School of Public Health

Predictors of Inappropriate Antibiotic Prescribing in Australian General Practice / Primary Care Settings

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DECLARATION

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains no material which has been accepted for any other degree or diploma in any university.

Human ethics

This research study received human research ethics approval from the Curtin University Human Research Ethics Committee, Approval number: HRE2016-0433.

MedicineInsight Data Governance Committee, Approval Number DG 2016-011.

Amy Elizabeth Harrison

12 September 2023

ABSTRACT

Increasing antibiotic resistance is a threat to human health globally. Unnecessary use of antibiotics needs to be reduced to preserve the effectiveness of current antibiotics. It is the unnecessary prescribing of antibiotics which needs to be researched, to gain insights into what factors drive it so the unnecessary prescribing can be reduced.

The aim of this study was to define and identify predictors of inappropriate prescribing of systemic antibiotics for initial presentations of acute upper respiratory tract infection (URTI) and urinary tract infection (UTI). The presenting condition groups of interest were acute, uncomplicated URTI, including acute rhinosinusitis / non-specific URTI, acute pharyngitis and / or tonsillitis, acute otitis media, and influenza / influenza-like illness, as well as UTI limited to the condition of acute cystitis.

Large-scale, longitudinal datasets were obtained from general practice in the state of Western Australia (WA). The reference point was the recommendations contained within the Australian national therapeutic guidelines (the guidelines) for each condition. Mixed-effects logistic regression models were used to elucidate patient- and practice-related factors associated with inappropriate prescribing. Potential predictors of interest included patient age, gender, socioeconomic status, comorbid conditions, as well as practice rurality / remoteness. Aggregate trends over time in inappropriate antibiotic prescribing and overall antibiotic prescribing were also examined.

Significant unnecessary antibiotic prescribing was identified for URTI conditions, and second-line antibiotics featured minimally for URTI. For both URTI and UTI conditions, there was substantial non-first-line antibiotic prescribing for initial presentations of infection. For UTI, culture and sensitivity testing were performed infrequently for children and men despite being recorded in the guidelines as mandatory for children and strongly recommended for men.

Young children had the lowest probability of inappropriate prescribing for URTI, but were at notably high probability of receiving non-first-line antibiotics for UTI. By URTI condition, the chance of receiving likely unnecessary prescribing was highest for the URTI condition of rhinosinusitis.

For URTI, the outcomes of likely unnecessary prescribing in general practice, the choice of antibiotic prescribed, and receiving prescriptions with repeats were all found to predict each other. For URTI models of various levels of inappropriate prescribing, predictors also included URTI condition, patient allergy label status, mental health condition status, comorbid conditions status, government concession status, socioeconomic disadvantage status and multiple URTI episode status. Non-patient-related predictors for URTI included weekend consultation status, primary health network, prescribing reason recorded status and practice size.

For UTI, antibiotic choice and receiving prescribing with repeats were also found to predict each other. Other predictors of likely inappropriate prescribing in UTI models included patient age, gender, comorbid condition status, repeat prescription status and urine dipstick and culture testing, temperature recording status and multiple UTI episodes.

Trend analyses identified downward trends in likely unnecessary antibiotic prescribing for URTI, however, increasing non-first-line prescribing was identified for both URTI and UTI.

The magnitude of likely inappropriate antibiotic prescribing occurring at several different levels and definitions suggests reason for concern. Despite some small improvements in prescribing practices found over time, more action is urgently needed. Among all models developed for URTI and UTI, individual general practitioners (GPs) were responsible for greater residual variation not explained by fixed effects than individual practices, indicating that individual practitioners' prescribing behaviour should be targeted in stewardship efforts.

This research presents multiple, new insights regarding predictors of likely inappropriate prescribing in WA general practice, and identifies several areas for further research. This research was supported with funding provided by the WA Primary Health Alliance. Expert advice was also obtained from practising GPs to guide this project and aid in the interpretation of results.

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We acknowledge that Curtin University works across hundreds of traditional lands and custodial groups in Australia, and with First Nations people around the globe. We wish to pay our deepest respects to their ancestors and members of their communities, past, present, and to their emerging leaders. Our passion and commitment to work with all Australians and peoples from across the world, including our First Nations peoples are at the core of the work we do, reflective of our institutions' values and commitment to our role as leaders in the Reconciliation space in Australia.

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LIST OF ACRONYMS

AOM	Acute otitis media
AOR	Adjusted odds ratio
AMR	Antimicrobial resistance
ARF	Acute rheumatic fever
AME	Average marginal effects
AURA	Antimicrobial Use and Resistance Australia
CALD	Culturally and linguistically diverse
CIs	Confidence intervals
CME	Continuing medical education
GPs	General practitioners
ICC	Intra-class correlation
ID	Identification number
ILI	Influenza-like Illness
MERs	Marginal effects at representative values
NAPS	National Antibiotic Prescribing Survey
NCAS	National Centre for Antimicrobial Stewardship
NAUSP	National Antimicrobial Utilisation Surveillance Program
NPS	National Prescribing Service
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PHN	Primary health network
RHD	Rheumatic heart disease
RPBS	Repatriation Pharmaceutical Benefits Scheme
RTI	Respiratory tract infection
SEIFA	Socioeconomic index for area
SES	Socioeconomic status
UK	United Kingdom
URTI	Upper respiratory tract infection
US	United States
UTI	Urinary tract infection
WA	Western Australia, state of Australia
WAPHA	WA Primary Health Alliance
WHO	World Health Organization

GLOSSARY OF MODEL OUTCOMES AND VARIABLES DEFINITIONS

This glossary provides a brief summary of outcomes and variables used in the statistical models, and is designed only for reference during the analyses chapters after having read the Methods chapter in detail. This glossary does NOT suffice for reading the Methods chapter in full.

Allergy label – the recorded history of a patient's sensitivity to a medication in the patient record. In the analyses of this research, an allergy label refers to the antibiotic penicillin or other antibiotics in the penicillin group. This is particularly relevant to the classification of first-line antibiotics for UTI.

Appropriate decision * – *likely* appropriate decision (URTI only) : contains appropriate non-prescribing and necessary prescribing combined together within the denominator of the Inappropriate *versus* Appropriate Decision Model.

Appropriate non-prescribing * – *likely* appropriate non-prescribing (URTI only) – not prescribing an antibiotic for the patient as an antibiotic is not clinically indicated or required for the condition.

Choice of antibiotic prescribed model – ordinal, increasing level of recommendations for specific antibiotics to be prescribed to treat an infection: starting at first-line, second-line, third-line (where relevant), last resort, and not recommended antibiotics. Third-line and last resort options are relevant to UTI only, and both options were combined into a single level for modelling purposes. The denominator was all antibiotics prescribed for that condition group (URTI or UTI).

First-line antibiotic – the recommended choice of antibiotic listed in the guidelines for the relevant condition as the first option to try for the patient. This should be chosen to prescribe at initial presentations of infection when prescribing an antibiotic. Note that patients with an allergy label for penicillin specifically, or other penicillins, who were prescribed a suitable penicillin sensitivity option for UTI according to the guidelines was also considered first-line prescribing. First-line antibiotics were included in the denominator of the Choice of antibiotic prescribed model and the Non-first-line antibiotic prescribing model for URTI and UTI.

Inappropriate *versus* Appropriate Decision Model * (URTI only):

Inappropriate decision * – *likely* inappropriate decision (URTI only) – this includes unnecessary prescribing. The inappropriate decision model examined inappropriate decisions as the outcome versus appropriate decisions as the base / reference. As such, the numerator was inappropriate decisions, which is the same as unnecessary prescriptions in the Unnecessary *versus* Necessary antibiotic prescribing model but a different denominator. The denominator was all diagnoses of URTI including influenza / influenza-like illness for initial presentations.

Last resort antibiotic – the last choice in the list of ordered recommendations for what antibiotic to prescribe for a patient (UTI only). Last resort options should ideally be tried at the fourth consultation if the first- to third-line options have been tried in that order and not been effective, and should have culture and sensitivity testing performed prior to prescribing one. Last resort antibiotics were included in the denominator of the Choice of antibiotic prescribed model and the Non-first-line antibiotic prescribing model for UTI.

Necessary prescribing * – *likely* necessary prescribing (URTI only) – prescribing an antibiotic in accordance with the recommendations in the guidelines for the particular URTI condition diagnosed. Necessary prescribing was included in the denominator of the Unnecessary *versus* Necessary antibiotic prescribing model for URTI excluding influenza / ILI.

Not recommended antibiotic – the prescribing of an antibiotic not listed anywhere in the guidelines of suggested antibiotics to prescribe for that condition. Not recommended antibiotics were included in the denominator of the Choice of antibiotic prescribed model and the Non-first-line antibiotic prescribing model for URTI excluding influenza / ILI as well as for UTI.

<u>Non-first-line prescribing model:</u>

Non-first-line prescribing – prescribing of an antibiotic other than the first-line recommended choice of antibiotic listed in the guidelines for the relevant condition. The model examined non-first-line antibiotics versus first-line antibiotics within the condition group (URTI excluding influenza / ILI or UTI). The denominator was all antibiotics prescribed for that condition group (URTI excluding influenza / ILI or UTI).

Repeat negative prescribing – repeat negative antibiotic prescribing – prescriptions issued without repeats on the prescription. Repeat negative prescriptions were included in the denominator of the Repeat prescribing model for URTI excluding influenza / ILI as well as for UTI.

Repeat prescribing model:

Repeat (positive) prescribing – repeat positive antibiotic prescribing – prescriptions issued with one or more repeats present on the prescription, prescriptions positive for repeats on the prescription. The numerator in this model was repeat positive prescriptions for the condition group (URTI excluding influenza / ILI or UTI). The denominator was all antibiotics prescribed for that condition group (URTI including excluding influenza / ILI or UTI).

Second-line antibiotic – the second choice in the list of ordered recommendations for what antibiotic to prescribe for a patient. This should ideally be tried at the second consultation if the first-line option antibiotic has been tried initially but was not effective. Second-line antibiotics were included in the denominator of the Choice of antibiotic prescribed model and the Non-first-line antibiotic prescribing model for URTI excluding influenza / ILI and UTI.

Third-line antibiotic– the third choice in the list of ordered recommendations for what antibiotic to prescribe for a patient (UTI only). Third-line options should ideally be tried at the third consultation if the first- and second-line options have been tried in that order and have not been effective. Third-line antibiotics were included in the denominator of the Choice of antibiotic prescribed model and the Non-first-line antibiotic prescribing model for UTI.

Unnecessary *versus* Necessary antibiotic prescribing model * (URTI only):

Unnecessary prescribing * – *likely* unnecessary prescribing (URTI only) – the prescribing of an antibiotic which was unlikely to have been required for the URTI condition. The numerator in this model was unnecessary prescribing for URTI excluding influenza / ILI. Note that unnecessary prescribing constitutes the numerator in both this model and the Inappropriate *versus* Appropriate Decision Model but has a different denominator. The denominator in this Unnecessary *versus* Necessary antibiotic prescribing model was all antibiotics prescribed for initial presentations of URTI excluding influenza / ILI.

*** Note:** this variable / outcome is considered to have "likely" as a prefix, as the guidelines cannot cover every situation and there are situations in which it may be appropriate or necessary to prescribe an antibiotic which may not be possible to identify from the data available

GLOSSARY OF MULTILEVEL MIXED-EFFECTS MODELING TERMINOLOGY

This glossary provides a brief description of statistical terms utilised in the mixed-effects models, and is designed for reference in conjunction with Methods chapter, and the analyses chapters. It does NOT suffice for reading the Methods chapter in full. This glossary provides only the briefest summary of each term, and I refer you to the references for further information. This glossary borrows frequently from STATA's Multilevel Mixed-effects Reference Manual (Release 17) Glossary (1).

Average Marginal Effects (AMEs) – a method of interpretation of a parametric model, and the simplest method of estimating effect of each variable in the model. This method is easy to both interpret and summarise in order to convey to others, however, the method can be deceptive as it, by definition, averages out the effect of each variable rather than provide the exact effect for each variable at its full range of values (1-4). It does not allow for the fact that effects of a variable on the outcome can in fact vary by other characteristics of the individual member of a level in the model (for example, at the patient, GP / provider or practice level) (1-4). An AME is the average change in the outcome variable for each one point change in the values of other independent variables in the model.

Adjusted Predictions at the Means – a method of interpretation of a parametric model, which calculates the effect of a variable in the model on the predicted value of the outcome when all other variables are held constant at sample means (1-4). This method does not show the full extent of how the effects of a variable in the model may change depending upon other characteristics of the individual observation or other characteristics of the individual member of a level in the model (for example, at the patient, GP / provider or practice level). This is the predicted value of the outcome variable at the average values of the explanatory variables in the model.

Fixed-effects model – a model which considers all variables to be constant (i.e. fixed) across all individual members within each level of a model: either not changing over time, or changing at a constant rate over time (1,5,6). (Note that many, seemingly constant, variables may in fact change over time, or even potentially change at a constant rate over time.) A fixed-effects model considers any random variables (and random-effects) to be fixed or non-random, and does not control for change over time (1,5,6). While one might

potentially consider using dummy variables to compensate for this issue within a fixed-effects model, the addition of numerous dummy variables can also negatively impact upon a model's accuracy (5,6).

Generalised linear mixed-effects model – a extended version of the generalised linear model allowing for the inclusion of random (and therefore mixed) effects.

Marginal effects (margins) – partial (i.e. marginal) derivatives of the regression equation for each variable in the model and each unit in the data (1,2). They measure the impact (incremental change) that an instantaneous change, in the unit of one variable in the model, has on the independent / outcome variable, while all other variables are held constant. This can also involve calculating the impact a unit change in one variable in the model has on the independent / outcome variable, as well as how the effect on the outcome variables changes across different values of a second variable in the model (1,2). There are many types of marginal effects, the most relevant of which include: average marginal effects, adjusted predictions at the means, and margins at representative values (1,5,6). Margins is an abbreviation for marginal effects, and is the term commonly used for the function in statistical packages which provides the marginal effects for a regression equation.

Marginal Predicted Mean – a method of interpretation of a parametric model, which calculates the average of the predicted value of the outcome, when other independent variables are held at specified different values or levels (1-4). This method does not show the full extent of how the effects of a variable in the model may change the outcome depending upon other characteristics of the individual observation or other characteristics of the individual member of a level in the model (for example, at the patient, GP / provider or practice level). This method predicts the average probability of the outcome occurring at each of the specified values / levels of the explanatory variables in the model.

Margins at Representative Values (MERs) – a method of interpretation of a parametric model, which demonstrates how the value of the dependent/outcome variable changes in response to changes in the values of the independent variables in the model. It is considered a superior method of interpretation, particularly in complex models with interaction effects or hierarchical models where the coefficients themselves can be difficult to interpret. MERs are interpreted as the difference in the outcome (versus the comparator) at the defined range of values of the explanatory variables.

Mixed-effects model – a model including both fixed and random effects (1,5,6).

Random coefficient – in a mixed-effects model, a random intercept can be considered to be equivalent to the slope in a fixed-effects equation (1). It can therefore be regarded as a randomly varying slope at the relevant level with the multilevel model.

Random intercept – in a mixed-effects model, a random intercept can be considered to be equivalent to the intercept in a fixed-effects equation (1). It can therefore be regarded as a randomly-varying intercept at the relevant level within the multilevel model.

Random-effects model – a model which allows for unobserved heterogeneity, thereby also controlling for variables which are either: non-constant across individuals or members of any level, or which change over time (1,5,6). Random effects are effects which can vary between members of any level within the multilevel model.

Residual variance – a term used in this research project to represent the remaining variance unexplained by the fixed-effects in a mixed-effects model. Calculating the intra-class correlation between the second and third levels in a three-level model provides the value of the residual variance for each of the two, higher levels.

Unobserved heterogeneity – where there may be unmeasured differences between members in the level of a model, in the form of an unmeasured / unobserved (but relevant) variable (1). This can occur when there is an unmeasured/unobserved variable, which is in fact related to the measured / observed variables within the study. For example, an unobserved/unmeasured variable might be correlated with an observed / measured (independent and / or dependent) variable. Statistical inferences may not be valid or correct if unobserved heterogeneity is present but not allowed for in a model. One way of ensuring that statistical inferences are valid and correct, in the presence of unobserved heterogeneity, is to use multilevel models with mixed effects.

1

CHAPTER 1 INTRODUCTION

1.1 The problem

Antimicrobial resistance (AMR) has been described as one of the most concerning threats to humanity (5-7), with global deaths from antibiotic resistant bacteria being estimated at 700,000 annually in 2016, and predicted to rise to 10 million in 2050 (8). Antibiotic use promotes the evolutionary process of bacteria developing antibiotic resistance (9-11).

Systemic antibiotic use is high in Australia when compared to other first-world countries (12-14). It is also known to be high in the Australian community setting (12,14-18). In 2014, 46% of the Australian population was dispensed one or more systemic antimicrobial in the community, and general practitioners (GPs) were responsible for prescribing 88% of these (12). By 2019, dispensing in the community had dropped to 40%, however, of these 50% were issued with at least one repeat on the prescription (18). While the majority of antibiotics are prescribed in community settings, rather than hospitals, antibiotic stewardship and surveillance of antibiotic prescribing and dispensing in Australia still predominantly focuses on hospital settings (19-21).

Antibiotic prescribing is termed ‘inappropriate’ when it is not in accordance with local prescribing guidelines (22-27). This is internationally accepted terminology and sets the benchmark against which prescribing is assessed (22-25,28). Guidelines are developed to minimise antibiotic resistance and side effects from antibiotics by recommending effective yet conservative use to preserve their efficacy (29). Australia’s national guidelines for antibiotic prescribing are titled the Therapeutic Guidelines: Antibiotic and will be referred to as the guidelines (29). These define the circumstances in which it is appropriate to prescribe a specific antibiotic for a particular condition or diagnosis (29).

Inappropriate antibiotic prescribing likely occurs in all Australian health settings (15,20,29-32). However, there are also notable difficulties with obtaining reliable, large-scale electronic patient data from Australian general practice (33), by which to investigate this. It is possible though, to collect data on antibiotic prescriptions yielding data about volumes and trends of antibiotic use.

However, importantly there is currently no substantial body of quantitative research about factors associated with inappropriate antibiotic prescribing for upper respiratory tract infection (URTI) and urinary tract infection (UTI) using patient data from Australian general practice, nor from the state of Western Australia (WA). Research in this field, such as this study, will contribute to the growing knowledge base internationally, and frame any issues for clinicians, system managers and policymakers.

The current body of research regarding the predictors of inappropriate antibiotic prescribing in general practice is limited, particularly in Australia. This is distinct to research regarding predictors of antibiotic prescribing generally. A deeper understanding of the drivers of the inappropriate prescribing of systemic antibiotics is vital to inform antimicrobial stewardship policy and practice in Australian primary care.

1.2 Hypothesis

The hypothesis was that there is substantial inappropriate antibiotic prescribing occurring for these conditions within WA general practice. It also included the proposition that there were likely to be patient, consultation, provider and practice-related predictors of inappropriate antibiotic prescribing. It is possible that patients with comorbid conditions, living in areas with varying measures of rurality or remoteness and accessibility to health care, with different SES, and of different ages, may be predisposed to receiving inappropriate antibiotic prescriptions when they technically should not. This might feasibly occur in response to concerns their treating GPs had about these patients' welfare and/or access to healthcare.

An Australian, national report from 2015 had found that antibiotic dispensing rates in the community were the highest in areas with the lowest SES, and dispensing rates decreased with increasing status (15). Another national report published in 2016 (12) had found that patients in major cities had the highest rates of prescribing of systemic antibiotics compared to those living in other areas (34,35). This publication (12) also found that patients living in the second-most socioeconomically disadvantaged quintile areas had the lowest antibiotic prescribing rates (36,37). One study of patients with sore throat presenting to general practice had found that chronically unwell patients were more likely to receive antibiotics (38), while another study of patients with bronchitis found that patient comorbid condition status may be linked to the choice of specific antibiotic patients were prescribed (39). A national survey of prescribing in hospitals had

also found that patients with comorbid conditions including chronic obstructive pulmonary disease (COPD) and asthma were more likely to receive antibiotic prescriptions (12,40). Subsequent to the commencement of this research, Bernardo et al. (41) had queried whether patient SES or comorbid conditions might affect antibiotic or antiviral prescribing for influenza-like illness (ILI) in general practice, on the basis of existing literature.

