibiotics**	**Encounters for UTIs with antibiotics and tests**	**Likelihood of testing in encounters for UTIs with antibiotics**		
	N	**N**	**N**	**Proportion (%) [a]**	**Adjusted OR (95% CI) [b]**	**p**
Total population [c]	**51 144**	**40 428**	**27 891**	**69.0**		
Sex						
Female	44 866	35 803	24 680	68.9	1.00	
Male	6278	4625	3211	69.4	1.02 (0.94-1.10)	0.69
Age (years)						**<0.001**
0-4	855	539	361	67.0	0.97 (0.79-1.19)	0.79
5-9	1088	829	630	76.0	1.46 (1.20-1.79)	<0.001
10-19	1817	1479	1073	72.5	1.26 (1.10-1.44)	0.001
20-44	9850	8157	5584	68.5	1.00	
45-74	20 118	16 251	11 024	67.8	1.00 (0.93-1.07)	0.93
≥75	17 416	13 173	9219	70.0	1.07 (1.00-1.16)	0.06
Area remoteness						**0.001**
Major cities	31 593	24 711	16 954	68.6	1.00	
Inner regional areas	12 780	9 933	7 065	71.1	1.11 (1.03-1.19)	0.004
Outer regional/remote areas	6771	5 784	3 872	66.9	0.95 (0.87-1.03)	0.18
Diabetes						
No	43 856	34 710	23 979	69.1	1.00	

Yes	7288	5718	3912	68.4	0.97 (0.89-1.05)	0.41
Chronic kidney diseases						
No	49 901	39 474	27 209	68.9	1.00	
Yes	1243	954	682	71.5	1.12 (0.93-1.35)	0.22
Female at 10-44 years old [d]	**11 104**	**9207**	**6379**	**69.3**		
Pregnancy						
No	10 802	8951	6169	68.9	1.00	
Yes	302	256	210	82.0	1.88 (1.35-2.62)	<0.001
People aged over 75 years old [e]	**17 416**	**13 173**	**9219**	**70.0**		
Living in RACF [f]						
No	15 361	11 901	8359	70.2	1.00	
Yes	2055	1272	860	67.6	0.90 (0.77-1.06)	0.20

a. Proportion= No. of encounters for UTIs with antibiotics and tests / No. of encounters for UTIs with antibiotics

b. OR: odds ratio; CI: confidence intervals. Base model included sex, age group, remoteness and socioeconomic index of general practice sites, patients' diabetes and chronic kidney diseases history, and clustering of encounters by patient and general practice site

c. N=40 428 for multivariable analyses

d. N=9207 for multivariable analyses

e. N=13 173 for multivariable analyses

f. RACF: residential aged care facilities

Table S3. General practice encounters for urinary tract infections (UTIs), proportion of encounters with antibiotics prescribed that had accompanying urine microbiology testing, and odds ratios for likelihood of urine microbiological testing, using 7-day as window for defining encounters with tests, Medicineinsight database, January 2013 to July 2018

Characteristics	**Encounters for UTIs with antibiotics**	**Encounters for UTIs with antibiotics and tests**	**Likelihood of testing in encounters for UTIs with antibiotics**		
	N	**N**	**Proportion (%) [a]**	**Adjusted OR (95% CI) [b]**	**P**
Total population [c]	**132 688**	**92 488**	**69.7**		
Sex					
Female	117 398	81 908	69.8	1.00	
Male	15290	10 580	69.2	1.02 (0.98-1.07)	0.26
Age (years)					**<0.001**
0-4	3081	2068	67.1	0.84 (0.78-0.91)	<0.001
5-9	3860	2928	75.9	1.32 (1.22-1.44)	<0.001
10-19	7317	5434	74.3	1.23 (1.16-1.31)	<0.001
20-44	38 252	26 905	70.3	1.00	
45-74	51 353	35 663	69.4	1.01 (0.98-1.04)	0.61
≥75	28 825	19 490	67.6	0.94 (0.90-0.97)	0.001
Area remoteness					**<0.001**
Major cities	83 153	58 260	70.1	1.00	
Inner regional areas	31 138	22 255	71.5	1.18 (1.14-1.23)	<0.001
Outer regional/remote areas	18 396	11 972	65.1	0.90 (0.87-0.94)	<0.001
Type of UTIs					