1.3 Objectives

The aim of this study was to define and identify, predictors of, guideline non-conforming antibiotic prescribing for initial presentations of acute URTI and UTI.

This research had included the following objectives:

1. to define and quantify the levels of inappropriate prescribing of systemic antibiotics for initial presentations of common infections to WA general practice using large-scale, routinely collected electronic patient data
2. to use quantitative methods to ascertain predictors of inappropriate prescribing of systemic antibiotics in WA general practice, including patient-, provider-, consultation- and practice-related factors associated with such prescribing
3. to determine trends in inappropriate antibiotic prescribing and in overall antibiotic prescribing by WA GPs over time.

The presenting condition groups of interest were acute, uncomplicated URTI, including acute rhinosinusitis / non-specific URTI, acute pharyngitis and / or tonsillitis, acute otitis media (AOM), and influenza / ILI, as well as UTI limited to the condition of acute cystitis (29).

Large-scale, longitudinal datasets were obtained from general practice in WA. A list of conditions of interest was developed from the data received. The reference point was the recommendations contained within the guidelines for each condition, the treatment (29), from which algorithms were developed to identify inappropriate prescribing. Data from patient records of initial consultations were utilised to assess the indication for prescribing and the appropriateness of antibiotic choice or selection when an antibiotic was prescribed.

The outcomes were then analysed using quantitative methods, specifically, mixed-effects logistic regression to elucidate patient- and practice-related factors associated with inappropriate prescribing. Relating back to the hypothesis, potential predictors of interest included patient age, gender, SES, comorbid conditions, as well as practice rurality / remoteness. Aggregate trends over time in inappropriate antibiotic prescribing and overall antibiotic prescribing were also examined.

This research was supported with funding provided by the WA Primary Health Alliance (WAPHA), which is the government-funded commissioning body with the responsibility for delivering all three primary health networks (PHNs) across the state (42). Expert advice was also obtained from GPs currently practising in WA to help guide this project and aid in the interpretation of results.

1.4 Significance

Antibiotic resistance is a growing global concern of critical importance (16,43,44). There is currently very limited empirical information regarding antibiotic prescribing in Australian general practice, particularly with respect to drivers of inappropriate prescribing. This thesis fills this important gap in the knowledge base. While there is research regarding drivers of prescribing generally, there is very limited research of such for inappropriate prescribing, which must be reduced to extend the effectiveness of current antibiotics (15).

This thesis supports antimicrobial stewardship programs in primary care, and adds to the work of the Antimicrobial Use and Resistance Australia (AURA) project, the national body doing work on antibiotic prescribing using large-scale data from community care (12,14,17,18). AURA reports provide quantities of inappropriate prescriptions for various conditions, however, they state that all prescribing for likely viral, respiratory conditions is inappropriate and do not differentiate appropriate from inappropriate prescribing for these conditions (12,14,17,18). Furthermore, these publications do not differentiate initial from non-initial consultations, to ascertain the quality of antibiotic prescribing and clinical management occurring at initial consultations (12,14,17,18). This thesis defines inappropriate and appropriate prescribing using more data than the diagnostic condition alone and limits the diagnoses included to initial consultations only, thereby facilitating enhanced analysis.

Research in this field is an urgent necessity borne from increasing antibiotic resistance globally (5-7). This project creates the potential for new knowledge regarding antibiotic prescribing in the community and primary care, with potential impact both nationally and internationally. The findings will inform policy and practice, and lead to further research on antibiotic prescribing in primary care. Its applications include informing the development of evidence-based interventions to reduce inappropriate antibiotic prescribing to stem the emergence of resistance.

To the best of my knowledge, at the time of writing, this is the first Australian research using quantitative methods and large-scale empirical data to identify predictors of inappropriate prescribing in general practice for UTI and URTI, using more clinical information than the condition diagnosed to differentiate inappropriate from appropriate prescribing. Furthermore, this is believed to be the first such analysis in Australia to allow for unobserved heterogeneity and also to limit analyses to initial presentations of infection.

1.5 Thesis structure

The overarching structure and focus of the thesis are outlined below.

The next section of this thesis, Chapter 2, outlines the problem of antibiotic resistance and how inappropriate antibiotic prescribing in primary care unnecessarily promotes the development of antibiotic resistance. It explains the resulting need for research to help identify what is driving inappropriate antibiotic prescribing in primary care and outlines the project objectives. It covers the development of antibiotic resistance, the use of antibiotics in human health, and the need for the preservation of antibiotic effectiveness by limiting any unnecessary antibiotic usage. The chapter also provides a summary of URTI and UTI conditions, and details some of the complexities regarding antibiotic prescribing for these conditions. The guidelines for treatment of URTI and UTI conditions are also discussed (29). Antibiotic stewardship and the surveillance of antibiotic use are briefly summarised for the Australian setting, including what is known about inappropriate antibiotic prescribing for URTI and UTI in Australian general practice. An overview of the published literature on predictors of inappropriate antibiotic prescribing identified using quantitative methods is presented. Brief summaries of qualitative research and interventions designed to improve prescribing practices are also provided.

Chapter 3 outlines the data source, methodological approaches, data cleaning and preparation. It explains how the guidelines were used to define multiple levels, or aspects, of inappropriate antibiotic prescribing for both URTI and UTI conditions (29).

Chapter 4 contains the results of the analyses of predictors of inappropriate antibiotic prescribing for URTI. Descriptive results for the various definitions of inappropriate antibiotic prescribing for the multiple URTI conditions: acute rhinosinusitis, acute pharyngitis and or tonsillitis, AOM, and influenza / ILI, are presented, followed by the regression results for the mixed-effects logistic models (generalised linear mixed modelling with random effects). The majority of prescriptions were found to be unnecessary, and over 50% of antibiotics prescribed were non-first-line when first-line antibiotics should have been used for these initial presentations of URTI.

Chapter 5 details the results of the analyses of predictors for inappropriate antibiotic prescribing for initial presentations of the condition of acute cystitis / UTI, with a focus on patient groups (women, men, children). The findings include substantial proportions of non-first-line antibiotics being prescribed to patients with initial presentations of UTI, most notably for children.

Chapter 6 provides a brief summary of the dataset from the perspective of analysis over time. Chapter 7 contains the results of the analyses of trends in prescribing for URTI over time. These were undertaken to identify any significant trends in prescribing over time, utilizing the same outcomes and variables defined and used in Chapter 4. There were significant downward trends in unnecessary prescribing over time for rhinosinusitis and pharyngitis but not AOM. While there was a significant decreasing trend in non-first-line prescribing over time for pharyngitis, upward trends were found for rhinosinusitis and AOM.

Chapter 8 presents the results of analyses for trends in prescribing for UTI, using response variables detailed in Chapter 5. This includes the presentation of trends in outcomes over time for all patients with UTI altogether, then for women, men and children separately. The results summarised also include trends in overall antibiotic prescribing over time for each patient group. There were upward trends in non-first-line

prescribing identified for adult patient groups but there was a downward trend for children.

The Discussion chapter follows in Chapter 9, summarising the most pertinent findings from the four analysis chapters. The results are further explained, and the findings are compared with those of the broader literature. This provides context regarding what the findings mean for WA general practice, as well from the broader perspective. It provides an overview regarding the substantial inappropriate antibiotic prescribing found for initial presentations of URTI and UTI. It summarises the most important predictors of inappropriate prescribing identified, as well as the trends over time in inappropriate prescribing. This is followed by discussion of the context and implications of these results for general practice policy and practice. In the Australian setting, although evidence of some progress is noted, the overall situation appears concerning. Priority areas for antibiotic stewardship and opportunities for improvement are identified, and potential areas for further research are raised. The limitations of the research are also discussed. It raises questions regarding the need for more proactive steps on this important topic and opportunities for future research.

Chapter 10 provides a brief overview of the pertinent findings and implications for Australian general practice in the context of inappropriate prescribing for URTI and UTI. It notes the limited progress identified on inappropriate prescribing in Australian general practice appears insufficient to have notable impact on curbing antibiotic resistance. It also highlights the value and significance of this research and what it contributes to the knowledge base both at the national and international levels.

CHAPTER 2 BACKGROUND

2.1 Introduction

2.1.1 The problem: growing, global antibiotic resistance

Antibiotic resistance is becoming an increasing problem globally, raising concerns about future capacity to control infections with antibiotics (6,16,44). Antibiotic resistance is encouraged by the frequent use of antibiotics in human health care, veterinary medicine, as well as agriculture, and exposure to antibiotics in the environment can also facilitate resistance (9,11). There is a strong association between antibiotic use and antibiotic resistance in individuals (45,46). An apt description of the situation is a rapidly progressing yet “silent pandemic” (47).

2.1.2 The problem locally: inappropriate antibiotic prescribing in Australian primary care

Australia’s First National Antimicrobial Resistance Strategy 2015–2019 (6,16) aims to develop and implement strategies to prevent and minimise growing AMR, whilst ensuring continuing effectiveness and availability of treatments for infectious diseases (6,16). Inappropriate antibiotic prescribing is thought to occur in all Australian health settings (15,20,26-28,30-32,48). It is believed to occur frequently in the community, of which general practice constitutes the majority of the patient interactions (15,20,26-28,30-32,48). Despite the existing quantitative research on antibiotic prescribing, resistance and its current surveillance within the Australian health system (14,17), there is limited surveillance or empirical information regarding how much of the prescribing in primary care is inappropriate for various conditions (49-51). Furthermore, there is no substantial body of quantitative research analysing large general practice data sets to identify factors associated with inappropriate antibiotic prescribing. There is qualitative research on inappropriate prescribing, and although not the focus of this research, a summary of qualitative studies is provided in **Section 2.6.2** for reference.

This thesis focuses on the state of WA, which poses unique challenges for health services due to its very large geographical area and small population density by area (52). It is also characterised by a proportionally high number of Aboriginal and Torres

Strait Islander peoples living in remote communities (52,53). People living in these rural and remote communities have high rates of infectious disease incidence, chronic disease prevalence, and poor health outcomes (52-58), as well as high rates of bacterial disease that should be treated by antibiotics.

2.2 Antibiotics, the development of antibiotic resistance and other side effects from taking antibiotics

2.2.1 Antibiotics and antimicrobials

Medically important microorganisms include bacteria, fungi, viruses and parasites, which are treated with antimicrobial agents: antibiotic, antifungal, antiviral and antiparasitic medications, respectively (59). Antibiotics typically treat bacterial infections, although there is some antibiotic use to treat non-bacterial pathogens (59). Antibiotic agents are ineffective against viruses. This is relevant to diagnosing respiratory tract infections (RTIs) with multiple aetiologies. Viruses are commonly cleared by the human body without specific antiviral treatment. Antibiotics have either systemic or topical mode of delivery. This research addresses systemic antibiotic prescribing.

Antibiotic use is distinct to prescribing, as many prescriptions written are not dispensed (60-64). However, prescribing is a necessary precursor to dispensing. Quantities of antibiotics dispensed are often reported as a proxy for prescribing. Antibiotic use can be classified into multiple different types. The most common antibiotic use is empirical prescribing, which is immediate treatment of a patient presenting with signs and symptoms of existing infection, if antibiotic use is indicated (65-67). There are also prophylactic uses for antibiotics, which prevent infection in the first place (66,67). Prophylaxis is common and recommended for chronic or recurrent infections or for patients with compromised immune systems (66,67). Definitive / directed therapy refers to antibiotic treatment following laboratory diagnosis of the causative pathogen, guiding the choice of an effective antibiotic (66,67). Delayed prescribing is a dispensing minimization strategy, where the patient is given a prescription but told to hold off filling it, and to wait and only fill the script several days later if the condition does not improve (68,69).

This research addresses the clinical decision whether to prescribe at initial presentations and what empirical prescribing occurs in these situations. A distinct weakness of empirical therapy is the absence of laboratory pathology results which guide effective antibiotic choice. The time (typically several days), for a pathology test to be performed and for the result to be available to the clinician, often requires that the clinician consider empirical prescribing initially without pathology results, if an antibiotic is indicated. With the development of rapid testing techniques, quicker access to pathology results is foreseeable in the future (70,71).

2.2.2 Antibiotic resistance concepts and side effects

Antibiotic resistance is encouraged by the frequent use of antibiotics in human health care (72,73). There is increasing risk of bacterial resistance with increasing duration and course number of antibiotics (45). In addition to promoting antibiotic resistance at the community (72,74) and individual level (45,46), taking antibiotics can lead to other serious side effects for individual patients (75-81). Antibiotic stewardship is the promotion of both awareness regarding growing antibiotic resistance and the careful use of antibiotics (82,83).

Clinicians must know the local epidemiology of infectious diseases, common pathogens, as well as their susceptibilities to available antibiotics, as well as local resistance patterns to make an informed decision including selecting an appropriate antibiotic (29,67,84). Any decision to prescribe an antibiotic must consider individual patient benefit against the potential harms of prescribing including side effects, antibiotic resistance, and the potentially serious sequelae of not prescribing (29,67).

2.3 Conditions commonly suspected of receiving inappropriate antibiotic prescribing

In Australia, epidemiological data on infection incidence, treatment efficacy and local resistance patterns are used by experts to develop therapeutic guidelines and treatment benchmarks to help guide clinicians. Despite this, antibiotic prescribing for URTI conditions occurs more often than the epidemiological data and benchmarks suggest it is required (12,14,17). There are also large quantities of non-first-line agents prescribed for both URTI and UTI conditions when the majority of patient interactions are believed to be initial presentations (12,14,17).

In different healthcare settings, there may be more than one set of guidelines available to guide clinicians. For example, in the hospital setting, there may be specialist paediatric guidelines which may address the multitude of factors influencing prescribing and therefore appropriateness.

The standard for assessment in this thesis was version 15 of Australia's Therapeutic Guidelines: Antibiotic (the guidelines), published in 2014, to reflect the timeframe of the data analysed (29). Narrow-spectrum antibiotics are recommended as the initial, first-line choice for treatment, as they are less predisposed to promoting antibiotic resistance than non-first-line agents (29). Resistance should be confirmed using sensitivity and susceptibility testing prior to using non-first-line antibiotics (29), however, note this takes several days. A brief description including an outline of the guidelines for each condition follows below. Please see the **Methods chapter** for details of how the guidelines were applied for each condition (29). For a summary of the prescribing guidelines published directly before and after the version used for analysis (85,86), please see **Appendix A.1**.

Note that prescribing can be appropriate despite not meeting guideline compliance, as there are many factors influencing antibiotic use, which cannot cover all scenarios. For example, patients living in remote areas may not have regular access to healthcare, such that issuing a prescription at an initial consultation may be reasonable.

2.3.1 Upper respiratory tract infection

URTI is the term given to a group of conditions affecting the upper regions of the respiratory tract, and these are most commonly viral in origin (29,87). This thesis defines URTI to include rhinosinusitis / common colds, influenza and ILI, pharyngitis and / or tonsillitis and AOM. GPs in all countries commonly see patients presenting with URTIs (88-90), which are difficult to diagnose correctly due to the multitude of possible aetiologies, despite most still being viral (91,92). URTI was the reason for 26% of GP presentations by Australian children (29) and the most frequent reason for presentation in infants (93). Most URTIs, regardless of aetiology, are self-limiting and full recovery is usual without treatment (29).

2.3.1.1 Acute rhinosinusitis / non-specific URTI

Acute rhinosinusitis is marked by inflamed paranasal sinuses and nasal passages (94,95). It is almost always a viral infection, although it can be bacterial (94,96). Approximately 20% of bacterial rhinosinusitis which does not resolve within two weeks may require antibiotic treatment (29). The common cold and non-specific URTI have been included in this condition. The guidelines used for analysis in this study suggest symptomatic treatment and recommend against the routine use of antibiotics for rhinosinusitis. Antibiotics can be considered in patients with symptoms over seven days, high fever in excess of three days from symptom onset, or double-sickening - a term describing symptoms which worsen after several days of initial, milder illness (29,97).

2.3.1.2 Acute pharyngitis / tonsillitis

Pharyngitis and / or tonsillitis are infections characterised by sore throat, and the strong majority of presentations are viral (98,99). The only indication for antibiotic treatment of pharyngitis / tonsillitis is Group A *Streptococcus* bacterial infection (29,57). This is an absolute indication for antibiotic treatment due to potentially fatal complications, including acute rheumatic fever (ARF) (57). Group A *Streptococcus* causes between 20-30% of paediatric, and 5-15% of adult, cases of pharyngitis (100-102). Australia has a very high rate of ARF and rheumatic heart disease (RHD) in remote, Indigenous communities in central and northern Australia (56,57,103). Patients 2-25 years of age in communities with high incidence of ARF, and / or any patient with current RHD or scarlet fever are high-risk patients requiring antibiotics (29,57).

2.3.1.3 Acute otitis media

AOM is inflammation of the middle ear, caused by viral or bacterial infection (29). It often presents in young children with ear pain and fever, and complications include tympanic membrane perforation and consequent conductive deafness (104,105). As there is high incidence among Aboriginal and Torres Strait Islander children, these children are considered high risk (29,106,107). The guidelines used for analysis in this study state that prescribing is appropriate for children with systemic features including vomiting, lethargy or high fever (29). Symptomatic treatment without antibiotics is recommended initially for children aged six months or more without systemic features. For children under six months without systemic features, antibiotic prescribing may be appropriate, however, symptomatic treatment may be sufficient initially but review of the patient is recommended after 24 hours.

2.3.1.4 Influenza and influenza-like illness

Influenza is infection with one of several influenza viruses which are typically seasonal (41,108,109). The infection is most often moderate in severity but can be fatal in young children, the elderly and people with chronic diseases (108,110). Estimated deaths from annual influenza epidemics exceed 500,000 people per year globally (108,111). ILI is a diagnosis based on a set of symptoms including fever, lethargy and cough (109,110). ILI can be caused by influenza viruses, as well as parainfluenza viruses, adenoviruses, respiratory syncytial virus (109). These viruses can also cause lower respiratory tract infection, which is out of scope for this thesis. The guidelines used for analysis recommend symptomatic treatment for influenza / ILI, as these are always viral in aetiology (112), and antibiotics are not recommended unless secondary bacterial complications are noted (108,113).

2.3.2 Urinary tract infection

2.3.2.1 Acute cystitis

Acute cystitis is a bacterial infection of the lower urinary tract, and it is a common presentation in primary care (114). Acute cystitis is common among women, particularly women of reproductive age (29,115). It is uncommon in men, usually presenting in older males with functional abnormality (29,116,117). Acute cystitis is a common infection of childhood (29,115). The condition can be painful, and serious side effects include potentially fatal urosepsis, which is uncommon but can happen in neonates (115,118).

Patients frequently receive non-first-line antibiotics for presumed, initial presentations of UTI, when first-line options are recommended (15,17,29,48,119). These patients also receive overly long durations of antibiotic therapy (119-122). Patients diagnosed with recurrent / chronic UTI have different implications for treatment (123).

Patient age, gender and anatomical differences are used to classify the infection into uncomplicated and complicated (123). The guidelines used for analysis in this study vary by patient age and gender, and include routine empirical prescribing for adult patients with this condition (29). Empirical prescribing is recommended for symptomatic children who are positive for nitrites or leukocyte esterase, or if bacteriuria is identified by microscopy. For patients under one month old, hospitalisation and intravenous antibiotics are required, and this is not covered in the guidelines.

2.3.3 Repeats issued on antibiotic prescriptions

Repeats issued on prescriptions for antibiotics can be considered another form, or level, of inappropriate prescribing. However, there are some medications for which a repeat is required in order for a patient to receive a guideline-concordant course of antibiotics. This relates to the pack size produced by the manufacturer. Some prescriptions for cefalexin fall within this category. However, for the majority of formulations for antibiotics repeats are not required for a single course of treatment. This is especially likely to be the case for initial presentations of an infection in urban areas.

Notable quantities of antibiotics are dispensed from repeat prescriptions in Australia (14,124) The dispensing of repeats often occurs a substantial time (months) after the original prescription (12,14,124), and therefore unlikely to be used for the same episode of infection (12). However, the default option in many medical practice software packages included repeats on the prescription (14), requiring prescribers to amend the prescription to remove. The aligning of manufacturing pack size with local guidelines has been raised as a stewardship opportunity (125,126).