First-onset UTIs	92 260	66 054	71.6	1.00	
Recurrent UTIs	40 428	26 434	65.4	0.78 (0.76-0.80)	<0.001
Diabetes					
No	118 756	83 177	70.0	1.00	
Yes	13932	9311	66.8	0.93 (0.89-0.98)	0.005
Chronic kidney diseases					
No	130 690	91 131	69.7	1.00	
Yes	1998	1357	67.9	1.03 (0.92-1.16)	0.61
Female at 10-44 years old [d]	**43 042**	**30 582**	**71.1**		
Pregnancy					
No	41 829	29 652	70.9	1.00	
Yes	1213	930	76.7	1.36 (1.18-1.57)	<0.001
People aged over 75 years old [e]	**28 825**	**19 490**	**67.6**		
Living in RACF [f]					
No	26 461	18 030	68.1	1.00	
Yes	2364	1460	61.8	0.78 (0.71-0.87)	<0.001

a. Proportion= No. of encounters for UTIs with antibiotics and tests / No. of encounters for UTIs with antibiotics

b. OR: odds ratio; CI: confidence intervals. Base model included sex, age group, remoteness and socioeconomic index of general practice sites, the types of UTI (first-onset or recurrent), patients' diabetes and chronic kidney diseases history, and clustering of encounters by patient and general practice site

c. N=132 688 for multivariable analyses

d. N=43 042 for multivariable analyses

e. N=28 825 for multivariable analyses

f. RACF: residential aged care facilities

Table S4. General practice encounters for urinary tract infections (UTIs), proportion of encounters with antibiotics prescribed that had accompanying urine microbiology testing, and odds ratios for likelihood of urine microbiological testing, using 21-day as window for defining encounters with tests, Medicineinsight database, January 2013 to July 2018

Characteristics	**Encounters for UTIs with antibiotics**	**Encounters for UTIs with antibiotics and tests**	**Likelihood of testing in encounters for UTIs with antibiotics**		
	N	**N**	**Proportion (%) [a]**	**Adjusted OR (95% CI) [b]**	**P**
Total population [c]	**132 688**	**97 209**	**73.3**		
Sex					
Female	117 398	85 810	73.1	1.00	
Male	15 290	11 399	74.6	1.10 (1.05-1.15)	<0.001
Age (years)					**<0.001**
0-4	3081	2138	69.4	0.83 (0.76-0.90)	<0.001
5-9	3860	3023	78.3	1.34 (1.23-1.46)	<0.001
10-19	7317	5582	76.3	1.23 (1.16-1.31)	<0.001
20-44	38 252	27 763	72.6	1.00	
45-74	51 353	37 403	72.8	1.04 (1.00-1.07)	0.04
≥75	28 825	21 300	73.9	1.08 (1.04-1.13)	<0.001
Area remoteness					**<0.001**
Major cities	83 153	61 016	73.4	1.00	
Inner regional areas	31 138	23 415	75.2	1.18 (1.14-1.23)	<0.001
Outer regional/remote areas	18 396	12 777	69.5	0.92 (0.88-0.96)	<0.001
Type of UTIs					

First-onset UTIs	92 260	68 540	74.3	1.00	
Recurrent UTIs	40428	28 669	70.9	0.85 (0.82-0.87)	<0.001
Diabetes					
No	118 756	87 041	73.3	1.00	
Yes	13932	10 168	73.0	1.01 (0.96-1.06)	0.74
Chronic kidney diseases					
No	130 690	95 705	73.2	1.00	
Yes	1998	1504	75.3	1.12 (0.99-1.27)	0.07
Female at 10-44 years old [d]	**43 042**	**31 493**	**73.2**		
Pregnancy					
No	41 829	30 466	72.8	1.00	
Yes	1213	1027	84.7	2.04 (1.74-2.40)	<0.001
People aged over 75 years old [e]	**28 825**	**21 300**	**73.9**		
Living in RACF [f]					
No	26 461	19 645	74.2	1.00	
Yes	2364	1655	70.0	0.82 (0.74-0.92)	<0.001

a. Proportion= No. of encounters for UTIs with antibiotics and tests / No. of encounters for UTIs with antibiotics

b. OR: odds ratio; CI: confidence intervals. Base model included sex, age group, remoteness and socioeconomic index of general practice sites, the types of UTIs (first-onset or recurrent), patients' diabetes and chronic kidney diseases history, and clustering of encounters by patient and general practice site