A national report published in 2019 by the Australian Commission for Safety and Quality in Health Care (the Commission) found that 50% of antibiotic prescriptions were issued with one or more repeats on the prescription (14). Potential solutions presented included amending either the default options in software or the amount dispensed at the pharmacy level to align with course recommendations for antibiotics with substantial course to pack size discrepancies (14,75). In 2017, Del Mar et al. (49) had raised the need for change on unnecessary, repeat antibiotic prescriptions (75). Effective April 2020, the Pharmaceutical Benefits Advisory Committee (PBAC) proceeded to limit prescribing authority for repeats on the following antibiotics: amoxicillin, amoxicillin with clavulanate, cefalexin, doxycycline and roxithromycin (127,128).

2.4 Antibiotic stewardship and the surveillance of antibiotic use

2.4.1 What is antibiotic stewardship?

Antibiotic stewardship promotes the prudent use of antibiotics, including both the prescribing by health professionals and the administration by patients (129-131). This

involves developing and implementing strategies to prevent and minimise the development of antibiotic resistance, whilst ensuring continuing effective and available treatments for patients with infectious diseases (6,16,129,130).

Antibiotic stewardship includes promoting awareness regarding antibiotic resistance among prescribers and the public (129,130,132). This includes implementing tools to improve antibiotic prescribing practices to prescribe only when required, and encouraging compliance with local prescribing guidelines (129,130,132). Stewardship also includes the monitoring and measurement of antibiotic use, for continuing improvement (129,130,132). Governance is also an important part of stewardship at the organizational level (130).

In the out of hospital setting, important aspects of antibiotic stewardship include commitment and policy, strategies for practice, monitoring and reporting of antibiotic use, and education tools and resources (132). Examples of suitable proactive activities include providing prescribing feedback to prescribers, the distribution of educational resources to patients, ongoing prescriber education and promotion of guidelines, and facilitating access to expertise in antibiotic stewardship for prescribers (132).

2.4.2 What is surveillance and its role in antibiotic stewardship

The surveillance of antibiotic use involves the collection and analysis of data on antibiotic prescribing, dispensing or consumption, in order establish patterns and provide population health information, as well as reducing harm from antibiotic misuse (16,133). This is a notable level above the monitoring and reporting typically required of routine antibiotic stewardship, which does not involve analysis, for example. The surveillance of antibiotic use also facilitates detailed evaluation of antibiotic stewardship strategies (16,134).

The World Health Organization (WHO) is leading the international collaboration on surveillance of both antibiotic use and resistance and to promote antibiotic stewardship (6,47). Antibiotic stewardship and surveillance go hand in hand and inform each other. While the surveillance of antibiotic use is a focus of this research, the surveillance of antibiotic resistance is outside its scope. Nevertheless, a summary of surveillance programs for antibiotic resistance within Australia in **Section 2.4.4** below.

2.4.3 Stewardship and surveillance of antibiotic use in Australian primary care

2.4.3.1 Government surveillance, stewardship and other initiatives

In Australia the government subsidises the costs of many pharmaceuticals including antibiotics under the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS) (17). Antibiotic prescriptions dispensed under the PBS and RPBS are collated in the Department of Human Services' Medicare pharmacy claims database (17). This includes dispensing claims for antibiotic prescriptions written by GPs, specialists, dentists, nurse practitioners, hospital discharge, public hospital outpatients, and private hospital inpatients (17). Antibiotics prescribed and dispensed in some remote Aboriginal Health Services, (and relevant to WA), fall outside the PBS and affect the accuracy of its reported prescribing rates in these remote communities (12). The PBAC makes decisions regarding which antibiotics and other medicines are included on the PBS / RPBS (135). In the case of antibiotics, the PBAC is currently advised by the Expert Advisory Group on Antimicrobial Resistance (135).

In the 1990s and early 2000s, following quinolones being registered in Australia, the PBAC restricted their use in human and food production, with specific indications requirements to limit their prescription (135). This was an early but important step (136). Another initiative was the then Australia's Chief Medical Officer sending peer-comparison letters to GPs with high rates of antibiotic prescribing in 2017 (137). This initiative's three forms of peer-comparison letters led to an overall nine percent reduction in antibiotic prescriptions from these GPs for a period of twelve months thereafter (138).

Australia's First National Antimicrobial Resistance Strategy 2015–2019 was published in 2015 by the Commission, to address AMR in humans, animals, agriculture, food production and the environment (16). This was followed by an updated strategy, endorsed in 2020, entitled Australia's National Antimicrobial Resistance Strategy – 2020 and Beyond (the 2020 Strategy) (139). While the majority of antibiotics are prescribed in community settings, rather than hospitals, at this time in Australia, stewardship on antibiotic prescribing predominantly focuses on hospital settings (19-21).

Using hospital data, the National Antimicrobial Prescribing Survey (NAPS) is a standardised tool for auditing the quantity and quality of antimicrobial prescribing, is coordinated by the National Centre for Antimicrobial Stewardship (NCAS) (140). NAPS includes surveys, such as, the Surgical NAPS, Hospital NAPS, and Aged Care NAPS, however, there is no survey specific to general practice (141). NCAS is developing stewardship in primary care through a current research project (142). In 2018, there were 324 participants from both public and private hospital involved in the Hospital NAPS (143,144). The 2019 Surgical NAPS involved 144 public and private facilities participating across Australia (18,143,144). NAPS also has a collaborative partnership with the Commission and the Department of Health. Furthermore, the National Antimicrobial Utilisation Surveillance Program (NAUSP) monitors antimicrobial consumption in participating private and public hospitals (145). In 2019, there were 219 acute-care hospitals participating in NAUSP (144,145), including 170 public and 49 private hospitals, with 100% involvement by principal referral hospitals. Both NAPS and NAUSP programs are involved in the AURA project (144), which is detailed in **Section 2.4.3.4** below.

The Commission has antibiotic stewardship initiatives (130), as does the WA Department of Health (146). The Antimicrobial Stewardship Clinical Care Standard (147,148) was developed to guide optimal practice across all human health sectors. It was published in 2014 (147) and updated in 2020 (148) and provides quality requirements for how to document the clinical indication for prescribing antimicrobials and outlines adherence to current guidelines. Having an antimicrobial stewardship program in place, and monitoring both antibiotic use and resistance are also accreditation requirements of hospitals and day procedure services in Australia (130,149). These requirements are contained within the National Safety and Quality Health Service Standards (Second Edition) (150,151), as specific requirements of the Preventing and Controlling Infections Standard of 2021 (152), replacing the 2017 Preventing and Controlling Healthcare-Associated Infection Standard. Government-funded stewardship and surveillance initiatives, past and present, which incorporate Australian primary care, are covered below in **Sections 2.4.3.2 - 2.4.3.5**.

2.4.3.2 Bettering the Evaluation and Care of Health survey

The Bettering the Evaluation and Care of Health (BEACH) survey of general practice was an annual report produced by the Faculty of Medicine and Health at the University

of Sydney (89,153,154). From 1998 until it lost funding in 2016, the voluntary BEACH survey reported the proportion of GP visits for URTIs for which antibiotics were prescribed (89,153,154). Its data from 2015–16 demonstrates that URTI and UTI were in the top 5 most frequently managed new problems (155). Over the decade 2006–07 and 2015–16, URTI as a newly managed problem declined from 4.4 to 4.2 per 100 encounters, whereas UTI decreased from 1.3 to 1.1 per 100 encounters (156). There was no meaningful change in the URTI management rate between 2006–07 and 2015–16 (156). Over the decade 2006–07 and 2015–16, the frequency of prescriptions for amoxicillin reduced from 2.2 to 1.8 per 100 problems managed (156). Roxithromycin prescriptions also declined over the decade, from 0.9 to 0.5 per 100 problems managed (156). There was, however, no significant change in the prescriptions of cefalexin, amoxicillin with clavulanate, or doxycycline over the same period (156).

2.4.3.3 NPS MedicineWise

Evolving from the National Prescribing Service (NPS), NPS MedicineWise was a leading authority on the quality use and prescribing of medicines (157,158). It focused on educating the public and primary health providers regarding responsible antibiotic prescribing from 1999 to 2022 but lost funding and ceased to continue (159,160). Its' early campaigns on viral URTI were believed to have decreased antibiotic dispensing (159,161). Activities for GPs typically included clinical auditing, visiting educational activities on appropriate prescribing, and academic detailing with peer-comparison prescribing feedback (159,162,163). NPS was known for its antibiotic stewardship campaigns targeting both health professionals and the public (159,164-167). Its 'Choosing Wisely' campaign consisting of written, educational publications, and the 'Resistance Fighter' was a multi-media consumer awareness campaign to support the fight against antibiotic resistance (159,164-167). NPS MedicineWise undertook surveillance of systemic antibiotic prescribing by participating GPs in Australia (157,158). Its program, called MedicineInsight (162,168,169), collected de-identified data from participating general practices, and was the data source for this research, and was utilised in AURA, as detailed below.

2.4.3.4 The Antibiotic Use and Resistance in Australia project

The Antibiotic Use and Resistance in Australia (AURA) project was established by the Commission, as part of the National Antimicrobial Resistance Strategy 2015–2019 (16). AURA also uses PBS and MedicineInsight data to examine antibiotic prescribing in

general practice. NAUSP provides hospital data to AURA (145), while NAPS provides hospital and surgical data, as well as data from the aged care setting (141,143,144). The first AURA report (12), published in 2016, found that non-first line antibiotics were prescribed in 68% of sinusitis presenting in primary care in 2014. The second AURA report found that in 2015 patients presenting primary care in major cities had increased antibiotic prescribing rates than patients in other areas (17). The third AURA report (14) identified patients 65 years and over and children two to four years of age presenting to general practice had the highest antibiotic use in 2017. It reported declining antibiotic use since 2010, however, in 2015 and 2017 women with UTI received first-line antibiotics 45-46% of the time (14).

The fourth AURA report (18) published in 2021 found overall increasing antibiotic use in the hospital setting but decreasing use in the primary care setting. Specific to the hospital setting in 2019, NAUSP reported the total antibiotic use across its participating hospitals had seen an increase from 848 defined daily doses per 1,000 occupied bed days in 2015, to 883 defined daily doses per 1,000 occupied bed days in 2019 (18). The Surgical NAPS of 2019 is an example of notable hospital-based findings on antibiotic use forming part of the fourth AURA report (18,143). The 2019 Surgical NAPS identified several issues in antimicrobial administration in the acute-care setting, relating to procedural surgical prophylaxis and post-procedural surgical prophylaxis, as well as specific problems with topical antibiotic use in both contexts (18,143). For procedural surgical prophylaxis, there were issues in documenting both incision time and antimicrobial administration time, whereas for post-procedural surgical prophylaxis, there were errors in the dose, frequency and duration of antibiotic administration (18,143).

Specific to community care setting, the fourth AURA report (18) utilised PBS / RPBS data to demonstrate a 15% reduction in the age-standardised rate of antibiotics prescribing per 1,000 persons between 2015 and 2019. It was also found that 50% of these prescriptions for antibiotics were issued with repeats. Specific to the GP setting, which is the focus of this research, the fourth AURA report (18) utilised MedicineInsight data and found declining antibiotic use from 2015 to 2019, and a marked reduction due to decreased patient consultation with GPs during the Covid-19 pandemic. In 2019, systemic antimicrobials were prescribed to 31% of patients attending practices participating in MedicineInsight. The fourth AURA report (18) found that despite

downward trends in antimicrobial prescribing in the MedicineInsight program since 2010, that antimicrobials still appeared to be prescribed too frequently based on guideline recommendations. For example, 82% of patients diagnosed with acute bronchitis and 80% of patients with sinusitis, presenting to MedicineInsight-participating practices were prescribed antibiotics, despite symptomatic treatment without antibiotics being the recommendation in the guidelines.

2.4.3.5 The Atlas of Healthcare Variation

The first and third Atlas of Healthcare Variation (Atlas), published in 2015 (15) and 2018 (75) respectively, contain relevant information regarding antibiotic prescribing using PBS / RPBS dispensing data. The first Atlas found that antibiotic dispensing rates appeared to increase with decreasing SES, in line with infection rates (15). Antibiotic prescriptions, particularly quinolones, dispensed in WA were notably lower in WA than other states and territories, although Aboriginal Health Services dispensing is not included (15). The third Atlas (75,170,171) found that for 2016-17, children 0-9 years of in inner regional and major city areas with lower SES had decreased antibiotic dispensing compared to children with other SES. However, this was not the case for children 0-9 years in other areas (75,170,171).

Despite these initiatives, antibiotic stewardship in the general practice setting is limited and requires sustained investment (126,172).

2.4.4 Surveillance of Antimicrobial Resistance in Australia

There are multiple systems in place for the surveillance of AMR in Australia, in both the hospital and community setting. These include the National Alert System for Critical Antimicrobial Resistance, and the National Notifiable Diseases Surveillance System. Pathogen-specific surveillance systems include the National Neisseria Network, and its component programs. There is also the Australian Group on Antimicrobial Resistance and the Australian Passive AMR Surveillance system.

Critical antimicrobial resistances are resistance profiles of microorganisms which are a dangerous threat to last-line antimicrobials. This means microorganisms demonstrating resistance to the last-line antimicrobials available (173). The Commission established the National Alert System for Critical Antimicrobial Resistances, which is abbreviated to the name, CARAlert (173). Its objective is to establish a nationally coordinated system

for critical antimicrobial resistance and to monitor and facilitate early response to any outbreaks of these organisms (173). There is a list of priority organisms for which participating laboratories regularly provide data (173). CARAlert functions as part of the AURA surveillance program (173).

The National Notifiable Diseases Surveillance System coordinates incidence data for 70 diseases which can pose a danger to Australians (174). This includes blood-borne viruses, certain sexually transmitted infections, childhood diseases, arthropod-borne diseases like malaria as well as respiratory infections like influenza and coronavirus-19 (174). Although it is not tailored specifically to antimicrobial resistance but infection incidence, several diseases have their own surveillance systems and those specific to resistance. The collation of data enables timely monitoring and surveillance and, where necessary, response (174).

The Australian Group on Antimicrobial Resistance involves microbiology laboratories from all states and territories nationally (175). This collaboration conducts surveillance and susceptibility testing of specific pathogens of concern (175). It also collates treatment, demographic and outcome data for diagnoses such as bacteraemia (175). It also forms part of AURA surveillance (175). Molecular testing is undertaken for some isolates for its blood-stream infection programs, including the Gram-negative Sepsis Outcome Program, the Australian Staphylococcal Sepsis Outcome Program, and the Australian Enterococcal Sepsis Outcome Program (175).

The National Neisseria Network involves a group of public and private laboratories that contribute to passive surveillance of resistance and susceptibility for the pathogenic *Neisseria* species, *Neisseria gonorrhoeae* and *Neisseria meningitidis* (176). It runs two programs on invasive disease: the Australian Gonococcal Surveillance Programme and the Australian Meningococcal Surveillance Programme (176).

The Australian Passive AMR Surveillance collates resistance data from pathology services across Australia, both public and private (177). It was established by the Commission with support from Queensland Health (177). It facilitates analysis and reporting on resistance and its output includes both cumulative antibiograms and resistance profiles during specified time frames (177).

2.5 Access to general practice prescribing data in Australia

Australia is lagging behind many developed countries in general practice data collection and access for primary care research (51). The Australian Government has limited oversight of general practice, as the strong majority is private enterprise (51,58,178). Unlike in England, for example, patients at general practices in Australia can move entirely freely between practices and attend multiple practices within the same time period (179). Due to the private business structure (58), a fear of losing patients has been noted as a reason for inappropriate prescribing in the Australian GP setting (180).

Patient data is routinely collected by administrative systems in daily general practice but is not well utilised in Australia, particularly for research, due to barriers in sharing and access (50,178,181,182). Some notable GP datasets include MedicineInsight (168), PenCS and its CAT4 program (183,184), the University of Melbourne's Patron data repository (185), and the Melbourne East Monash General Practice Database, formerly known as MAGNET, operating as POLAR by Outcome Health (186-188). These datasets do not include all GP practices, however, they provide opportunities for research and feedback to general practice (26). Data are typically not linked to PBS / RPBS dispensing data or to either secondary or tertiary care, which limits the research (182). Substantial change is needed to improve access to administrative datasets (189). MedicineInsight offered a high quality, large-scale data source for general practice research, however, it ceased operation in 2022 (160).

The detailed review of individual patient records enables the most accurate classification of inappropriate from appropriate prescribing. As this is not feasible on a large-scale, a common trade-off with the analysis of large-scale prescribing data in Australia has been the use of basic classification of appropriate from inappropriate prescribing, such as, using the diagnostic condition alone to determine appropriateness (12,14,17,18). For example, some publications note that all URTIs are presumably viral and therefore all antibiotics for these conditions are inappropriately prescribed (12,14,17,18). However, this thesis presents a middle ground, in which more patient data is incorporated to enhance the differentiation between inappropriate and appropriate prescribing whilst using large-scale data, and thereby improve our understanding of inappropriate prescribing. Albeit, the approach taken here in this thesis requires additional resources for further data cleaning, preparation and analysis.

2.6 Literature on primary care interventions and qualitative research on inappropriate prescribing

Australia has followed the international trend of quantitative research on interventions aiming to limit antibiotic prescribing (28,137,138,190-193) as well as qualitative research on exploring reasons for inappropriate prescribing (180,194,195). While both qualitative and intervention studies are important in their own right, and help to understand why inappropriate prescribing occurs, and how to reduce antibiotic prescribing, respectively, they do not address the research question and fill the gap in knowledge that this project does. Brief summaries of the literature on interventions and qualitative studies follow in Sections 2.6.1 and 2.6.2, respectively.

2.6.1 A summary of interventions to reduce inappropriate prescribing in primary care

There is a significant body of research on interventions designed to reduce inappropriate prescribing. These can be separated into interventions for clinicians, pharmacists, patients, as well as communication between these groups. The majority of community care interventions focus on acute respiratory infections, rather than a single condition, with greater potential for impact (196).

In their 2017 systematic review of interventions for reducing URTI prescribing in primary care, Tonkin-Crine et al. (197) found that the strongest evidence was for shared decision-making, C-reactive protein and procalcitonin testing, while they found low evidence for patient- and clinician-targeted education-related interventions. Other reviews have found that electronic decision support systems, adult procalcitonin testing, and educational interventions, particularly when multifaceted and addressing several levels, show benefit without notable adverse effects (198-201). Meeker et al. (202) found commitment letters on display within the practice were effective. Peer-comparison-based feedback to clinicians appears to be one of the most useful strategies (203-212). However, as Bell et al. (213) note, the likely uptake of any interventions as well as their population impact also require consideration.

Shared decision-making appears to be a promising strategy to facilitate improved guideline compliance through enhanced communication between clinicians and patients (214,215). Delayed prescribing strategies also appear useful although it is unclear about

their uptake (126,216-219). Pharmacist involvement appears promising for improving guideline concordance (220-222). Studies exploring point-of-care testing to resolve diagnostic uncertainties offer possible solutions, despite potentially increasing follow-up consultations (28,70,223-225).

Advancing information technology and large-scale data offer new opportunities for interventions and stewardship. A Chinese study validated an algorithm created for reading free-text outpatient antibiotic prescribing data (226). Another study explored the potential for social marketing to help improve prescribing by GPs (227). Tsopra et al. (228) used preference learning to find inconsistences in antibiotic prescribing guidelines, and created a decision aid for such situations (229). A computer game was also created for medical students to teach the appropriate prescribing of antibiotics in primary care (230). For a useful summary of information technology applications for interventions and stewardship, please see Chapter 4 of the Commission's report, *Antimicrobial Stewardship in Australian Health Care* (231).

2.6.2 A summary of qualitative research on inappropriate prescribing

It remains unclear why over-prescribing of antibiotics appears to continue in Australia and internationally despite the presence of specific national guidelines. It likely involves a complex array of interconnected factors relating to the individual prescriber, the practice, the patient, as well as socio-cultural influences. Some of these factors are thought to include patient demand, perceived patient demand, time pressure and / or high patient loads, and complacency by the prescriber (23,180,232-241). Other factors include uncertainty regarding the correct diagnosis on the part of the prescriber, which is commonly termed, 'diagnostic uncertainty', and ignorance regarding antibiotic resistance by both patients and prescribers (23,180,232-241).