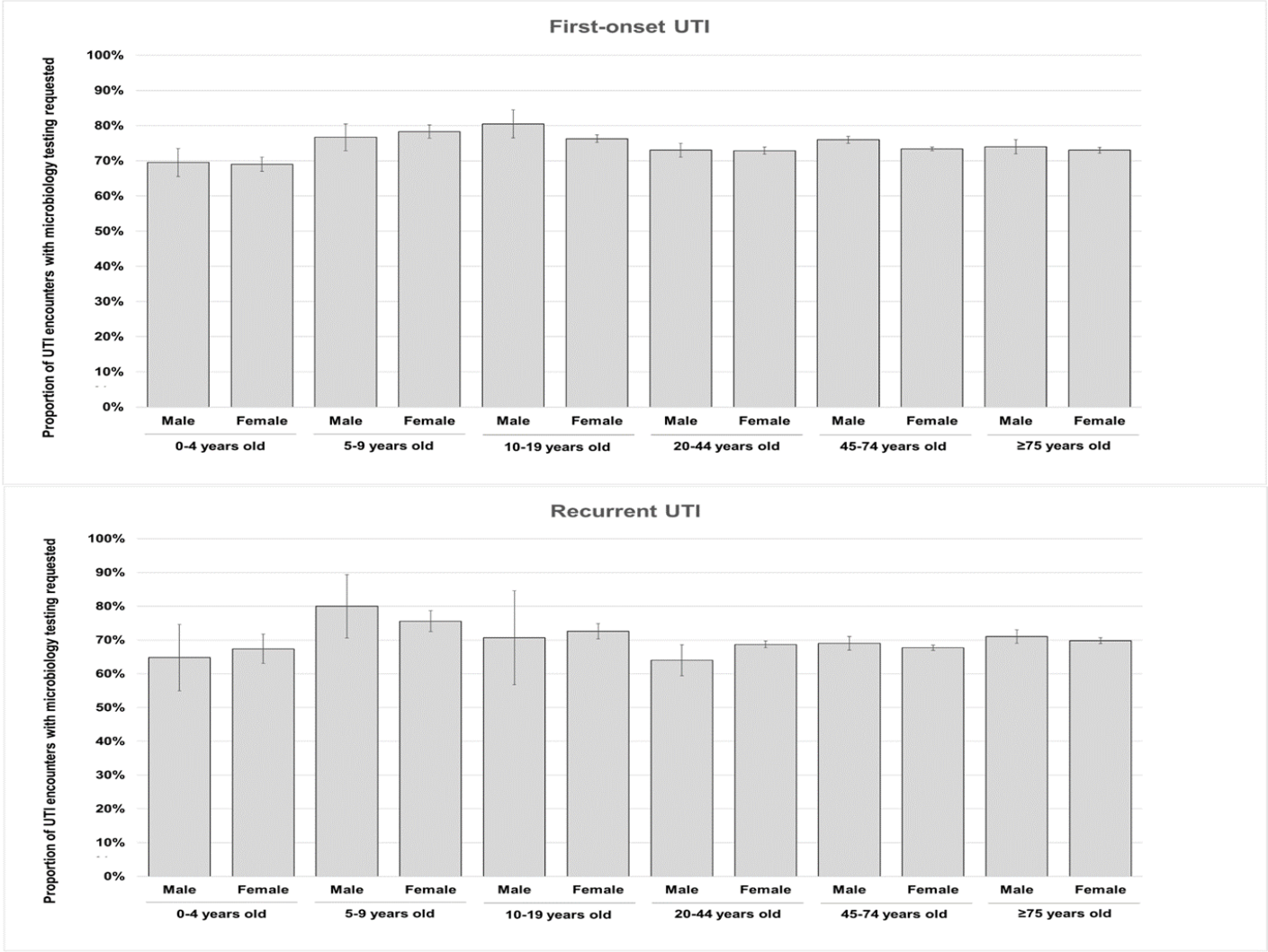
c. N=132 688 for multivariable analyses

d. N=43 042 for multivariable analyses

e. N=28 825 for multivariable analyses

f. RACF: residential aged care facilities

Figure S1. The proportion and 95% confidence interval of encounters with antibiotics prescribed that had accompanying urine microbiology testing for urinary tract infections (UTIs) by patients' sex and age, Medicineinsight database, January 2013 to July 2018


First-onset UTI
Proportion of UTI encounters with microbiology testing requested
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Male
Female
0-4 years old
5-9 years old
10-19 years old
20-44 years old
45-74 years old
≥75 years old
Recurrent UTI
Proportion of UTI encounters with microbiology testing requested
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Male
Female
0-4 years old
5-9 years old
10-19 years old
20-44 years old
45-74 years old
≥75 years old

Appendix 3. Supplementary methods and tables for Chapter 4

Supplementary Table 1. Search terms used in the identification of upper respiratory tract infections (URTIs) [a]

Search terms
cough
otitis media
tonsillitis
URTI
sinusitis
pharyngitis
laryngitis
sore throat
Upper Respiratory tract infection

a. We searched the “encounter reason” field in the Encounter dataset, “diagnosis reason” field in the Diagnosis dataset, and “reason” field in the Prescription dataset. Those records containing any one of the terms in the list were defined as URTI episodes. Records were excluded from the analysis if containing any of the following terms: “whooping” "allerg", "vac", "immunisation", "asthma", and “prophylaxis”.

Supplementary Table 2. Search terms used in the identification of immune deficiency status [a]

Search terms
transplant
immunodeficien
immunocomprom
immunosuppress
Immune deficien
Immune suppress
HIV
asplenia
purpura
Thyroiditis, subacute
Subacute thyroiditis
autoimmun
Lupus erythematosus
Inflammatory bowel disease
Multiple sclerosis
Myasthenia gravis
cirrhosis
Ankylosing spondylitis

a. We searched the "encounter reason" field in the Encounter dataset, "diagnosis reason" field in the Diagnosis dataset, and "reason" field in the Prescription dataset. Those records containing any one of the terms in the list were defined as immune deficiencies. Patients with records of Crohn's disease, rheumatoid arthritis, and ulcerative colitis in the Conditions dataset were also regarded as immunocompromised population.

Supplementary Table 3. Search terms used in the identification of antibiotic prescriptions [a]

Search terms	Search terms
DOXYCYCLINE	AMPICILLIN
CHLORTETRACYCLINE	AMOXICILLIN
TETRACYCLINE	AMOXYCILLIN
MINOCYCLINE	PIPERACILLIN
TIGECYCLINE	TICARCILLIN
CHLORAMPHENICOL	PENICILLIN
CLOXACILLIN	DICLOXACILLIN
TAZOBACTAM	MEROPENEM
CEFALEXIN	ERTAPENEM
CEPHALEXIN	IMIPENEM
CEFALOTIN	TRIMETHOPRIM
CEFAZOLIN	SULFAMETHIZOLE
CEFOXITIN	SULFATHIAZOLE
CEFUROXIME	SULFAMETHOXAZOLE
CEFACLOR	SULFADIAZINE
CEFOTAXIME	ERYTHROMYCIN
CEFTAZIDIME	ROXITHROMYCIN
CEFTRIAXONE	CLARITHROMYCIN
CEFEPIME	AZITHROMYCIN
AZTREONAM	CLINDAMYCIN
LINCOMYCIN	OFLOXACIN
TOBRAMYCIN	NORFLOXACIN
GENTAMICIN	MOXIFLOXACIN
NEOMYCIN	GATIFLOXACIN
AMIKACIN	NALIDIXIC
VANCOMYCIN	COLISTIN
TEICOPLANIN	POLYMYXIN
NITROFURANTOIN	METRONIDAZOLE
FOSFOMYCIN	TINIDAZOLE
SPECTINOMYCIN	DAPTOMYCIN
METHENAMINE	BACITRACIN
LINEZOLID	

a. We searched the “medicine active ingredient” field in the Script Item dataset. Those records containing any one of the terms in the list were defined as antibiotic prescriptions.

To exclude topical antibiotics, episodes with prescriptions of topical antibiotics were excluded from the analysis. Topical antibiotics were defined as containing any one of the following terms in the "medicine active ingredient" field: "chloramphenicol", "neomycin", or "ofloxacin", or any one of the following terms in the "medicine name" field: "ear drop", "eye drop", "oint", or "topical".