Diagnostic uncertainty and low uptake of diagnostic testing methods are potential reasons for unnecessary prescribing (242,243). Fletcher-Lartey et al. (244) summarised what they termed "patient expectations" as the predominant reason why inappropriate prescribing occurs, and this term included time limitations, diagnostic uncertainty, and suboptimal communication. In their study of over-prescribing, Rose et al. (240) grouped their findings into three categories: GP fears, including anxieties and attitudes, patient factors including expectations/demands and limited patient education, as well as external factors, such as financial and time pressure concerns. In a Canadian study of

primary care physicians (245), a lack of continuity of care, such as in the case of single, episodic consultations (and the absence of established trust) has been linked to clinicians reporting lower confidence in their skills of avoiding antibiotic prescribing. One study found GPs perceived more pressure to prescribe in the after-hours settings and with fee-paying patients (246). Pharmaceutical company representatives were a source of prescribing pressure in another study from general practice (243).

In a study comparing general practices with lower and higher volumes of antibiotic prescribing (247), prescribers in lower prescribing practices detailed helpful tools and mechanisms to support not prescribing an antibiotic during the consultation. These included helpful practice policies, sufficient consultation time, increased communication with colleagues, and consistent prescribing behaviours within the practice (247). Whereas, a qualitative study of Australian GP trainees found that antibiotic prescribing was more likely among patients of Aboriginal or Torres Strait Islander descent, older patient age, and affluent practice location (30,248).

Several studies note GPs' concerns regarding a lack of access to resistance data and guidelines (243,249). Public awareness regarding antibiotics and the accessibility and usability of the guidelines for Australian GPs has also been questioned (250,251). Internationally, issues have been raised with both the comprehension and the incorporation of the guidelines (246,252), as well as questions on prescribing metric validity (253). Studies have found that prescribing decisions are frequently made based on individual, past experience instead of guidelines and resistance data (246,252). Tyrstrup et al. (254) highlight the need to consider GPs' preconceptions in guideline development. The potential for using real-world patient data for guideline development has also been raised (255).

It is notable that several of these potential reasons, for either over-prescribing or inappropriate prescribing of antibiotics as listed above, also feature in Lam et al.'s (256) thematic framework of reasons for over-testing by clinicians, albeit not necessarily GPs. While interactions with colleagues were raised as a supportive mechanism against (unnecessary) antibiotic prescribing (247), there were several instances of pressure from colleagues linked to over-testing in Lam et al. (256). It may be possible that there may be a relatively common, risk-adverse behaviour spanning multiple areas of clinical medical care including both inappropriate antibiotic prescribing and over-testing (and

overdiagnosis), functioning under the guise of (potentially misguided) medical diligence and / or self-protection.

2.7 Literature review of studies using quantitative methods

As detailed above in **Sections 2.6.1 and 2.6.2**, there is a substantial body of research on interventions designed to reduce inappropriate antibiotic prescribing and qualitative research to try to explain why it occurs. While these studies can help provide insights regarding the question, neither truly address the crux of the problem – which is, ascertaining what factors drive inappropriate prescribing. Quantitative research analysing patient-level data to identify what drives inappropriate prescribing is limited. Stedman et al. (257) note that influencing prescribing inherently requires knowledge of its drivers locally. One must firstly research inappropriate prescribing in detail in order to truly understand it, prior to developing interventions or qualitative explorations of why it occurs (239).

Given the focus of the empirical research presented in this thesis, it was considered important to focus on quantitative studies which use real, patient consultation data in primary care to identify what factors are associated with inappropriate prescribing. The definition of the general practice / primary care setting used in this research excludes settings such as the emergency department, hospital inpatients, aged care, dental, and other medical specialist care in the community. However, it is important to note that there are differences in the setting and terminology of primary care provision internationally. For the purposes of direct comparison with Australian general practice at an international level, the review focused on medical professionals in the primary care setting, although it is noted that nurse practitioners and physician assistants can also provide primary care. For example, in the United Stated (US), paediatricians and family medicine physicians provide primary care. However, in contrast, paediatricians do not provide primary but secondary and tertiary care in Australia and the United Kingdom (UK), and GPs are the main primary care providers. Despite variations in the terminology, it was considered important not to exclude research involving health professionals that perform the same function in primary care as GPs. Furthermore, these differences have also led to the inclusion of some studies encompassing general practice or primary care alongside other healthcare settings outside primary care, such as outpatient or emergency care. Excluding such research would result in a limited

number of relevant studies identified. These differences in primary care providers does add complexity to making international comparisons with general practice in the Australian primary care context.

Please note there are multiple, existing quality indicators which have been developed to measure antibiotic prescribing (258-265). These tend to measure proportions of diagnoses and / or prescriptions meeting specific criteria, and they can be useful for comparing prescribing rates across areas / countries or against benchmarks. However, quality indicators do not typically classify inappropriate from appropriate prescribing, which facilitates analysis of predictors of inappropriate prescribing using individual-level data. For a summary of prominent antibiotic prescribing quality indicators, please see **Appendix A.2**.

2.7.1 Different definitions of inappropriate antibiotic prescribing

Due to the multiple levels of advice within prescribing guidelines, this leads to multiple different definitions of inappropriate prescribing (259-262,266-269). This ranges from prescribing for conditions where not indicated, such as for viral URTIs where antibiotics would be ineffective (210,270-274), to the use of non-first-line antibiotics when first-line antibiotics have not yet been tried (22,270,275-280). The evaluation of situations in which an antibiotic was indicated but not prescribed is another possibility (25,281).

Some studies consider prescribing by specific antibiotic class, such as fluoroquinolones, to represent inappropriate prescribing (282-285). Many studies focus on the use of non-first-line antibiotics (22,270,277-280,286). Antibiotic prescriptions can further be evaluated against the recommended dose / frequency and duration recorded in guidelines such as excessive duration (22,285,287-291). An alternate approach taken in one study was to define all prescriptions with missing indication field as inappropriate, as well as examining prescriptions with non-specific indications entered by the GP (292). The definitions used in this thesis are explained in detail in the Methods chapter.

Due to the multiple definitions of inappropriate prescribing and the various terms for general practice or its equivalent internationally and the many types of antibiotics, the search strategy is not listed here but can be found in **Appendix A.3**.

2.7.2 Considerations regarding the literature criteria

When examining the existing literature, it was considered relevant to focus on research investigating what is intrinsically driving inappropriate prescribing, when the objective was to identify predictors from within patient-, consultation-, provider-, and practice-related factors. Published literature was limited to studies which clearly differentiate inappropriate from appropriate prescribing. Most primary care research use only the condition diagnosed to separate inappropriate from appropriate prescribing (12,14,17,18,274,293,294). Internationally, there is limited quantitative research from large-scale primary care data which differentiates inappropriate from appropriate prescribing using more than diagnostic condition alone.

Most studies also do not classify initial from non-initial consultations by order of occurrence in time to ascertain the quality of clinical management occurring at initial (or subsequent) consultations for the same episode of infection (12,14,17,18,26,277,279,293,295). This includes AURA using large-scale GP data (12,14,17,18). Although it is typical to exclude diagnoses coded as “chronic” (295), which may represent a different condition or guideline, few studies indeed limit analysis to initial consultations for the infection of interest by examining consultations longitudinally and selecting the first occurrence (296). Fossum et al. (297) took a different approach, by limiting the analysis to the first antibiotic prescription per patient - although this does not necessarily imply it was the initial consultation.

There are also quantitative studies which analyse predictors despite having not differentiated inappropriate prescribing from appropriate prescribing, thereby identifying predictors of overall antibiotic prescribing (257,298-303). Although these can provide useful information, it is the inappropriate prescribing which requires curbing, while appropriate prescribing may prove dangerous to reduce, hence the need for research which both distinguishes between the two and identifies predictors. Alternatively, there are studies which define (in)appropriate prescribing using predominantly descriptive statistics but do not use analytical methods to identify factors associated with such (in)appropriate prescribing (26,87,288,304-308).

This overview of the literature includes only published literature based on real patient data rather than hypothetical vignettes or questionnaires, for which clinician awareness

regarding the study and subsequent participation may in itself influence prescribing (309). There are multiple small-scale questionnaires of prescribers which directly ask what influences decision-making, and small, vignette studies which may elicit responses with more ideal prescribing behaviour (123,310-312). For quality control, if the prescribing data was obtained via questionnaire / vignette, these were excluded from this overview of the literature, apart from national surveys with strong design which were considered less likely to be biased. Multiple studies which combined real patient-prescriber data obtained from the electronic record, with prescriber demographics obtained by survey, were considered suitable for inclusion (313,314).

2.7.3 Literature review overview

Much of quantitative research on inappropriate antibiotic prescribing as per the definition used in this research is from the US. The Netherlands, Canada, Denmark, Sweden, Norway, Iceland, Germany, France, the UK, and Spain also contribute. It may be the accessibility of primary care data for research that facilitates such research. From the available literature, predictors of inappropriate prescribing can be classified as factors relating to the patients, or factors relating to the consultation and practice setting, or factors relating to GPs themselves.

2.7.3.1 Patient factors

Patient age has been found to be a risk factor for inappropriate antibiotic prescribing in several studies, however, with inconsistent direction of effect (25,39,280,281,283,284,291,294,296,297,315-325). Several paediatric studies found that the youngest patients had higher odds of inappropriate prescribing than older children (297,321-323), while others found the that the odds increased with increasing child age (280,296). Increasing probability of inappropriate prescribing was found with increasing age in several studies including adults or patients of all ages (25,281,283,284,316,324). Antibiotic prescriptions received without an encounter with a clinician in the US was found to be linked to increased patient age (318). However, multiple studies found insufficient evidence of an association between inappropriate prescribing and patient age (270,276,295,315,319,326,327). One study found that increasing patient age was associated with unnecessary prescribing for presumably viral infections, while decreasing patient age was linked to suboptimal choice of antibiotic for bacterial infections (294). Another study including many types of infection

found that children were more likely to receive an antibiotic dosing error, while adults were more likely to receive the wrong duration of antibiotic (320).

Whether patient gender is a genuine predictor of inappropriate antibiotic prescribing - for conditions unrelated to anatomical gender differences - remains uncertain. Several studies found male patients at higher risk of inappropriate prescribing than females (280,291,328), while others found that females were more predisposed (294,321,326). Malo et al. (39) found that the direction of effect differed between definitions of inappropriate prescribing, with males more likely to receive inappropriate decisions but less likely to receive a non-recommended antibiotic selection than females. Several authors, however, found no association between inappropriate prescribing and patient gender (276,281,297,319,329,330).

SES and whether patients are from culturally and linguistically diverse (CALD) backgrounds may potentially be linked to inappropriate prescribing. Health insurance status, as a proxy for SES, has also been linked to inappropriate prescribing, with no, or cheaper, health insurance being found to be a predictor of lower rates of non-first-line prescribing (276,295). However, patients with public health insurance had a high risk of unnecessary prescribing in another study (316). Wattles et al. (317) found that insurance and CALD background status had no influence on inappropriate prescribing for AOM, however. Studies in US ambulatory care, in which inappropriate prescribing was compared between patient groups with different CALD backgrounds status, have found an association between patients from CALD backgrounds and less inappropriate antibiotic prescribing (276,295,326).

Patient comorbidity may prove to be another important factor in predicting inappropriate antibiotic prescribing. It has been linked to increasing inappropriate antibiotic prescribing in studies in several studies, with consistent direction of effect (39,281,289,294,317,318,326,331). Dekker et al. (281) found that patients with comorbidities had increased likelihood of inappropriate prescribing by 70%, while Singer et al. (294) found that with every increasing comorbid condition, there was an eleven percentage point increase in unnecessary prescription risk.

The presence of inflammatory signs, such as fever, may also influence inappropriate prescribing (25,281,332). Patients with antibiotic allergy were independently associated

with less chance of receiving appropriate choice of antibiotic as well as less chance of a prescription with appropriate duration (289). A study of UTI patients found inappropriate fluoroquinolone prescribing was more likely among patients with a history of resistance to nitrofurantoin and recent nitrofurantoin use (283). Fernandez-Urrusuno et al. (333) found that UTI and dental infection were more likely to be treated appropriately, whereas URTI and skin infections were predisposed to inappropriate treatment. Amoxicillin and amoxicillin with clavulanate have specifically been associated with less appropriate treatment (333). In one study, patients being treated with multiple antibiotics simultaneously were more likely to receive appropriate treatment (333). Fischer et al. (318) found that prescriptions issued without a patient encounter occurred more frequently among patients with multiple encounters, and Singer et al. (294) found increasing risk of inappropriate prescribing with increasing number of patient visits.

2.7.3.2 Clinician and healthcare setting factors

Multiple studies compared the appropriateness of antibiotic prescribing between healthcare settings or the type of medical specialist or health professional (237,295,296,321,322,324,329,330). Several studies found these to be significant drivers of inappropriate prescribing (237,295,296,324,329,330), while others found no such association (321,322,324,329). For example, Barlam et al. (326) found that family medicine physicians more frequently prescribed inappropriately than general internal medicine physicians, while another study found the opposite (276). Regardless of the type of prescriber, the primary care setting does seem prone to inappropriate prescribing (237,280,295,315,328,330). Chen et al. (296) found higher rates of guideline non-adherence for UTI prescribing in community clinics as opposed to medical centres, which may suggest a link to patient SES.

Measures of rurality, such as the health care provided to patients living in urban or rural areas (290,294,317,334) may also affect inappropriate antibiotic prescribing. Several North American studies have found that inappropriate prescribing was linked to patients living in rural areas (294,317,334). Women with UTI in rural areas were found to receive antibiotics with excessive duration compared to women in urban areas (290).

Some GP-related factors associated with more non-first-line prescribing by GPs that were identified in studies in the Netherlands include: working in solo general practice (271); frequency of consultation for RTIs; less frequency of use of national prescribing

guidelines; and willingness to try prescribing new drugs (277). In 2007, Cadieux et al. (270) found inappropriate prescribing was linked to high-volume practices, and GPs with foreign medical degrees, whereas another study found large practices were predisposed to inappropriate prescribing (294). One study in after-hours care found improving antibiotic choice was correlated with decreasing patient to prescriber ratio, however, there was no relationship with practice size (335). Multiple studies found that prescribers with both higher volumes of patient turn-over and higher antibiotic prescribing rates were predisposed to inappropriate prescribing (270,277,284,297,321,329). Lindberg et al. (322) found no association between first-line prescribing and median consultation duration or days between work sessions, however.

The prescriber's age or their duration in practice was a significant factor in several studies but with inconsistent direction of effect (270,280,294,296,328,336). Several of these suggest increasing age adds to the risk of inappropriate prescribing (270,296,336). Kozyrskyj et al. (328) found that older prescriber age was linked to higher probability of prescribing for viral RTI but to lower probability of non-first-line prescribing for bacterial infections than younger prescribers. Blommaert et al. (280) found that prescribers in the 40-44 age group tended to prescribe non-first-line antibiotics more frequently than their older or younger colleagues. Chang et al. (316) found that clinicians who were recently employed or with less professional post-graduate education were predisposed to inappropriate prescribing of antibiotics. Several other studies found no association between the prescriber's age and the odds of inappropriate antibiotic prescriptions (291,297,321,329).

2.7.3.3 Conclusions from the literature overview

The literature suggests that patient age may influence inappropriate prescribing. It is possible that the impact of patient age, if any, varies by condition, and the youngest and oldest patients may be most risk of inappropriate prescribing for some conditions. For conditions other than UTI, the literature regarding patient gender is less convincing, and if true, it appears to have less influence than patient age.

Clinicians may have increased concern for the health of patients with comorbid conditions, such that clinicians may prescribe for these patients when technically not required. Patients with multiple attendances is also a feasible driver of inappropriate prescribing, however, in many publications it is unclear whether multiple consultations

include follow-up or multiple initial consultations for separate episodes of infection. Furthermore, these do not differentiate initial from non-initial consultations. To this end, the AURA project (12,14,17,18), which uses large-scale data from Australian primary care but uses only the condition to classify inappropriate from appropriate prescribing. This highlights the importance of research in identifying initial from non-initial consultations in Australian primary care.

The literature suggests the possibility of a link between inappropriate prescribing and patients with different SES, measures of rurality and CALD background status. It would appear plausible that patients in affluent, urban areas may attend nearby care providers for minor ailments, exert more pressure on clinicians, receive more inappropriate prescribing, and, that infectious diseases are known to occur more frequently in disadvantaged areas which may increase the chances of appropriate prescribing in these areas. Similarly, patients in rural areas may access care less easily, less frequently and for more serious ailments. However, rurality, by virtue of less accessible healthcare, may be a reasonable reason for providing a technically unnecessary prescription. SES is also known to be complex to measure (337,338).

With regard to clinician factors, the literature suggests that increasing workload may be a highly viable option as a potential driver of inappropriate prescribing. Prescriber age or year of certification, as a potential predictor, may be a complex mix of years of experience working in primary care and degree of involvement in continuing medical education (CME) or peer-group activities. It seems feasible that optimal prescribing behaviours may occur after several years of experience in general practice but this may begin to taper off when GPs are closer to retirement, less involved in CME, and less actively engaged in changing policy and guidelines and consulting with peers.

In the international studies conducted specifically assessing inappropriate prescribing in primary care, several are not limited purely to general practice (25,270,277,281). Partly due to international differences, many studies including general practice / primary care also cover other areas of ambulatory / outpatient care (237,296,323,326,332,339) or emergency departments (295,324,330). Many studies are also limited to either child (271,296,297,315,323) or adult (237,276,281,326,332) populations. The clinical conditions covered by each study also tend to differ, such as AOM, UTI, URTI, or multiple conditions (237,271,276,281,283,294,296,297,315-320,323,326,332). This is

in addition to the fact the populations and disease epidemiology from different nations are not homogenous. Furthermore, there are multiple, different definitions of inappropriate prescribing utilised within the identified studies (25,39,280,281,283,284,291,294,296,297,315-325), and this adds to the difficulty of drawing meaningful comparison across them.

Much of the existing literature does not appear to allow for multiple types or levels of unobserved heterogeneity, such as, at the patient, GP, and practice levels (22,48,277,281,286,295,296,315,323,325,326,329,330,332,340-342). Studies which do not allow for (potentially important) unobserved heterogeneity at each level may lead to reliance on spurious results.

This literature review highlights that inappropriate prescribing requires quantitative studies that go to the trouble of differentiating appropriate from inappropriate prescribing, with clear definitions. This highlights that the research question is very specific, and it needs a data-driven approach, with real-world patient data at large-scale and at an individual patient-provider level, as well as sound methodology in statistical modeling, to accurately address.

There is currently limited information on inappropriate antibiotic prescribing in Australian general practice, and primary care internationally, particularly with respect to empirical evidence of drivers of inappropriate prescribing. This review has the overarching finding of the need for more research to identify factors driving inappropriate antibiotic prescribing for specific conditions in certain settings and populations (294).

2.7.3.4 What this thesis contributes

This thesis will begin to fill this important knowledge gap, by identifying predictors of inappropriate antibiotic prescribing for initial presentations of URTI and UTI from large-scale patient data from WA general practice. It will also explore and identify trends in inappropriate prescribing for these conditions over time.

This thesis will use quantitative analytical methods and large-scale patient data to identify predictors of inappropriate prescribing in general practice for UTI and URTI, using more clinical information than the condition diagnosed to differentiate inappropriate from appropriate prescribing. It will provide a more detailed definition of

inappropriate prescribing and it will also limit analyses to initial presentations of infection, to examine clinical management occurring at initial consultations. Furthermore, this thesis will utilise statistical methods which allow for potentially important unobserved heterogeneity at each level of the data, which should lead to increased accuracy in the results of analyses.

To the best of the author's knowledge, at the time of writing, this is the first Australian research using quantitative methods and large-scale empirical patient data to identify predictors of inappropriate prescribing in general practice for UTI and URTI, using more clinical information than the condition diagnosed to differentiate inappropriate from appropriate prescribing, and to limit analyses to initial presentations of infection. This is also believed to be the first analysis of inappropriate antibiotic prescribing within Australian primary care to allow for unobserved heterogeneity.

This thesis falls within the second strategic objective of WHO's Global Action Plan on Antimicrobial Resistance, *"to strengthen knowledge through surveillance and research"* (6). In the Australian context, it falls under the national strategy's objective five to develop a research agenda and promoting investment in new means of preventing and containing AMR (16). While there is research regarding drivers of antibiotic prescribing, there is limited research of such for inappropriate prescribing - that which must be reduced to extend the effectiveness of current antibiotics (15).