Supplementary Table 4. Proportion of first-time upper respiratory tract infections (URTI) episodes with immediate antibiotics prescribed in weekends v weekdays, by diagnoses

	Weekdays		Weekends	
	N	Proportion with antibiotics prescribed, %	N	Proportion with antibiotics prescribed, %
Tonsillitis	29574	89.5	4014	93.0
Pharyngitis	16347	70.8	2232	77.7
Sinusitis	33737	84.3	3471	88.0
Otitis media	29703	88.1	4028	90.1
Unspecified URTIs	211710	28.2	22471	35.6

Supplementary Table 5. Multivariable analysis evaluating the association between temporal factors and the proportion of immediate antibiotic prescribing in upper respiratory tract infection (URTI) episodes by age groups.

	Pre-school age (0-5)		School age (6-17)		Young/middle-aged adults (18-64)		Old population (65+)	
	Proportion, %	OR (95% CI) [a]	Proportion, %	OR (95% CI)	Proportion, %	OR (95% CI)	Proportion, %	OR (95% CI)
Day of a week								
Weekdays	36.9	1.00	45.4	1.00	53.1	1.00	54.7	1.00
Weekends	43.1	1.31 (1.23-1.39)	54.6	1.36 (1.27-1.45)	63.1	1.41 (1.35-1.47)	60.6	1.33 (1.17-1.51)
Seasons								
Winter	37.7	1.00	43.2	1.00	51.6	1.00	54.6	1.00
Spring	39.3	0.99 (0.94-1.04)	47.5	1.04 (0.99-1.09)	54.9	1.04 (1.01-1.07)	55.9	1.00 (0.91-1.09)
Summer	38.8	0.97 (0.92-1.03)	52.5	1.08 (1.02-1.15)	58.8	1.07 (1.03-1.11)	55.6	0.87 (0.78-0.97)
Autumn	35.0	0.98 (0.93-1.03)	44.9	1.00 (0.95-1.06)	53.4	1.03 (1.00-1.07)	55.0	0.93 (0.84-1.02)
Public Holidays								
No	37.5	1.00	46.1	1.00	53.9	1.00	55.1	1.00
Yes	42.5	1.00 (0.87-1.15)	57.2	1.02 (0.87-1.19)	63.2	1.15 (1.05-1.26)	59.4	1.28 (1.04-1.59)

a. Logistic Generalised Estimating Equation model adjusting for sex, the socio-economic index, the remoteness of areas, the number of antibiotic prescriptions for a patient in the previous year, body temperature, aetiology labels, the diagnosis of URTIs, and clustering in patients and practices; OR: odds ratio; CI: confidence intervals

Supplementary Table 6. Multivariable analysis evaluating the association between temporal factors and the proportion of antibiotic prescribing in upper respiratory tract infection (URTI) episodes, by patients' body temperature, aetiology labelled by general practitioners, and URTI diagnoses.

	URTIs with fever or "bacterial origin" label		URTIs without fever nor "bacterial origin" label		URTIs with a specified diagnosis [a]		Unspecified URTIs	
	Proportion, %	OR (95% CI) [b]	Proportion, %	OR (95% CI) [b]	Proportion, %	OR (95% CI) [c]	Proportion, %	OR (95% CI) [c]
Day of a week								
Weekdays	81.5	1.00	45.0	1.00	84.7	1.00	28.2	1.00
Weekends	87.9	1.60 (1.43-1.80)	52.5	1.37 (1.33-1.41)	88.4	1.38 (1.30-1.46)	35.6	1.39 (1.34-1.43)
Seasons								
Winter	80.4	1.00	43.8	1.00	85.6	1.00	27.8	1.00
Spring	81.6	1.02 (0.94-1.12)	46.9	1.03 (1.00-1.05)	85.1	0.96 (0.92-1.01)	29.7	1.06 (1.03-1.09)
Summer	85.4	1.24 (1.11-1.39)	49.8	1.03 (1.00-1.06)	84.8	0.96 (0.91-1.01)	31.5	1.09 (1.06-1.13)
Autumn	84.0	1.27 (1.15-1.40)	44.3	1.00 (0.98-1.03)	84.8	0.95 (0.91-1.00)	28.3	1.03 (1.00-1.06)
Public Holidays								
No	82.2	1.00	45.5	1.00	85.2	1.00	28.8	1.00
Yes	87.2	1.03 (0.79-1.34)	54.6	1.10 (1.03-1.17)	84.3	0.92 (0.83-1.03)	40.0	1.21 (1.13-1.31)

a. Included episodes specifically diagnosed as tonsillitis, pharyngitis, sinusitis, and otitis media.

b. Logistic Generalised Estimating Equation model adjusting for sex, age group, the socio-economic index, the remoteness of areas, the number of antibiotic prescriptions for a patient in the previous year, body temperature, aetiology labels, the diagnosis of URTIs, and clustering in patients and practices; OR: odds ratio; CI: confidence intervals

c. Logistic Generalised Estimating Equation model adjusting for sex, age group, the socio-economic index, the remoteness of areas, the number of antibiotic prescriptions for a patient in the previous year, body temperature, aetiology labels, and clustering in patients and practices.

Appendix 4. Supplementary methods and tables for Chapter 5

Identification of respiratory tract infection (RTI) episodes

I searched the “encounter reason” field in the Encounter dataset, “diagnosis reason” field in the Diagnosis dataset, and “reason” field in the Prescription dataset. Those records containing any one of the terms in the list below were defined as RTI episodes. Records containing "allerg", "vac", "immunisation", "asthma", and “prophylaxis” were excluded.

Search terms
cough
bronchitis
otitis media
tonsillitis
pertussis
influenza
rhinitis
URTI
RTI (respiratory tract infection)
sinusitis
bronchiolitis
pharyngitis
pneumonia
laryngitis
sore throat
Respiratory tract infection
LRTI

Identification of RTI types

I then classified the RTIs into upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs). Records containing any one of the following terms were defined as URTIs: “sinusitis”, “otitis media”, “pharyngitis”, “tonsillitis”, “pertussis”, “laryngitis”, “rhinitis”, “influenza”, “upper respiratory tract infection”, and “URTI”. Records containing any one of the following terms were defined as LRTIs: “bronchitis”, “bronchiolitis”, “pneumonia”, “lower respiratory tract infection”, and “LRTI”. The remaining records were defined as unknown RTI type.

Identification of systemic antibiotic prescriptions

I searched the "medicine active ingredient" field in the Script Item dataset. Those records containing any one of the terms in the list below were defined as antibiotic prescriptions.

Search terms	Search terms
DOXYCYCLINE	AMPICILLIN
CHLORTETRACYCLINE	AMOXICILLIN
TETRACYCLINE	AMOXYCILLIN
MINOCYCLINE	PIPERACILLIN
TIGECYCLINE	TICARCILLIN
CHLORAMPHENICOL	PENICILLIN
CLOXACILLIN	DICLOXACILLIN
TAZOBACTAM	MEROPENEM
CEFALEXIN	ERTAPENEM
CEPHALEXIN	IMIPENEM
CEFALOTIN	TRIMETHOPRIM
CEFAZOLIN	SULFAMETHIZOLE
CEFOXITIN	SULFATHIAZOLE
CEFUROXIME	SULFAMETHOXAZOLE
CEFACLOR	SULFADIAZINE
CEFOTAXIME	ERYTHROMYCIN
CEFTAZIDIME	ROXITHROMYCIN
CEFTRIAXONE	CLARITHROMYCIN
CEFEPIME	AZITHROMYCIN
AZTREONAM	CLINDAMYCIN
LINCOMYCIN	OFLOXACIN
TOBRAMYCIN	NORFLOXACIN
GENTAMICIN	MOXIFLOXACIN
NEOMYCIN	GATIFLOXACIN
AMIKACIN	NALIDIXIC
VANCOMYCIN	COLISTIN
TEICOPLANIN	POLYMYXIN
NITROFURANTOIN	METRONIDAZOLE
FOSFOMYCIN	TINIDAZOLE
SPECTINOMYCIN	DAPTOMYCIN
METHENAMINE	BACITRACIN
LINEZOLID	

To exclude topical antibiotics, those records containing any one of the following terms in the “medicine active ingredient” field: “chloramphenicol”, “neomycin”, or “ofloxacin”, or any one of the following terms in the “medicine name” field: “ear drop”, “eye drop”, “oint”, or “topical”, were defined as topical antibiotics. Episodes with these prescriptions were excluded in the analysis.