Research in this field is an urgent necessity borne from increasing antibiotic resistance globally (16,43,44). This project creates the potential for new knowledge regarding antibiotic prescribing in the community and primary care, with potential impact both nationally and internationally. The findings from this research will be published in peer-reviewed journals. The findings will inform policy and practice, with feedback to be provided to general practice, and to support antibiotic stewardship, as well as lead to further research on antibiotic prescribing in primary care. Its applications include informing the development of evidence-based interventions to reduce inappropriate antibiotic prescribing to stem the emergence of resistance.

CHAPTER 3 METHODS

3.1 Introduction

This research is a quantitative analysis of large-scale data obtained from general practice in WA to identify predictors of inappropriate antibiotic prescribing. The intention was to establish empirical evidence with respect to antibiotic prescribing in this setting for two main condition groups: URTI and UTI. The overall objective was to identify and quantify the inappropriate prescribing of antibiotics for these conditions, and to identify predictors of, and trends in, inappropriate antibiotic prescribing. The methods employed are depicted in **Figure 3-1**.

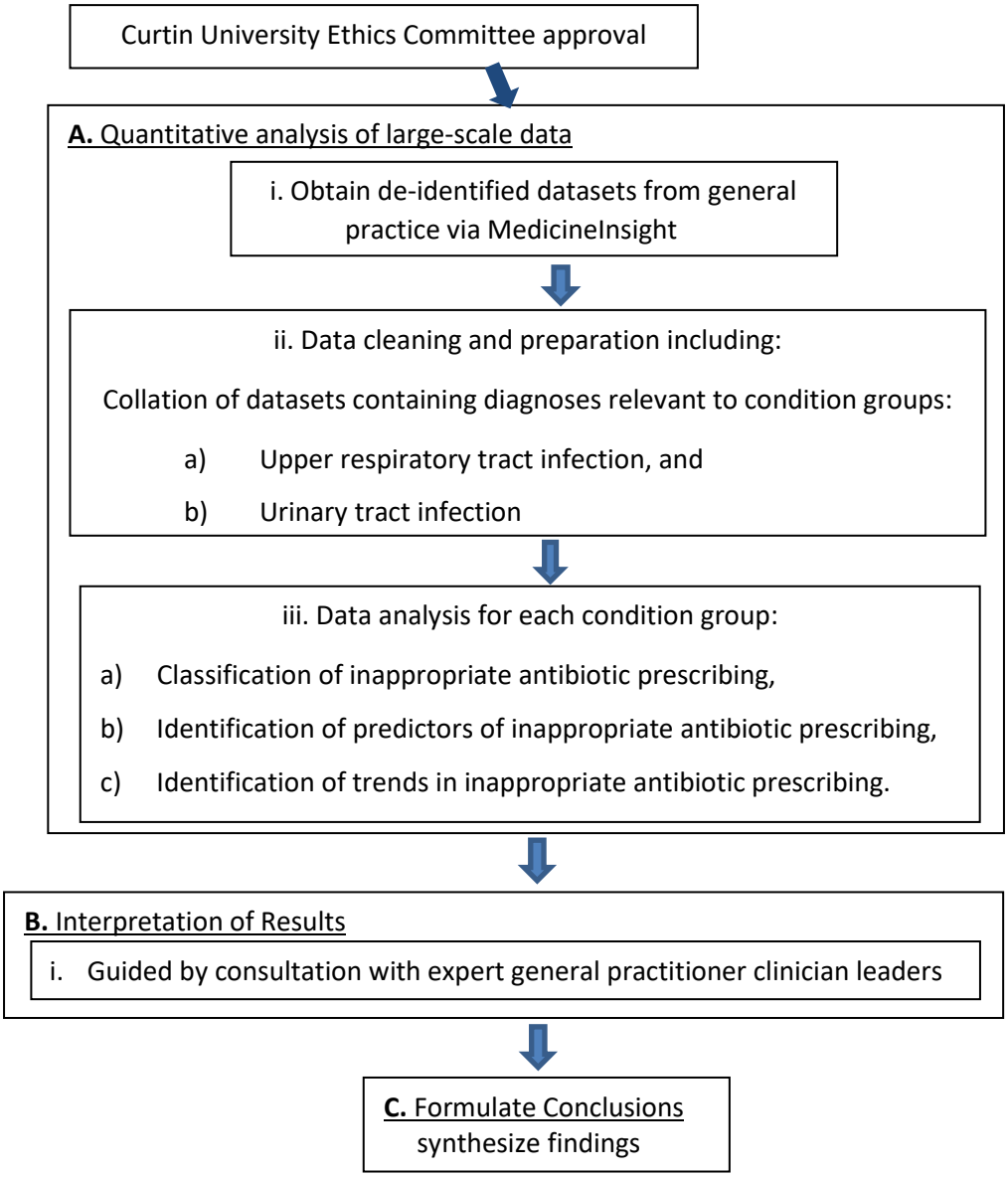


Figure 3-1: Project flow diagram

3.2 Establishment of steering committee

The steering committee was established to provide expert guidance throughout the project. Consultation with experts in the field occurred to help explain the results and guide interpretation. As well as having a member of supervisory panel with experience working as a general practitioner (GP), it was considered particularly important to have GPs on the steering committee. In addition to two GP experts and leaders in their field, membership of the steering committee also included an infectious diseases physician, a pharmacist and representatives from WAPHA (343). Consultation included redirecting specific avenues of enquiry, potential explanations to explore and the provision of contextual advice.

3.3 Data source and sample size

De-identified, patient-GP consultation data was obtained from the MedicineInsight program for patients attending enrolled general practices in WA, with at least one GP visit between January 2012 and June 2017, inclusive (168,344,345). The MedicineInsight program was run by the NPS and collects patient-GP-practice level consultation data from 500 consenting general practices nationally, including over 2,000 GPs and over 2 million patients at the time of data access (157,158,168,344,346). The data were found to be reasonably comparable to the patient demographics of national Medicare Benefits Schedule data for 2016 to 2017 (344).

At the time of extraction, there were 74 practices enrolled in WA, with 68% practices in major cities, 14% inner regional, and 11% in outer regional areas, 5% in remote and 2% in very remote areas (34,35). Of these, 52 practices in WA had data available for the entirety of the study period.

These data included the date of consultation, prescriptions issued at each consultation, free-text reason for visit / presentation, one or multiple free-text diagnoses entered at each consultation, pathology and radiology results, and clinical observations made by the GP during the consultation. Key patient characteristics were also collected, including age, Indigenous status, allergy status and information, smoking status and various indicators of socioeconomic status (including government pension status, healthcare concession status and veteran status). MedicineInsight also created algorithms for patient comorbid conditions, resulting in a dichotomous indicator of whether the patient

ever had a history of various comorbid conditions based on consultation, pathology and diagnostic information (168,345).

Patient-related datasets were comorbid conditions, allergy information, diagnoses, encounters, prescriptions, atomical and non-atomical pathology, observation files. The patient characteristics dataset contained year of birth and age, residential rurality based on Accessibility / Remoteness Index of Australia, Aboriginal and Torres Strait Islander status, smoking status, and indicators of SES including Socio-Economic Indexes for Areas (SEIFA), an Index of Relative Socio-Economic Disadvantage using postcode of residence, pension status, government concession status and veteran status (34-37). The patient comorbid condition dataset consisted of binary dichotomous variables indicating whether the patient has a history of ever having each of the following: cardiovascular disease, heart failure, atrial fibrillation, stroke, transient ischaemic attack, asthma, chronic pulmonary obstructive disease, cancer, chronic liver disease, chronic kidney disease, mental health problems and substance abuse (see **Appendix B.4.10** for more details). The prescription dataset provided 40 million prescriptions, as well as the dosage, frequency, duration and date of the prescription.

The separate datasets were linked prior to analysis. Each patient has a unique de-identified patient ID, and these patient data are linked within but not across practices. As a result of this, an individual patient who happened to attend multiple MedicineInsight-participating practices during the period would appear in the data as several different patients. There are also repeated visits within the same practice in the data: the same individual patient seeing the same individual provider multiple times, as well as the same patient seeing different providers at the same practice, and the fact that the same provider consults multiple different patients within a single practice. Each GP / provider and each practice also has a unique de-identified ID to allow for linking of records (patient ID, provider ID and practice ID, respectively).

3.4 Data cleaning and preparation

3.4.1 Diagnoses

The presenting conditions of interest were: URTI (consisting of rhinosinusitis, the common cold, influenza / ILI, sore throat, tonsillitis, pharyngitis, AOM) and UTI (consisting of acute cystitis).

The initial diagnoses file received included 1,557,387 observations, with 275,880 different diagnoses. Removing impossible/erroneous dates and missing or blank diagnoses resulted in 1,489,540 observations. As detailed below, to explore prescribing for patients with acute URTI and UTI, patients were filtered by the free-text string entered by GP in the diagnosis field. Frequency tables were created for diagnostic terms used, and relevant key words were collated and refined for conditions of interest. These keywords were used as search terms within the original datasets to create datasets containing conditions of interest, which were subsequently matched with antibiotic prescriptions for the same patient, provider and practice occurring on the same date as the diagnosis.

In the dataset received, patient diagnosis was predominantly entered and coded using the International Classification of Diseases (10th edition) or the International Classification of Primary Care (347,348), which translate across to specific diagnostic conditions listed in national antibiotic prescribing guidelines, or the Therapeutic Guidelines: Antibiotic (the guidelines) (29). However, the diagnosis field in general practice software was typically a free-text entry completed by the GP. As a result, there was usually substantially more variation in the diagnoses received from general practice than ideal, requiring significant cleaning and grouping of relevant diagnoses to form useful datasets. **Figure 3-2** below is a snapshot of some diagnoses within the original dataset and potentially relevant to acute otitis media (AOM) prior to refinement into appropriate, final search terms. Please note that the diagnoses included in this research always refer to acute infections, even if the term acute is not always mentioned.

Character string functions were used to search and refine datasets containing relevant search terms for each condition. This process included removal of irrelevant terms, allowance for acronyms, spelling mistakes, spelling variations and punctuation. For conditions where empirical prescribing is appropriate, first-line antibiotics should be tried at the initial visit before trying non-first-line options. Whereas if empirical prescribing is not recommended for a condition, it may be appropriate to prescribe for an ongoing infection at a subsequent consultation. Therefore, accurate analysis requires separation of initial from non-initial presentations. Diagnoses were limited to initial presentations for the episode of infection (295,296), including removing diagnoses within fourteen days of a previous consultation for the same condition group (29). Note that the term diagnoses refers to initial presentations throughout.

OM 60
EFFUSION EAR 35
SECRETORY OTITIS MEDIA 32
ROM 35
OTITIS EXTERNA 19013
OE 5
OE L 1
OE RIGHT EAR L 1
OE WITH CELLULITIS LEFT EAR L 1
OE/ OM WITH ? PERF L 1
OE/OM L 1
BLOCKED EARS 43
OTOMYCOSIS 99
OTITIS MEDIA 31733
OTITIS MEDIA RECURRENT 979
OTITIS EXTERNA RECURRENT 1070
EAR PAIN 1120
OTITIS MEDIA, RECURRENT 606
OTITIS EXTERNA, RECURRENT 692
EARACHE 1133
OTITIS MEDIA, SUPPURATIVE 502
OTITIS MEDIA;ACUTE 503
RIGHT EAR EFFUSION 3
RIGHT EARACHE 3
RIGHT SIDED OTITIS MEDIA 3
SEROUS OTITIS MEDIA 567
OTALGIA 491
BLOCKED EAR 485
GLUE EAR 1180

Figure 3-2: Picture of example list of terms appearing in the diagnosis field relating to ear infection, followed by frequency of their exact occurrence in the dataset

3.4.1.1 Upper respiratory tract infection

The URTI condition group was defined to include uncomplicated, acute URTIs, influenza / ILI, acute rhinosinusitis / common cold, acute pharyngitis and / or tonsillitis, and AOM, in accordance with the guidelines (29). For acute rhinosinusitis, allergic diagnoses were excluded (29). Pharyngitis, laryngitis, and tonsillitis diagnoses were collated and included symptomatic diagnoses of sore throat and throat pain (29). Search terms for AOM focused on otitis media and both otitis externa and chronic suppurative otitis media were excluded (29). Note that influenza / ILI diagnose referred to standalone diagnoses of influenza and/or ILI, and this excluded diagnoses mentioning secondary bacterial infection or lower respiratory tract infection. For more detailed information regarding search terms, please see **Appendix B.2.1**.

3.4.1.2 Urinary tract infection

UTI was defined to include acute cystitis, as per the guidelines, and relevant search terms included UTI, urinary tract infection, acute cystitis, and cystitis (29). Exclusion

criteria included diagnoses with any mention of prostatitis, pyelonephritis, complicated, catheter-related UTI, UTI prophylaxis, or sepsis / septicaemia. For more information regarding search terms, please see **Appendix B.2.2**.

3.4.2 Antibiotic prescriptions

For each condition of interest, patients with at least one presentation for this condition were included in the analysis. From this patient group, patients who were prescribed a systemic antibiotic were identified from a list of antibiotic agents compiled using predominantly MIMS Australia (Integrated or Annual edition) (349). All prescriptions using the medicine active ingredient field were string-searched against the sample list of antibiotics which had been collated. Simple spelling / typographical errors obtained from a list of brand names were allowed for. Antibiotic prescriptions for the URTI and UTI diagnoses groups were then collated into two, separate datasets. Note that the term antibiotics refers to systemic antibiotics throughout.

Anatomical Therapeutic Chemical classification codes were completed and sorted into classes created (350). The string variables for prescription dose, frequency and duration variables were cleaned. For more detailed information, please see **Appendix B.3**.

3.5 Data analysis variables

3.5.1 Response variables

3.5.1.1 Antibiotic prescribing: standard used for assessment

The individual guideline publication covering the largest proportion of 2012 to mid-2017, the 2014 edition, was therefore selected as the standard for assessment for the duration of the study period (29).[1] The unique patient-GP pairing was defined as the unit of observation. Categorical data analysis was used to analyse dichotomous (antibiotic considered necessary for the condition: yes / no), nominal or ordinal variables with three or more categories (for example, choice of antibiotic prescribed: first-line, second-line, or third-line).

[1] For more information regarding differences in published guidelines, please see Appendix A.2.

Although there are multiple ways to define the appropriateness of antibiotic prescribing (259-262,266-268), the following outcomes will be defined to represent different aspects of inappropriate prescribing (see **Figure 3-3**)

0. likely inappropriate decision including non-prescribing – 'inappropriate decision'

1. likely unnecessary antibiotic prescribing – 'unnecessary prescribing'

2. ordered, increasing level of choice of antibiotic prescribed at initial consultation: starting from first-line, second-line, third-line or last resort (where relevant), to not recommended – 'antibiotic choice'

3. prescribing any other antibiotic other than first-line – 'non-first-line prescribing'

4. repeat positive antibiotic prescribing (prescriptions issued with one or more repeats present on the prescription) – 'repeat positive prescribing'.

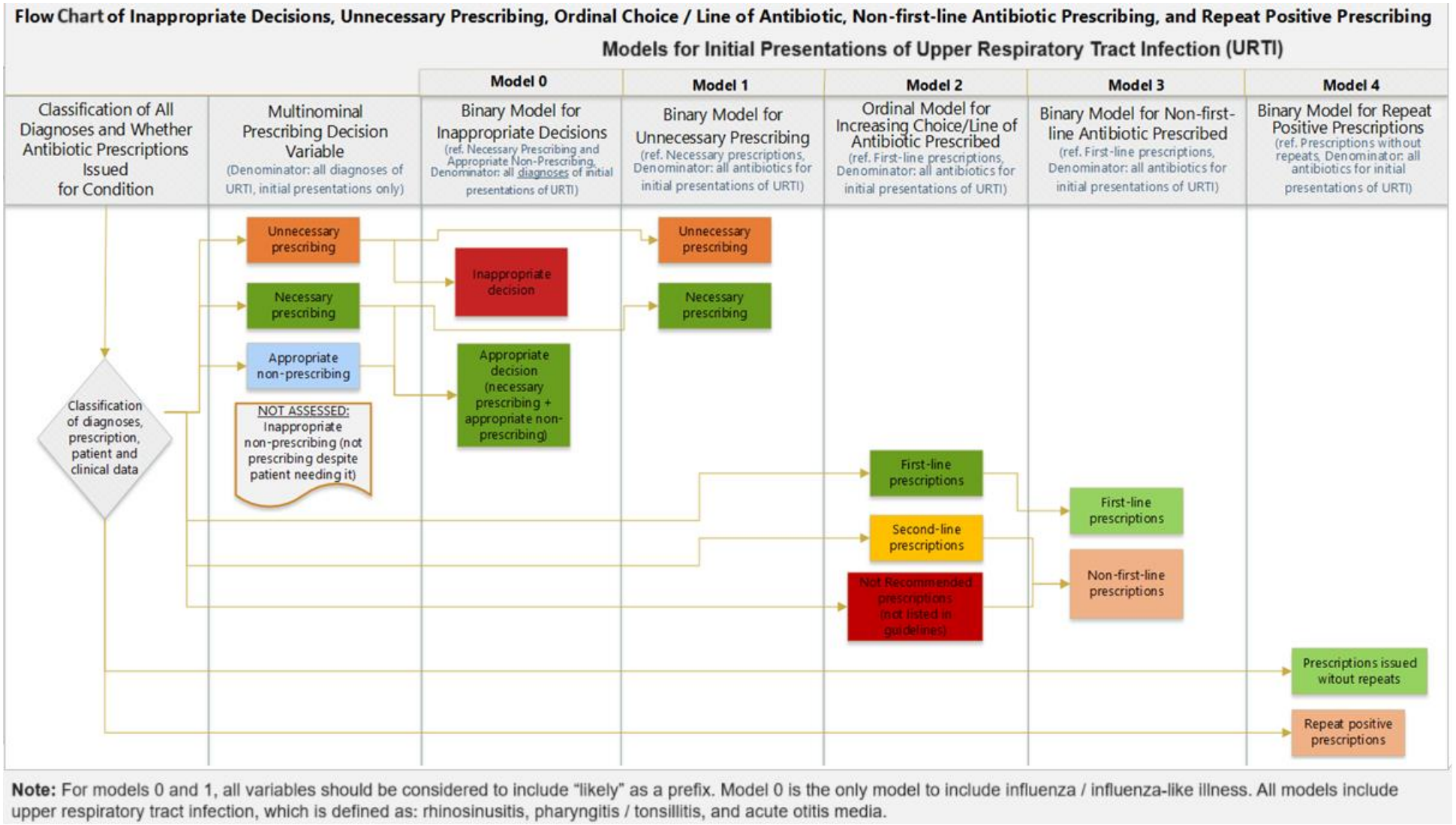
Note that outcomes 0 and 1 will be referred to as inappropriate decision and unnecessary prescribing, respectively, from now on. However, these two outcomes should always be considered to have "likely" as a prefix, as the guidelines cannot cover every situation. There are also situations in which it may be appropriate and necessary to prescribe an antibiotic but this may not be identifiable from the data (29).

Please note that outcomes 0 to 4 are relevant to URTI. As empirical antibiotic prescribing is appropriate for UTI, only outcomes 2 to 4 are relevant for this condition.

A summary of these definitions and the analyses approaches follows. Patients receiving inappropriate decisions (namely, unnecessary prescriptions) were compared with patients receiving appropriate decisions (either necessary prescriptions or appropriately not receiving a prescription) for URTI, with the denominator of all patients with initial presentations of the condition group. Note that there was considered to be insufficient information available to assess patients not receiving antibiotic prescriptions despite truly needing them, which could also be termed 'under-prescribing', and were therefore excluded from the analysis.

Patients receiving unnecessary antibiotic prescriptions were also compared with patients receiving necessary prescriptions for URTI, with the denominator being all patients prescribed an antibiotic for the same condition group.

Figure 3-3: Flow chart of outcome variables for identification of predictors of inappropriate prescribing for initial presentations of upper respiratory tract infection



Note: For models 0 and 1, all variables should be considered to include "likely" as a prefix. Model 0 is the only model to include influenza / influenza-like illness. All models include upper respiratory tract infection, which is defined as: rhinosinusitis, pharyngitis / tonsillitis, and acute otitis media.

Patients receiving increasing choice of antibiotic line for each condition group (URTI or UTI) were compared to patients receiving first-line antibiotics for that group, with the denominator being all patients receiving any antibiotics for that same condition group (URTI or UTI). Patients receiving non-first-line antibiotic were compared to patients receiving first-line antibiotics for a condition, with the denominator being all patients receiving any antibiotic for the same condition group. Patients receiving antibiotic prescriptions with one or more repeats issued on them, when that was technically not required for a guideline-concordant course for the condition, were also compared against patients not receiving a repeat on the prescription. Definitions are covered in detail in the next few sections (3.5.1.2 to 3.5.1.4).

Algorithms were derived from the guidelines for each condition (29), to record the indication / patient criteria (age, gender, demographics and clinical observations obtained during the consultation) required for an antibiotic prescription to have been most likely justified. Although culture and other pathology testing was examined to assess compliance with guideline recommendations, these were not incorporated in the assessment of antibiotic choice, as these would not have been available to the prescriber at the time of the consultation.

Patient symptoms were not always recorded by the GP, and sometimes not all symptom information was available for analysis. However, there were many conditions for which patient demographics alone provide sufficient information to assess prescribing. There were conditions, such as acute pharyngitis / tonsillitis, for which the only reason to prescribe – to prevent serious sequelae, such as, ARF – is uncommon in Australia, except in remote Aboriginal and Torres Strait Islander communities which are not attended by mainstream general practice. Therefore, in affluent / urban situations, there is no valid justification to prescribe an antibiotic for this condition unless the patient has a history of ARF (29,351). Although one cannot assume there were no GPs in areas with cases of ARF, it was considered rare and therefore unlikely (352). While Monaghan et al. (26) noted there were insufficient data to assess the criteria for pharyngitis and therefore assumed criteria were met, the approach here is opposite (important data such as temperature recording should be available in the clinical examination field, and that even in the absence of progress notes, on balance, a genuine indication for prescribing for pharyngitis was unlikely). Each condition was assessed separately during algorithm development as to the potential impact of any unrecorded or missing information and is covered in more detail below.

3.5.1.2 Upper respiratory tract infection: inappropriate decision, unnecessary antibiotic prescribing and ordered choice of antibiotic prescribed

For URTI, among all antibiotic prescriptions issued, a binary 'prescribing status' variable was created for *unnecessary prescribing -versus- necessary prescribing*. Among situations when prescriptions were not issued, *appropriate non-prescribing* was also identified, however, there was insufficient data available to assess not prescribing when a prescription was in fact necessary. An *inappropriate decision* variable was created consisting of *unnecessary prescribing* situations*.* Meanwhile, an *appropriate decision* variable was created to include both *necessary prescribing* and *appropriate non-prescribing.* A binary 'decision' variable included *inappropriate decisions versus appropriate decisions* among all URTI diagnoses.

As can be seen in **Figure 3-4**, note that the numerator was the same for *inappropriate decision and unnecessary prescribing.* However, the denominators differ: all diagnoses of URTI for *inappropriate decision*, and all antibiotic prescriptions for URTI for *unnecessary prescribing.*

Prescribing for acute rhinosinusitis was coded into: *necessary; possibly unnecessary;* and *unnecessary prescribing* using the definition by Jørgensen et al. (268). *Necessary prescribing* was classified as either fever recorded or symptom duration of at least five days. *Unnecessary prescribing* was for symptoms of less than five days and no fever recorded (268). *Possible unnecessary prescribing* was symptoms for less than five days or no fever (268) and these 236 prescriptions were excluded from further analyses.

Prescriptions for acute pharyngitis / tonsillitis were *necessary* in the presence of fever, otherwise *unnecessary prescribing*. As the indicators of Aboriginal and Torres Strait Islander status and RHD were considered unreliable, the 650 diagnoses of pharyngitis / tonsillitis for these patients were excluded from later multivariable analyses. Meanwhile, for AOM, prescribing was considered *necessary* for patients with fever, and for children one year and under (29), with other prescriptions classified as *unnecessary*.

Although the guidelines do not recommend an antibiotic for diagnoses of influenza / ILI (29), antibiotics may however be required in rare instances of secondary, bacterial superinfection. It was therefore of interest for this thesis to establish whether patients with influenza / ILI

diagnoses were receiving antibiotics. These diagnoses were included in the *inappropriate decision* model but not included in the *unnecessary* prescribing model, as these diagnoses would invariably be classified as *unnecessary,* and therefore cannot be modelled. The small number of antibiotic prescriptions for influenza / ILI and *possible unnecessary prescribing* were also excluded from *ordinal choice of antibiotic prescribed*, *binary non-first-line prescribing*, and *repeat positive antibiotic prescribing* models for the same reason (see **Figure 3-5**). A brief summary of definitions is provided in the **Glossary of Model Outcomes and Variables Definitions** for reference when reading later chapters, however, note the glossary does not suffice for reading this Methods chapter in full.

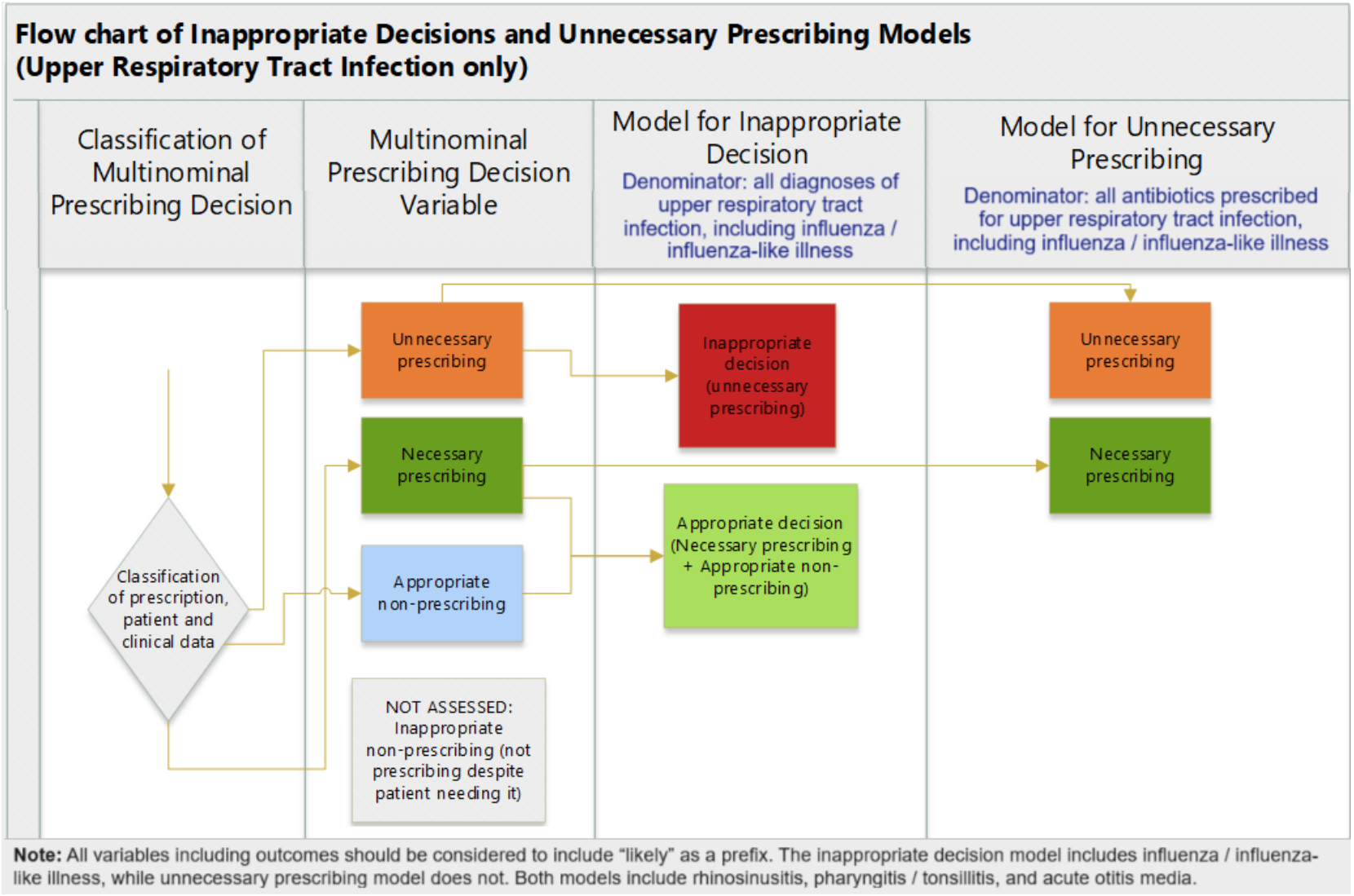


Figure 3-4: Flow chart of inappropriate decisions and unnecessary prescribing models for initial presentations of upper respiratory tract infection

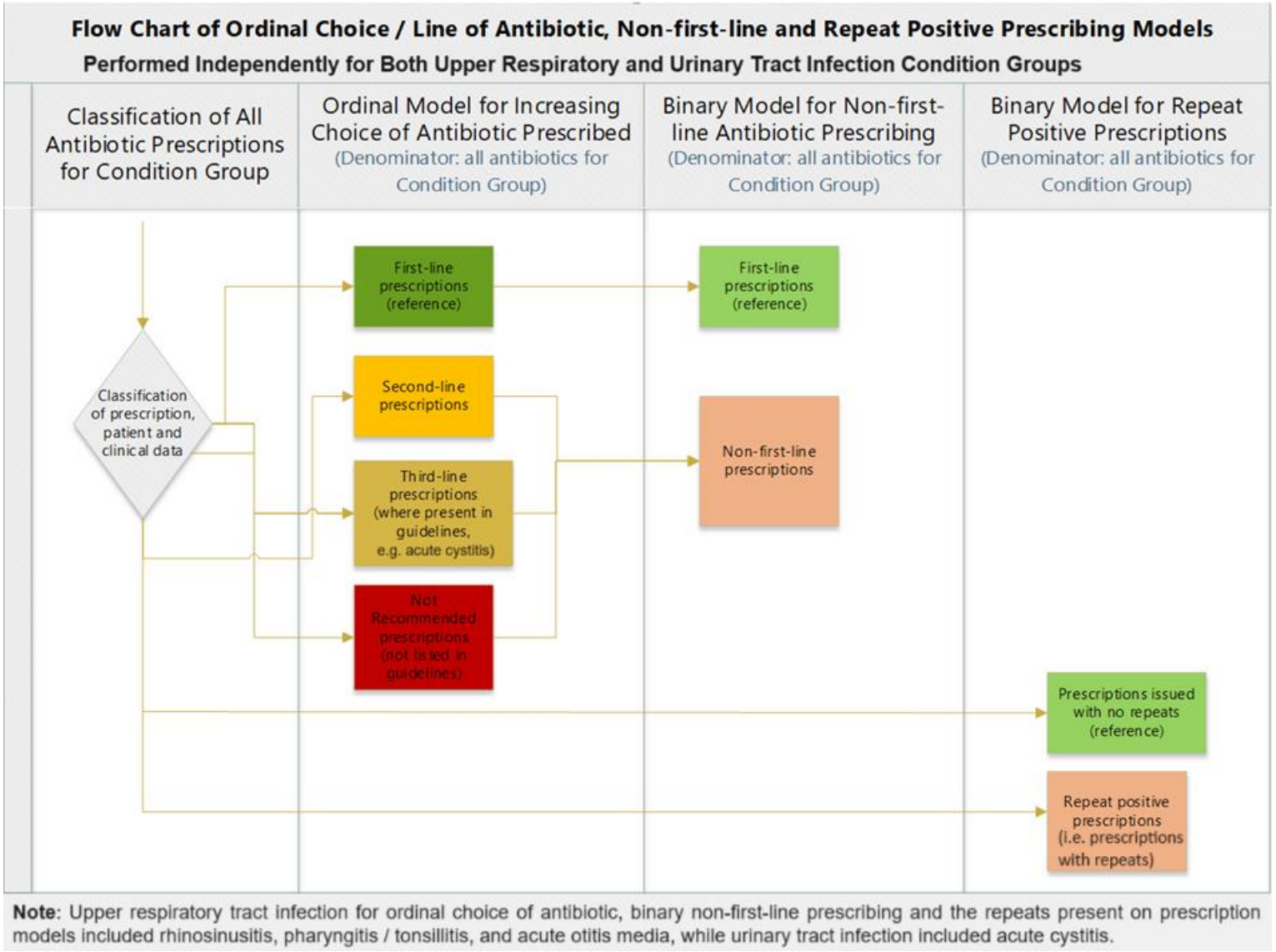


Figure 3-5: Flow chart of response variables and models for ordinal choice of antibiotic prescribed, non-first-line prescribing, and repeat positive antibiotic prescribing for upper respiratory tract infection and urinary tract infection analyses

Table 3-1 details how the guidelines were used to classify individual antibiotics into an ordered variable termed choice, based on order of appearance in the guidelines for each condition (29), with the denominator of all antibiotics prescribed for URTI. Penicillin hypersensitivities were allowed for, and suitable alternative antibiotics were also classified as first-line choices where the patient had an allergy label for penicillin (332). Antibiotics which were prescribed but are not listed in **Table 3-1** were classified as not recommended, as was the use of penicillin hypersensitivity only options despite the patient having no record of a relevant allergy label. A categorical variable was created for the URTI condition from which the diagnosis came.

Table 3-1: Antibiotic classifications for the ordered choice variable for upper respiratory tract infection conditions, based on the order of antibiotics recommended in the Therapeutic Guidelines: Antibiotic (29), by condition

Condition	Line / Choice	No penicillin hypersensitivity	Penicillin non-immediate hypersensitivity	Penicillin immediate hypersensitivity
Acute rhinosinusitis	**First-line**	amoxicillin	cefuroxime	Doxycycline
	Second-line	amoxicillin + clavulanate	doxycycline	
Acute pharyngitis / tonsillitis	**First-line**	phenoxymethylpenicillin	cefalexin	Azithromycin
	Second-line	benzathine penicillin		
Acute otitis media	**First-line**	amoxicillin	cefuroxime	trimethoprim + sulfamethoxazole
	Second-line	amoxicillin + clavulanate	trimethoprim + sulfamethoxazole	

Note: A first-line antibiotic should be prescribed at initial consultations where prescribing is indicated. Where the antibiotic prescribed is not listed as an option for the condition diagnosed, the prescription was classified as 'not recommended'.

3.5.1.3 Urinary tract infection: ordinal choice of antibiotic prescribed

As empirical prescribing is considered appropriate for UTI (29), the focus of this research is on what was prescribed and how closely this matches the guidelines for the specific patient. The choice / line of agent prescribed was coded as ordinal categorical variable according to the guidelines for each patient group: women, men and children (29), with the denominator of all antibiotics prescribed for UTI. Although the guidelines vary for pregnant women, as pregnancy was not easily detected from the data, all adult women were assumed to be non-pregnant. Urine cultures and susceptibility testing are mandatory for children, and recommended for all men and pregnant women but are stated as not mandatory for non-pregnant women with uncomplicated cystitis. A urine culture is required for diagnostic confirmation of the pathogen (115).

Table 3-2 details how the guidelines used in the analysis for classifying individual antibiotic agents into an ordinal choice variable, based on the order of their recommendation in the guidelines for UTI (29), with the denominator of all antibiotics prescribed for UTI. First-line agents included trimethoprim for adults, and either trimethoprim with sulfamethoxazole or trimethoprim for children, and cefalexin as second-line (29). Third-line amoxicillin with clavulanate (or nitrofurantoin for adults), and last resort norfloxacin were combined into a single category when defining the ordinal line of antibiotic agent variable. Quinolones such as norfloxacin are reserved as the last resort and resistance to lower-line options must be confirmed prior to use (29). Antibiotics which were prescribed but are not listed in the guidelines or Table 3-2 were classified as not recommended.

Table 3-2: Antibiotic classifications for the ordered choice variable for acute cystitis, based on the order of antibiotics recommended in Therapeutic Guidelines: Antibiotic (29), by patient group

Choice	Non-pregnant Women	Men	Children >= 1 month
First-line	trimethoprim	trimethoprim	trimethoprim
Second-line	cefalexin	cefalexin	cefalexin
Third-line	amoxicillin + clavulanate	amoxicillin + clavulanate	amoxicillin + clavulanate
Third-line	nitrofurantoin	nitrofurantoin	
Last resort	norfloxacin	Norfloxacin	norfloxacin

Note: A first-line option should be the antibiotic prescribed at initial consultations.
Third-line and last resort options were combined into the third ordinal level for analysis.
Where the antibiotic prescribed is not listed as an option for the condition diagnosed, the prescription was classified as 'not recommended'.

3.5.1.4 Additional response variables common to upper respiratory tract infection and urinary tract infection

Following classification of ordinal line of antibiotic agents for both URTI and UTI condition groups, a binary variable for non-first-line prescribing was also created for each (**Figure 3-5**). Non-first-line was defined to mean all antibiotics other than the first-line recommendations for the relevant condition (or patient group in the case of UTI). Culture and other pathology test results were not incorporated in classifying antibiotic choice, as these would not have been available to the prescriber at the time of the consultation.

A binary dichotomous variable was created for whether one or more repeats were issued on each antibiotic prescription, as a repeat issued without justification can itself be considered

a level of inappropriate prescribing. Descriptive analysis of antibiotics issued with repeats occurred, and individual cefalexin prescriptions were examined to quantify the proportion likely requiring repeats on prescriptions. Due to manufacturing pack size, a repeat may be required for a single guideline-concordant course of cefalexin. Dummy variables for cefalexin, or repeats issued on cefalexin prescriptions, were included where possible.

3.5.2 Predictor / confounder variables

3.5.2.1 Patient-related variables

All patient-related data included an individual patient identifier to enable longitudinal follow-up. Demographic variables included: date of consultations; antibiotics prescribed; reason for presentation; diagnosis (271,276,353); patient age (25,281,283,284,296,316,324,353); sex (39,280,291,294,296,321,326,328,353); and approximate geographic location (270,276). As CALD background status has been found to be a predictor of inappropriate prescribing in a number of US studies (276,295,326), it was considered particularly relevant to consider whether patient Aboriginal and Torres Strait Islander status might have been linked to more or less appropriate prescribing. However, the variable for self-identification of Aboriginal and Torres Strait Islander peoples was found to be poorly recorded (354,355), with positive status recorded in only 0.01% of patients and information missing in 45% of all patients, and was not utilised.

Comorbid condition variables (122,276,281,294,326) were combined into a single if-any variable. However, COPD was not included in the comorbid condition for URTI, as different guidelines exist for patients with this condition (29,270). Similarly, mental health conditions and drug-and-alcohol problems were also combined into a single mental health condition variable. The resulting variables were coded as positive for any history of a relevant condition, negative for none, and a third category for missing data (356). A binary variable was also created for whether the patient had (any history of) an allergy label for penicillin specifically or for other penicillins (289).

Indicators of SES (270,276,295,316) included the SEIFA Index of Relative Socio-Economic Disadvantage quintiles of disadvantage based on postcode, based on census data up to and including 2011 (36,37) and ARIA for patient remoteness (290,294,317,334) based on postcode was used, also based on census data up to and including 2011 (34,35). Two categorical variables for socioeconomically disadvantaged and remote patients were

created as indicators for the top two quintiles (top 40%) of disadvantage and remoteness, respectively, as well as categories for missing data. Another variable was created to flag patient government concession status, and a missing data category. The PHN of the patient's residential address was coded into a variable with a missing data category.

3.5.2.2 Clinical observations and pathology data

Binary variables were created for whether a patient's temperature was recorded during the consultation and whether the temperature reading was indicative of fever (281,332) of at least 37.5C. Logical Observation Identifiers Names and Codes (LOINC) version 2.66 (357,358) aided with interpretation of pathology testing performed. Binary pathology variables were subsequently created for whether-or-not culture testing, and sensitivity testing were performed. For UTI, binary variables were created for whether any form of urine dipstick testing (blood, nitrites, or leucocyte esterase) was recorded for the patient.