Table S1. Multivariable analysis evaluating the interaction between prior practice- and individual-level antibiotic prescribing in respiratory tract infection (RTI) episodes in 2018

	Patient individual-level antibiotic prescriptions in the past year				**P for interaction** [b]
	No & Low (0-3)		High (≥4)		
	OR (95% CI) [a]	P	OR (95% CI) [a]	P	
Practice-level Ratio of broad- to narrow-spectrum antibiotic prescriptions [c]		<0.001		0.576	0.023
Low	1.00		1.00		
Medium	1.11 (1.03-1.21)	0.011	0.94 (0.82-1.08)	0.358	
High	1.19 (1.09-1.30)	0.001	0.99 (0.85-1.15)	0.885	

[a.] Logistic Generalised Estimating Equation models were used, adjusting for patient demographic information (sex, age), practice-level remoteness of areas, socioeconomic index of areas, and clustering in patients and practices

b. Included the interaction term of patient individual-level antibiotic prescriptions and practice-level ratio of broad- to narrow-spectrum antibiotic prescriptions in the past year

c. Broad-spectrum antibiotics included penicillin and beta-lactamase inhibitor combinations, second- and third-generation cephalosporins, macrolides (except erythromycin), lincosamides, and fluoroquinolones; narrow-spectrum antibiotics included narrow-spectrum penicillins (e.g. penicillin, amoxicillin, and ampicillin), first-generation cephalosporins, and erythromycin.

Table S2. Multivariable analysis evaluating the association between prior practice- and individual-level antibiotic prescribing and antibiotic treatment non-response in respiratory tract infection (RTI) episodes in 2018, additionally including referral within 14 days in the outcome [a]

	OR (95% CI) [b]	P value
Practice-level antibiotic prescribing in the past years		
Antibiotic prescriptions per patient		0.154
Low	1.00	
Medium	1.05 (0.97-1.12)	0.211
High	0.98 (0.91-1.05)	0.585
Ratio of broad- to narrow-spectrum antibiotic prescriptions [c]		0.011
Low	1.00	
Medium	1.07 (1.00-1.15)	0.058
High	1.12 (1.04-1.21)	0.003
Patient individual-level antibiotic prescriptions in the past year		<0.001
0	1.00	
Low (1-3)	1.22 (1.14-1.30)	<0.001
High (⩾4)	1.63 (1.52-1.76)	<0.001

[a.] Additionally included records of referral to a specialist or an emergency department within 14 days after the original RTI episode in the definition of treatment non-response.

[b.] A Logistic Generalised Estimating Equation model was used, adjusting for demographic information (sex, age), practice-level remoteness of areas, socioeconomic index of areas, and clustering in patients and practices

[c.] Broad-spectrum antibiotics included the penicillins and beta-lactamase inhibitor combinations, second- and third-generation cephalosporins, macrolides (except erythromycin), lincosamides, and fluoroquinolones; narrow-spectrum antibiotics included narrow-spectrum penicillins (e.g. penicillin, amoxicillin, and ampicillin), first-generation cephalosporins, and erythromycin.

Table S3. Multivariable analysis evaluating the association between prior practice- and individual-level antibiotic prescribing and antibiotic treatment non-response in respiratory tract infection (RTI) episodes in 2018, using different time windows and treatment non-response definitions

	Re-prescription of different antibiotics				**Re-prescription of same or different antibiotics**			
	7-day	14-day	21-day	30-day	7-day	14-day	21-day	30-day
No. of treatment non-response (%)	1953 (2.3)	3373 (4.0)	4290 (5.1)	5570 (6.6)	3162 (3.7)	5349 (6.3)	6847 (8.1)	8370 (9.9)
	OR (95% CI) [a]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Practice-level antibiotic prescribing in the past years								
Antibiotic prescriptions per patient								
Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Medium	1.03 (0.92-1.16)	1.05 (0.96-1.15)	1.06 (0.98-1.16)	1.04 (0.97-1.12)	1.02 (0.93-1.13)	1.04 (0.97-1.12)	1.05 (0.99-1.13)	1.04 (0.98-1.11)
High	1.06 (0.94-1.19)	1.02 (0.93-1.12)	1.03 (0.95-1.12)	0.99 (0.92-1.06)	0.99 (0.90-1.09)	1.02 (0.95-1.10)	1.04 (0.97-1.11)	1.04 (0.08-1.11)
Ratio of broad- to narrow-spectrum antibiotic prescriptions [b]								
Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Medium	1.08 (0.96-1.21)	1.03 (0.95-1.13)	1.03 (0.95-1.12)	1.07 (1.00-1.15)	1.07 (0.98-1.18)	1.02 (0.95-1.10)	0.99 (0.93-1.06)	1.00 (0.94-1.06)
High	1.16 (1.03-1.31)	1.13 (1.03-1.24)	1.11 (1.02-1.21)	1.14 (1.05-1.23)	1.09 (0.99-1.21)	1.03 (0.96-1.12)	1.00 (0.94-1.07)	0.99 (0.93-1.06)
Patient individual-level antibiotic prescriptions in the past year								
0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Low (1-3)	1.05 (0.94-1.17)	1.17 (1.07-1.27)	1.19 (1.10-1.28)	1.22 (1.14-1.31)	1.02 (0.94-1.11)	1.14 (1.06-1.22)	1.16 (1.09-1.23)	1.21 (1.15-1.28)
High (≥4)	1.27 (1.13-1.43)	1.50 (1.37-1.64)	1.55 (1.42-1.68)	1.64 (1.52-1.77)	1.23 (1.11-1.35)	1.41 (1.30-1.52)	1.48 (1.38-1.58)	1.59 (1.50-1.70)

[a.] Logistic Generalised Estimating Equation models were used, adjusting for patient demographic information (sex, age), practice-level remoteness of areas, socioeconomic index of areas, and clustering in patients and practices

[b.] Broad-spectrum antibiotics included penicillin and beta-lactamase inhibitor combinations, second- and third-generation cephalosporins, macrolides (except erythromycin), lincosamides, and fluoroquinolones; narrow-spectrum antibiotics included narrow-spectrum penicillins (e.g. penicillin, amoxicillin, and ampicillin), first-generation cephalosporins, and erythromycin.

Table S4 Multivariable analysis evaluating the association between prior practice-level antibiotic prescribing and antibiotic treatment non-response in respiratory tract infection (RTI) episodes in 2018, accounting for the number of patient general practice visits and RTI treatment non-response in 2017

	Model 1 [a]		Model 2 [b]	
	OR (95% CI)	P value	OR (95% CI)	P value
Practice-level antibiotic prescribing in the past year				
Antibiotic prescriptions per patient		0.417		0.366
Low	1.00		1.00	
Medium	1.05 (0.97-1.13)	0.221	1.05 (0.97-1.13)	0.224
High	1.01 (0.94-1.09)	0.801	1.00 (0.93-1.08)	0.958
Ratio of broad- to narrow-spectrum antibiotic prescriptions [c]		<0.001		<0.001
Low	1.00		1.00	
Medium	1.09 (1.01-1.17)	0.023	1.08 (1.00-1.16)	0.039
High	1.17 (1.08-1.27)	<0.001	1.16 (1.07-1.26)	<0.001
Patient individual-level antibiotic prescriptions in the past year		<0.001		<0.001
0	1.00		1.00	
Low (1-3)	1.17 (1.09-1.25)	<0.001	1.16 (1.08-1.24)	<0.001
High (≥4)	1.45 (1.33-1.57)	<0.001	1.34 (1.23-1.46)	<0.001

a. Model 1: Logistic Generalised Estimating Equation models were used, adjusting for patient demographic information (sex, age), practice-level remoteness of areas, socioeconomic index of areas, the number of patient general practice visits in the past year (continuous variable), and clustering in patients and practices

b. Model 2: Model 1+ the number of patient previous RTI treatment non-response in the past year (continuous variable)

c. Broad-spectrum antibiotics included penicillin and beta-lactamase inhibitor combinations, second- and third-generation cephalosporins, macrolides (except erythromycin), lincosamides, and fluoroquinolones; narrow-spectrum antibiotics included narrow-spectrum penicillins (e.g. penicillin, amoxicillin, and ampicillin), first-

generation cephalosporins, and erythromycin.