3.5.2.3 Consultation-related variables

Consultation-related variables received included the duration of consultation (short, standard and long consultations), whether the consultation was outside of normal business hours, and if the consultation was bulk-billed. However, duration of consultation and time of consultation were found to be unreliable. Day-of-the-week of the consultation was included, as was a variable identifying a weekend (359). The binary variable for whether the reason for prescribing field had been completed by the GP, was also considered as a potential predictor variable.

3.5.2.4 Practice-related variables

Practice-related variables included PHN (42), SEIFA (36,37) and ARIA (34,35) of the practice. A binary dichotomous variable was also created for small practices *versus* larger practices (an average of 5-14 providers working simultaneously) (271,294).

3.6 Analytical methods

3.6.1 Predictors of inappropriate antibiotic prescribing

Exploratory data analyses were undertaken, which alongside the relevant previous literature, help identify the most appropriate choice of predictor variables. STATA release 16 was used for analysis (360).

The data structure for modelling purposes was potentially very complicated, with patients within providers within practice clusters. Moreover, there are also repeat visits at the individual patient to individual provider level, (as well as repeated individual patients seen by multiple different providers), in addition to repeated visits at the provider-practice level. As a result, the assumption of independence across observational units is very likely to be violated (361,362) and therefore must be taken into account in estimation. Indeed, due to this dependence (and three-level hierarchical structure), standard multivariable logistic regression was not deemed appropriate. Instead, a three-level *random-effects* logistic hierarchical model was considered ideal to allow for *unobserved heterogeneity* (363) at each level, including for example repeated measures.

Although different terminology exists across various disciplines, note that we used the terms: *fixed-effects models* for when *unobserved heterogeneity* is treated as fixed (essentially including dummy variables for them), while *random-effects models* treat the *unobserved heterogeneity* as random effects (364). *Mixed-effects* refers to the combination of the two. *Mixed-effects* logistic regression modelling (*generalised linear mixed modelling* with random effects) was used to systematically identify the variables associated with several different definitions of appropriate antibiotic prescribing.[2,3] As antibiotic prescribing may be seasonal, and is certainly for URTI (366-368), and as prescribing behaviours may change over time, both seasonal dummy variables and time effects were also allowed for.

Much of the existing literature does not appear to use, or allow for, multiple types or levels of *unobserved heterogeneity*, such as (simultaneously) at the patient, GP, and practice levels (22,48,276,277,281,286,295,296,315,323,325,326,329,330,332,340-342). This is potentially important, as, on the assumption that there are multiple observations at potentially each level, then if there is indeed *unobserved heterogeneity* at these levels, and this is ignored in estimation, then spurious results are likely to follow. This is simply a result of the fact that an incorrect, or mis-specified, likelihood is being maximised. For example, the independence of observations is an assumption underlying generalised linear models used (361,362); however, many authors do not allow for repeated measures such as

[2] Although the intention for all models was to include both *random intercepts* and *random coefficient* / slope at each level, due to convergence issues, it was only possible to include the former. Where both practice and provider levels could not be accounted for, a random intercept for the unique combination of practice and provider was included (365).

[3] While random intercepts for practice-related variables, namely practice size, were intended for inclusion at the practice level, this was not feasible due to effect size so small that CIs were unable to be calculated, so were therefore included at the patient level instead of practice level.

multiple visits by the same patient, consultations by the same GP or at the practice level. Clearly, once these effects have been allowed for, the approach explicitly allows for dependence across these factors, such that conditional on these, the observations are now, indeed, independent as the approach explicitly requires. Although highly complex and computer-intensive, fortunately recent improvements in computing power have made the allowance for / of such unobserved heterogeneity at multiple levels more feasible. Accordingly, this thesis allows for multiple levels of unobserved heterogeneity, which should significantly reduce the likelihood of any estimation bias resulting for erroneous omission of such.

Some other studies have used mixed models with random effects (284,294,297,321,326,328,363,369-372), however, it is unclear how many types or levels of unobserved heterogeneity were allowed for. Some authors used random effects to allow for clustering at the individual patient-level only (294,363) or the clinician level only (372). Some studies used generalised estimating equations to allow for 'clustering' (270,274,276,280,373), however, typically did not allow for the practice level. Poisson regression models were also utilised by some authors (271,374). Some studies used fixed effects only but added GPs as clusters in the model (276,322), which does not rectify for ignoring unobserved heterogeneity. The method used in this thesis controlled directly for a wide range of unobserved effects simultaneously, including at the GP and practice levels, and therefore provides a more nuanced approach.

As described by Stroup (375), generalised linear mixed models are of the form described below in **Figure 3-6**, where **y | b** is the distribution of the data or observations, **y**, conditional on the random effects, **b**. Furthermore, **μ** and **R** are the mean and variance of the population, respectively. Despite the added complexity, there was sufficient variation in the data, and enough degrees of freedom, to adequately identify all these random components in a model. Subject to the nature of the dependent model, both ordinal and binary multilevel random effects models were considered.

A brief summary of statistical terminology is also provided in the **Glossary of Multilevel Mixed-effects Modeling Terminology**. However, this glossary does not suffice for reading this chapter in full.

Observations	Link	Linear Predictor	Mean Modeled by[a]
$\mathbf{y} \mid \mathbf{b} \sim G(\boldsymbol{\mu}, \mathbf{R})$ G denotes general distribution	$\boldsymbol{\eta} = g(\boldsymbol{\mu} \mid \mathbf{b})$	$\mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{b}$ $\mathbf{b} \sim N(\mathbf{0}, \mathbf{G})$	$\hat{\boldsymbol{\mu}} = h\left(\hat{\boldsymbol{\eta}}\right)$ $= h\left(\mathbf{X}\hat{\boldsymbol{\beta}} + \mathbf{Z}\hat{\mathbf{b}}\right)$

[a] $h(\boldsymbol{\eta})$ denotes *inverse link* function, for example, $h(\boldsymbol{\eta}) = e^{\eta}/(1+e^{\eta})$ for logit link.

Figure 3-6: Illustration of the form of the generalised linear mixed model, using direct quotation from Stroup WW. Generalized linear mixed models: modern concepts, methods and applications. 1st ed. Boca Raton, FL: CRC Press, an imprint of Taylor and Francis; 2012. Table 1.4, Typology of Linear Models; p. 20. (375)

The denominator for all models common to URTI / UTI was all systemic antibiotic prescriptions for each respective condition group: URTI or UTI. However, note for all URTI models, possibly unnecessary prescriptions were excluded, as were situations where antibiotics were indicated but not prescribed. Antibiotics prescribed for influenza / ILI were included only in the inappropriate decision model for URTI (**Figure 3-5**). Due to small sample sizes, the denominator of all antibiotics prescribed for URTI (for both necessary and unnecessary prescribing) was chosen. A flow chart of models common to URTI and UTI is provided in **Figure 3-6** [4] .

A range of specifications were experimented with, including allowing for interactions between such variables as patient age and gender. Final model specifications followed multiple specification and model selection tests and metrics, including likelihood ratio tests for joint (in)significance and Akaike Information Criterion, and to a greater extent, Bayesian Information Criteria (376,377). Brant testing of the parallel regression assumption was also performed for ordinal models to establish whether antibiotic lines can be considered equidistant (378,379).

While the primary aim of the modelling was essentially to most accurately identify / estimate the predictor coefficients, a secondary aim was to interpret the final models to allocate the source of variance unexplained by fixed effects (380,381). This involved calculating the intraclass correlation (ICC) to determine how much variation unexplained by fixed effects, each level in the model was responsible for (380-382). This specifically related to between-level ICC for calculating the variation explained by random effects at each of the provider and practice levels, for comparison. Where the data was unsuited to a three-level model,

[4] For information regarding the variables included in each base model, please see Appendix B.6.4.

two-level models with patient level and either the practice or the provider level were used to calculate ICC, and then compared to give an approximate estimation of the difference in source of variance explained by random effects between each level.

Due to the nature of the multilevel model, one cannot interpret effects directly from adjusted odds ratios (AORs) appearing in the final model, as one would do in a single-level model, as the effect may vary across members of higher-levels in the model (383). Although there are multiple approaches to the estimation of various effects in multilevel models, *average marginal effects* (AMEs) were predominantly used for ease of exposition. *Marginal effects at representative values* (MERs) were calculated between covariates but are only presented in text to illustrate effect modifications identified. *Adjusted predictions at the means* (with all other covariates held constant at sample means) and *marginal predicted mean* were also used. MERs were compared to AMEs with limited notable difference identified.[5] For information regarding these values, please see the **Glossary of Multilevel Mixed-effects Modeling Terminology**.

3.6.2 Trends in inappropriate antibiotic prescribing

Having identified predictors of inappropriate prescribing at an individual level, are there aggregate trends over time for URTI and UTI (384-389). All prescribing-related outcomes were analysed, firstly, for all URTI or UTI diagnoses altogether, then for each URTI condition individually, and for UTI by each patient group (**Figure 3-7**).

For each outcome within each sub-population of interest, rates were calculated as aggregate count data over units of time (weekly, fortnightly, monthly, quarterly, half-yearly). The denominators remained the same as in previous predictor identification analyses, please see **Appendix B.7** for more details. Graphical depictions of outcomes as rates were examined and compared using different units of time. The most appropriate unit of time was then selected, using a trade-off between “noise” and the number of data points, resulting in monthly mean rates for all trends analyses (390).

[5] Please see the Appendix to each (URTI/UTI) predictors chapter. Full results are also available on request.

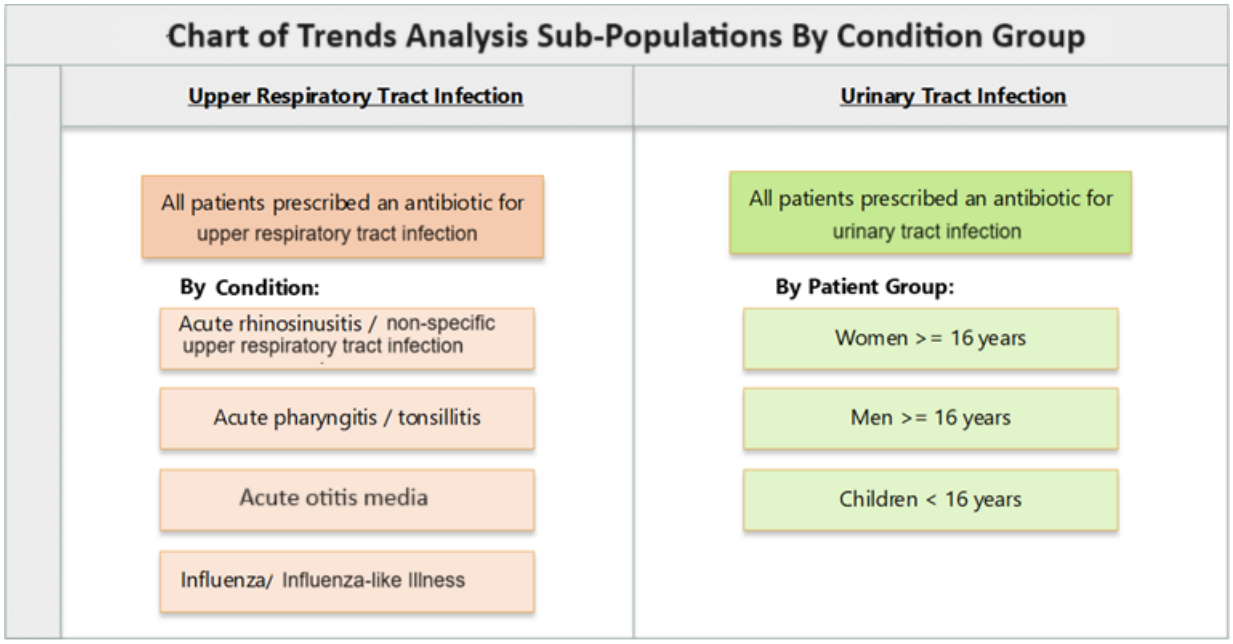


Figure 3-7: Groups of interest in trends analyses for upper respiratory tract infection, including influenza / influenza-like illness and urinary tract infection, by condition group

For the purposes of basic smoothing and to eliminate any seasonal effects, a simple moving average was utilised (391). Different time windows were experimented with these, and invariably simply graphical depiction was used to select what was deemed the most appropriate. A six-monthly simple moving average was tested initially, being half the twelve-month time period in use (392). Among several others tried, a five-monthly time period was finally selected as this was not noticeably different from six-monthly but with slightly less noise. This use of predicted values obtained from moving average smoothing reduces the possibility of distortion using of end points only, which may be extreme and not be representative of the entire sample. There were many outcomes analysed for URTI and UTI, as well as for each URTI condition and each UTI patient group independently, as well as individual antibiotics use for each condition. Only the most notable trends identified are presented for each condition, such as major outcomes of non-first-line or second-line prescribing, and interesting trends in the prescribing of individual antibiotics. Additional results are presented in the appendix to each trends chapter.

The graphical depiction of the final smoothed, moving average outcome rates for each outcome within each sub-population followed. Fitted lines, 95% confidence intervals (CIs), and Lowess rates were added to the smoothed rates (393-396), as seen in **Figure 3-8** below, which is included purely as an example.

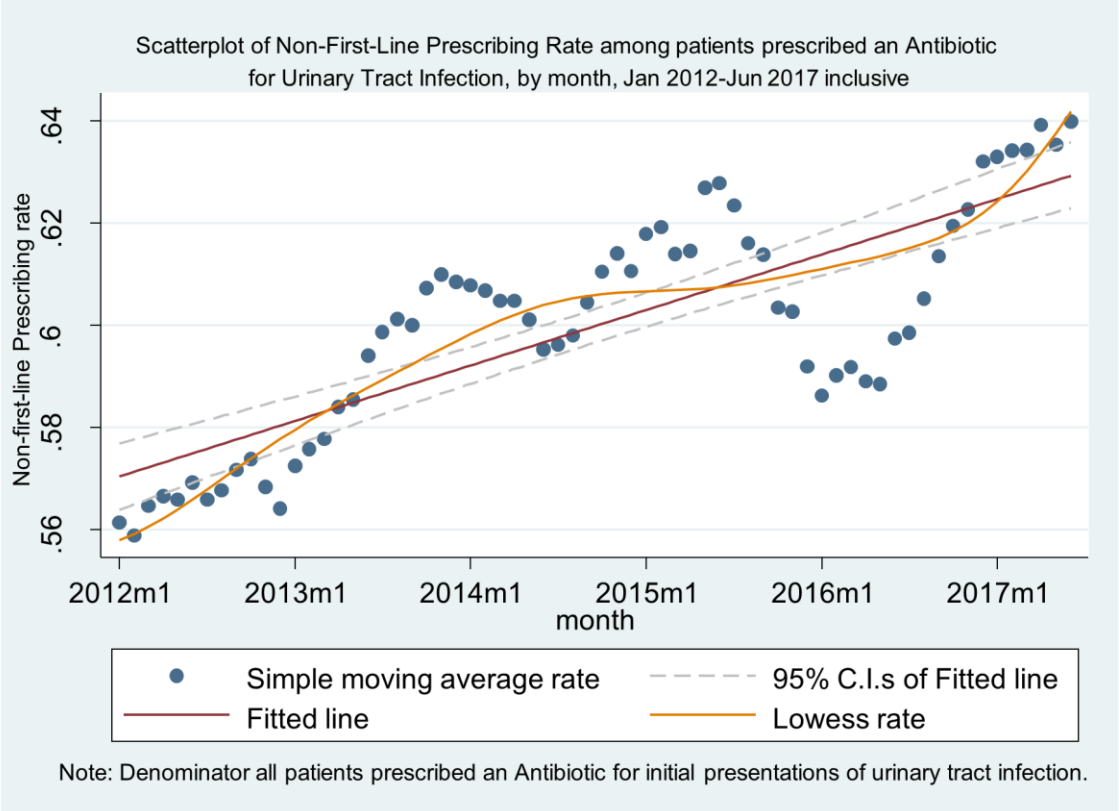


Figure 3-8: Example simple moving average of outcome rate, with fitted lines, 95% confidence intervals, and Lowess rates

Simple linear regression was then used to test for a significant trend (330,397,398). As URTIs are subject to seasonal variation (366,367), influenza notifications from WA were incorporated into the linear regression models to check for any remaining seasonal effects following the smoothing process (399). An insignificant influenza season result would imply that the smoothing technique was sufficient, and *vice versa*.

The mean rate over study period was then calculated for each outcome using the smoothed moving averaged data. The difference between the first and last predicted values over the study period formed the basis of the estimated percentage change.

3.7 Synthesise findings

The synthesis of findings involved interpretation of results obtained, in discussion with the steering committee, with careful consideration of the complex, multifaceted situations in which antibiotic prescribing occurs. This helps provide context to, and a more comprehensive understanding of, the results.

The methodological development of this research has also aided in the identification of further avenues for study. The evaluation of the relative strengths and weaknesses of various methods employed was also undertaken wherever possible, such as comparison with the results from studies utilising other methods.

CHAPTER 4 PREDICTORS OF INAPPROPRIATE PRESCRIBING FOR UPPER RESPIRATORY TRACT INFECTION

4.1 Introduction

URTI encompasses several common conditions for which inappropriate antibiotic prescribing is known to occur (14,17,18,87), due in part to their frequent viral aetiology. URTI is also responsible for the most antibiotic utilization of any condition group commonly presenting in primary care (75). URTI was therefore a key focus area of this project. The national guidelines titled, Therapeutic Guidelines: Antibiotic (the guidelines), were developed to recommend effective antibiotics, minimise antibiotic resistance and limit side effects (29). Reducing unnecessary use of antibiotics for URTI is considered crucial to managing the spread of antibiotic resistance (6,13,16,49) and improving quality of care.

The aim of this chapter was to quantify the prescribing of guideline non-conforming systemic antibiotics in Australian general practice for patients presenting with initial episodes of URTI (29). The aim was also to elucidate patient-, practice- or consultation- related predictors of inappropriate antibiotic prescribing for patients presenting with URTI. The focus was on assessing any association of inappropriate prescribing with patient age, patient comorbid conditions, and practice remoteness / accessibility. This inherently involved the identification of inappropriate prescribing for patients presenting for initial episodes of care for URTI. As detailed in the Background chapter, the guideline advice on diagnosis, treatment, indications for prescribing, and recommended antibiotics, differs by URTI condition (29). Assessing compliance with the guidelines can help provide new insights and identify opportunities for interventions and policy.

4.2 Specific methods

A multinominal categorical variable was created for prescribing-related decisions including: unnecessary prescriptions, necessary prescriptions, and appropriate non-prescribing. It was considered that there were insufficient data to assess under-prescribing when a prescription may have been necessary. Splitting the above variables by appropriate / necessary and inappropriate / unnecessary, a binary dichotomous variable was created for inappropriate versus appropriate decisions (**Figure 4-1**). A binary dichotomous variable was also created

referred to as the prescribing status variable. A discrete categorical variable was created to indicate which URTI condition the diagnosis related to.

The standard used for assessment of prescribing was version 15 of the guidelines (29). As explained in chapter 3, prescribing for acute rhinosinusitis / non-specific URTI was coded into: necessary, possibly unnecessary, and unnecessary prescriptions using definitions by Jørgensen et al. (268). If fever was present or symptoms had lasted at least five days (using diagnosis onset date) prescribing was considered to be likely necessary (268). If symptoms were present and symptoms lasted at least five days and no fever was recorded, prescribing was considered to be unnecessary (268). Possibly unnecessary prescribing was classified as symptom duration of less than five days or no fever (268), and was excluded from multivariable analyses (see **Methods chapter**). Prescriptions for acute pharyngitis / tonsillitis were considered necessary in the presence of fever, otherwise they were considered unnecessary. As the indicators of Aboriginal and Torres Strait Islander status and RHD were considered unreliable, decisions for acute pharyngitis / tonsillitis provided to Aboriginal and Torres Strait Islander peoples and patients with RHD were excluded from multivariable analyses. It was considered appropriate to prescribe for AOM for children one year or under, or those with fever recorded.

The choice of antibiotic prescribed was coded as an ordinal categorical variable according to the guidelines: including first-line, second-line and not recommended antibiotics (29). First-line agents included amoxicillin, phenoxymethylpenicillin, and amoxicillin, for acute rhinosinusitis, acute pharyngitis / tonsillitis and AOM, respectively (**Table 4-1**) (29). Penicillin sensitivity was allowed for, such that use of a suitable agent in a patient with an allergy label for penicillin was recorded as first-line. Antibiotics prescribed for each increasing choice were compared to first-line prescriptions, with the denominator of all antibiotics prescribed for URTI. A binary variable for non-first-line prescribing was also created, defined as all non-first-line agents.

A binary dichotomous variable was created for whether one or more repeats were issued on the antibiotic prescription, as issuing a repeat without indication can be considered a level of inappropriate prescribing. Individual cefalexin prescriptions were assessed by strength, dosage and duration to identify prescriptions requiring a repeat.

Table 4-1: Choice of antibiotic for upper respiratory tract infection conditions, by condition, and by patient allergy label for penicillin, based on the order of recommendations and penicillin hypersensitivity options listed within Therapeutic Guidelines: Antibiotic (29)

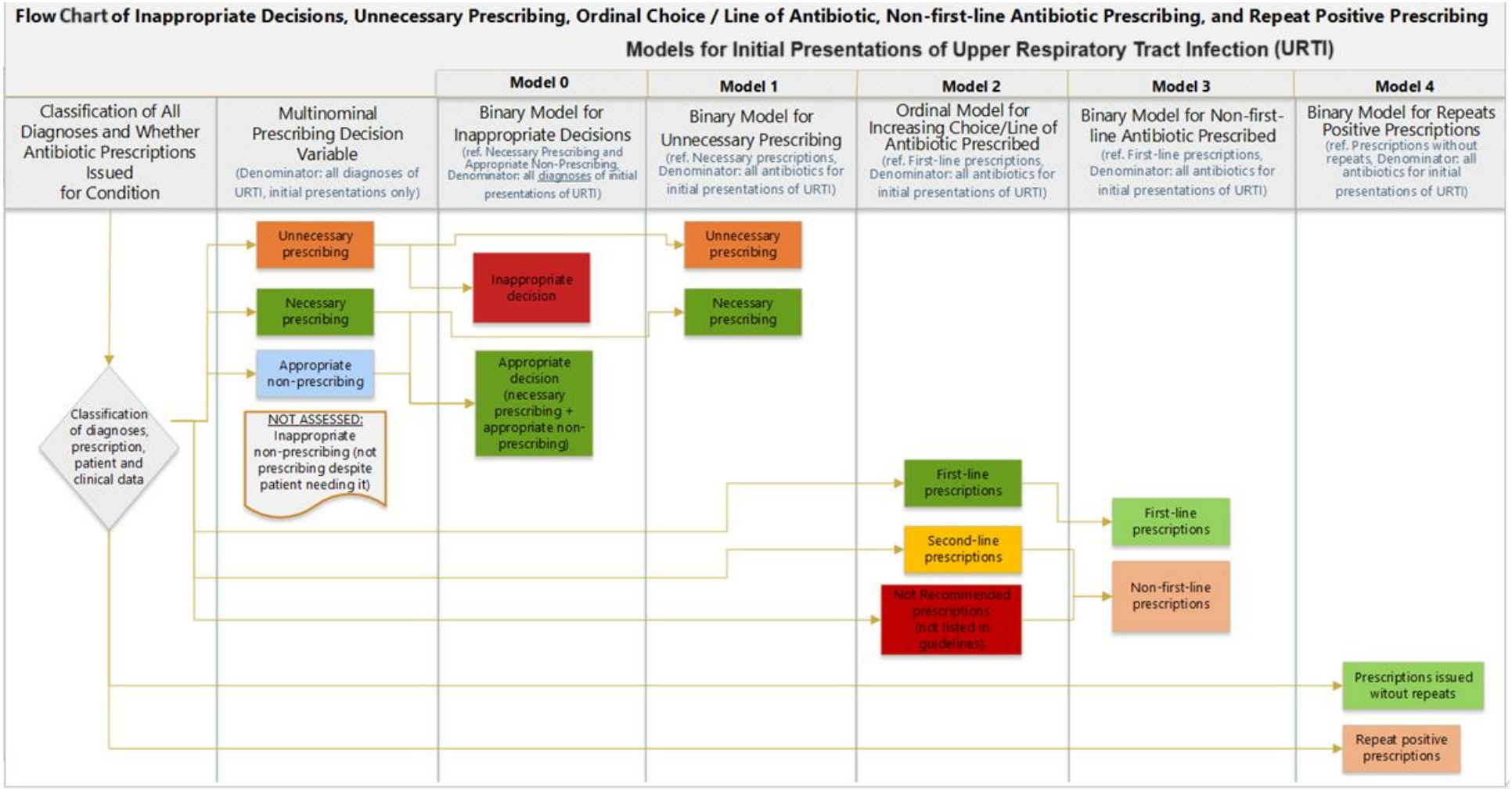
Condition	Line / Choice	No penicillin hypersensitivity	Penicillin non-immediate hypersensitivity	Penicillin immediate hypersensitivity
Acute rhinosinusitis	**First-line**	amoxicillin	cefuroxime	doxycycline
	Second-line	amoxicillin + clavulanate	doxycycline	
Acute pharyngitis / tonsillitis	**First-line**	phenoxymethylpenicillin	cefalexin	azithromycin
	Second-line	benzathine penicillin		
Acute otitis media	**First-line**	amoxicillin	cefuroxime	trimethoprim + sulfamethoxazole
	Second-line	amoxicillin + clavulanate	trimethoprim + sulfamethoxazole	

Note: A first-line antibiotic should be prescribed at initial consultations where prescribing is indicated. Where the antibiotic prescribed is not listed as an option for the condition diagnosed, the prescription was classified as 'not recommended'.
For more information, please refer to the Methods chapter.

Mixed-effects logistic regression modelling (generalised linear mixed modelling with random effects) was utilised to identify variables associated with inappropriate decisions, unnecessary antibiotic prescribing, increasing choice / order of antibiotic prescribed, non-first-line prescribing, and repeat prescribing (**Figure 4-1**). The model for inappropriate decisions versus likely appropriate decisions, with the denominator being all diagnoses of URTI including influenza / ILI, is presented as Model 0. Model 1 is unnecessary prescriptions versus necessary prescriptions, with denominator of all systemic antibiotic prescriptions for URTI excluding influenza / ILI. The model for the outcome of ordinal line of antibiotic agents is then presented as Model 2, with denominator of all systemic antibiotic prescriptions for URTI excluding influenza / ILI. Additional modelling was performed including but not limited to mixed effects logistic regression for non-first-line prescribing (Model 3, **Appendix C.8**), and repeats being issued on antibiotic prescriptions (Model 4, **Appendix C.9**). [6]

[6] For more information, please refer to the Methods chapter (Chapter 3).

Figure 4-1: Flow chart of variables, numerators and denominators used in models for initial presentations of upper respiratory tract infection



Note: For models 0 and 1, all variables should be considered to include "likely" as a prefix. Model 0 is the only model to include influenza / influenza-like illness. All models include upper respiratory tract infection, which is defined as: rhinosinusitis, pharyngitis / tonsillitis, and acute otitis media.

By encompassing random effects, this allowed for multiple visits by the same patient, and multiple consultations with or without prescriptions by the same GP / provider. The intention was to develop three-level hierarchical models with patient, provider and practice levels. Due to the clustering / non-independence of observations, random intercepts were included, where possible, for both practice ID and provider ID.

As the guidelines never recommended prescribing an antibiotic for a standalone diagnosis of influenza / ILI (29), antibiotic prescriptions for influenza / ILI were not included in the models for unnecessary prescribing, ordinal choice, non-first-line prescribing or repeat positive prescribing. Diagnoses for influenza / ILI were included in the model for inappropriate decisions, however. Possibly unnecessary prescriptions and prescriptions for influenza / ILI were excluded from the ordinal line of agent and binary non-first-line prescribing models.

4.3 Results

There were 112,734 diagnoses of URTI, for initial consultations, during the study period 1 January 2012 to 30 June 2017, inclusive, with an antibiotic prescribing rate of 46% for these URTI diagnoses (**Table 4-2, Table 4-3**). By patient age, consultations and antibiotic prescribing peaked at five and six years, respectively. Penicillins with extended spectrum represented 28% of all antibiotics prescribed, followed by penicillin combinations (23%), beta-lactamase sensitive penicillins (20%), macrolides (14%), and first-generation cephalosporins (11%) (**Table 4-4**, **Appendix C.2**). The reason for prescribing field was completed in 12% of antibiotic prescriptions.

A temperature reading was recorded in 35% consultations, within which 24% of these were indicative of fever of at least 37.5C. While laboratory pathology results were not incorporated in modelling, as they would not have been available at the time of decisions regarding prescribing, a result for culture testing was available in 0.2% (n=272) consultations, and within these, 85% of cultures were positive for growth. There were no results for sensitivity / susceptibility testing available for any initial episodes of care for URTI, despite the availability of results for other diagnoses.

Table 4-2: Frequency table of patient characteristics for all patients, and patients with initial episodes of care for upper respiratory tract infection (column percentage)

	All patients	All visits	Initial care episode URTI	Initial care episode acute rhino-sinusitis	Initial care episode acute pharyngitis / tonsillitis	Initial care episode AOM	Initial care episode influenza / ILI
Characteristic	n=791,280	n=1,925,985	n=112,734	n=62,236	n=28,899	n=19,424	n=2,175
Patient							
Female gender, %	52.8	59.1	54.6	54.3	58.4	50.6	49.6
Mean age, years (s.d.) *	38.1 (22.07)	48.0 (23.69)	25.0 (20.09)	26.8 (21.19)	25.7 (17.33)	17.1 (18.19)	36.2 (18.78)
Patient's Primary Health Network, %							
Country WA	12.9	32.8	18.7	14.9	22.9	24.5	21.8
Perth South	33.1	33.5	45.5	48.1	43.4	40.1	50.1
Perth North	34.8	31.8	33.4	34.8	31.4	32.8	25.6
Interstate	2.2	0.5	0.9	0.8	0.9	0.9	1.1
Missing	1.5	1.3	1.5	1.4	1.5	1.7	1.5
Patient concession status positive, %	34.1	35.6	17.1	17.1	16.8	18.0	13.2
Comorbid condition positive, %	1.9	10.2	15.4	16.0	14.8	14.1	17.7
Missing	3.4	2.5	3.3	4.2	2.3	2.2	3.7
Mental health condition positive, %	12.9	28.7	12.3	12.5	14.5	7.8	18.5
Missing	3.4	2.5	3.3	4.1	2.3	2.2	3.7
Patient remote, % (remote & very remote Australia, ARIA)	6.0	4.4	4.3	3.0	5.8	5.9	5.0
Missing	1.1	1.0	0.6	0.5	0.7	0.7	0.9
Patient disadvantaged, % (top 40 percentiles most disadvantage, SEIFA IRSD)	11.7	10.3	9.5	8.8	10.6	9.7	11.0
Missing	1.5	1.3	12.4	11.6	12.2	15.4	12.9
Penicillin allergy label positive %			5.3	5.4	5.5	4.6	5.6
Multiple URTI episodes, % (same or other URTI condition)			77.0	77.5	76.9	75.0	83.1
Consultation							
Temperature recorded, %, (% of which fever positive >=37.5C)			34.5 (24)	36.6 (19)	34.2 (32)	28.5 (31)	31.3 (47)
Culture performed, %, (% of which positive for growth of any pathogen)			0.2 (34)	0.1 (18)	0.5 (32)	0.2 (85)	0.3 (43)
Sensitivity performed, %			0.0	0.0	0.0	0.0	0.0
Weekend consult, %			10.2	10.3	10.3	10.4	4.8
Prescription & classification							
Prescribing rate, %, (prescriptions over diagnoses)			46.3	32.2	70.9	58.5	11.6
Multinominal prescribing decision, % (denominator of all diagnoses per condition/ condition group) **#** (classification purposes only, see Outcomes)							
Appropriate non-prescribing			52.3	67.8	28.4	34.2	88.4
Necessary prescribing			7.7	3.1	9.1	21.2	0.0
Unnecessary prescribing			39.2	28.7	60.2	44.6	11.6
Excluded (insufficient information)			0.6	0.0	2.3	0.0	0.0
Possibly Unnecessary Prescribing (excluded)			0.2	0.4	0.0	0.0	0.0

	All patients	All visits	Initial care episode URTI	Initial care episode acute rhino-sinusitis	Initial care episode acute pharyngitis / tonsillitis	Initial care episode AOM	Initial care episode influenza / ILI
Characteristic	n=791,280	n=1,925,985	n=112,734	n=62,236	n=28,899	n=19,424	n=2,175
Outcome							
Binary Inappropriate Decision % (denominator of all diagnoses per condition/ condition group) #							
Appropriate decision (numerator: appropriate non-prescribing + necessary prescribing)			60.0	70.9	37.5	55.4	88.4
Inappropriate decision (numerator: Unnecessary prescribing)			39.2	28.7	60.2	44.6	11.6
Excluded total			0.7	0.4	2.3	0.0	0.0

* Note: Patient age was missing for n=10 initial episodes of care for URTI and these observations were excluded from multivariable analyses.

Note: insufficient information was available to assess under-prescribing (not prescribing despite indication).

Table 4-4: Frequency table of active ingredients prescribed for initial presentations of upper respiratory tract infections (denominator all antibiotics including influenza / influenza-like illness)

Active ingredient	Frequency	Percent	Cumulative Percent
Amoxicillin	14,722	28.22	28.22
Amoxicillin with clavulanate	11,843	22.7	50.92
Azithromycin	896	1.72	52.64
Benzathine benzylpenicillin	2	0	52.64
Cefaclor	939	1.8	54.44
Cefalexin	5,701	10.93	65.37
Ceftriaxone	4	0.01	65.38
Cefuroxime	247	0.47	65.85
Ciprofloxacin	108	0.21	66.06
Clarithromycin	1,773	3.4	69.45
Clindamycin	43	0.08	69.54
Dicloxacillin	5	0.01	69.55
Doxycycline	481	0.92	70.47
Erythromycin	1,498	2.87	73.34
Flucloxacillin	105	0.2	73.54
Gentamicin	4	0.01	73.55
Minocycline	25	0.05	73.6
Nitrofurantoin	2	0	73.6
Norfloxacin	4	0.01	73.61
Phenoxymethylpenicillin	9,060	17.37	90.97
Procaine benzylpenicillin (procaine penicillin)	1,156	2.22	93.19
Roxithromycin	3,084	5.91	99.1
Tobramycin	2	0	99.1
Trimethoprim	47	0.09	99.19
Trimethoprim with sulfamethoxazole	420	0.81	100
Total	52,171	100	

Table 4-3: Frequency table of patient, consultation, and prescription characteristics for antibiotic prescriptions issued at initial episodes of care for upper respiratory tract infection, including by condition (column percentage)

	Initial care episode URTI	Antibiotic Prescribed for URTI including influenza / ILI	Antibiotic prescribed for rhinosinusitis	Antibiotic prescribed for pharyngitis / tonsillitis	Antibiotic prescribed for AOM	Antibiotic prescribed for influenza / ILI	No antibiotic prescribed for URTI including influenza/ILI
Characteristic	n=112,734	n=52,171	n=20,064	n= 20,500	n=11,354	n=253	n=60,563
Patient							
Female gender, %	54.6	55.5	55.4	58.2	50.6	54.6	53.9
Mean age, years (s.d.) *	25.0 (20.09)	25.8 (19.81)	31.4 (21.74)	24.8 (16.73)	17.6 (18.12)	35.7 (19.71)	24.4 (20.31)
Patient's Primary Health Network, %							
Country WA	18.7	18.5	12.4	23.7	20.0	14.6	18.9
Perth South	45.5	46.0	47.8	44.1	45.9	60.5	45.1
Perth North	33.4	33.1	37.7	29.8	31.4	23.7	33.7
Interstate	0.9	0.9	1.0	1.0	0.9	0.0	0.8
Missing	1.5	1.5	1.2	1.5	1.8	1.2	1.5
Patient concession status positive, %	17.1	17.3	18.8	16.3	16.7	15.0	17.0
Comorbid condition positive, %	15.4	15.4	17.9	13.8	13.6	20.6	15.4
Missing	3.3	3.9	5.9	2.3	3.1	7.9	2.8
Mental health condition positive, %	12.3	12.8	14.2	13.7	8.2	24.5	11.9
Missing	3.3	3.9	5.9	2.31	3.1	7.9	2.8
Patient remote positive, % (remote & very remote Australia, ARIA)	4.3	4.6	2.2	6.3	5.6	6.7	4.0
Missing	0.6	0.6	0.4	0.6	0.6	0.0	0.6
Patient disadvantaged positive, % (top 40% percentiles of most disadvantage, SEIFA IRSD)	9.5	9.0	6.5	11.2	9.4	10.7	9.8
Missing	12.4	11.8	11.2	11.1	14.0	6.3	13.0
Patient penicillin allergy label positive %	5.3	6.4	7.4	5.8	5.8	12.3	4.3
Multiple URTIs positive patient, %	77.0	77.0	78.5	76.9	74.3	77.9	77.0
Consultation							
Temperature recorded, %, (% of which >=37.5C)	34.5 (8)	34.8 (11)	37.5 (10)	36.0 (13)	27.8 (9)	37.2 (25)	34.2 (18)

	Initial care episode URTI	Antibiotic prescribed for all URTI diagnoses including influenza / ILI	Antibiotic prescribed for rhinosinusitis	Antibiotic prescribed for pharyngitis / tonsillitis	Antibiotic prescribed for AOM	Antibiotic prescribed for influenza / ILI	No antibiotic prescribed for URTI including influenza/ILI
Characteristic	n=112,734	n=52,171	n=20,064	n= 20,500	n=11,354	n=253	n=60,563
Consultation							
Culture performed, %, (% of which had positive growth for any pathogen)	0.2 (34)	0.3 (36)	0.1 (14)	0.6 (34)	0.2 (88)	0.8 (50)	0.2 (31)
Sensitivity performed, %	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Weekend consult, %	10.2	11.4	12.3	10.8	10.9	5.9	9.2
Prescription							
Prescribing rate, %, (prescriptions over diagnoses)		46.3	32.2	70.9	58.5	11.6	
Reason for prescribing recorded, %		5.4	2.0	10.4	9.8	0.1	
Outcomes (denominators :all antibiotics prescribed for specific condition / condition group)							
Unnecessary/necessary prescribing % †							
Likely unnecessary prescribing, %		84.7	89.1	84.9	76.2		
Likely necessary prescribing, %		14.1	9.7	12.8	23.8		
Excluded, %		1.4	1.2	2.3	0.0		
Choice/line of antibiotic prescribed, % †							
First-line, %		39.3	32.4	42.4	46.8		
Second-line, %		17.0	25.2	0.0	32.8		
Not recommended, %		39.4	42.4	57.6	20.6		
Excluded, % (influenza, n=235)		0.5	0.0	0.0	0.0		
Non-first-line antibiotic prescribed, % †							
First-line, %		39.3	32.4	42.4	46.8		
Non-first-line (non-first-line), %		60.2	67.6	57.6	53.2		
Excluded, % (influenza, n=235)		0.5	0.0	0.0	0.0		
Repeat(s) issued on prescription, % †							
Positive for one or more repeats		32.3	36.0	25.9	37.3		*
Negative (no repeats on prescription)		67.7	64.0	74.1	62.7		
Excluded, % (influenza, n=235)		0.5	0.0	0.0	0.0		

Note: Patient age was missing for n=10 initial episodes of care for URTI and these observations were excluded from multivariable analyses.

† Note: As antibiotics are not recommended for standalone diagnoses of influenza/ILI, prescriptions for this were excluded from models for these outcomes.

Inappropriate decisions (i.e. unnecessary prescribing) occurred in 39% situations of the total 112,734 URTI diagnoses, compared to 61% of appropriate decisions (comprising both appropriate non-prescribing and appropriate prescribing situations). Pharyngitis had the highest proportion of inappropriate decisions (60%), followed by AOM (45%), rhinosinusitis (29%) and influenza / ILI (12%). Pharyngitis also had the lowest rate of appropriate non-prescribing (28%), followed by AOM (34%), rhinosinusitis (68%), and influenza / ILI had the highest (88%), as seen in **Figure 4-2**. Children 0-8 years had lower proportions of inappropriate decisions (29%) than other age groups, which increased by age group, ranging from 39% for 9-21 years to 45% for patients 35 years and over (**Appendix C.2: Table C-2**).

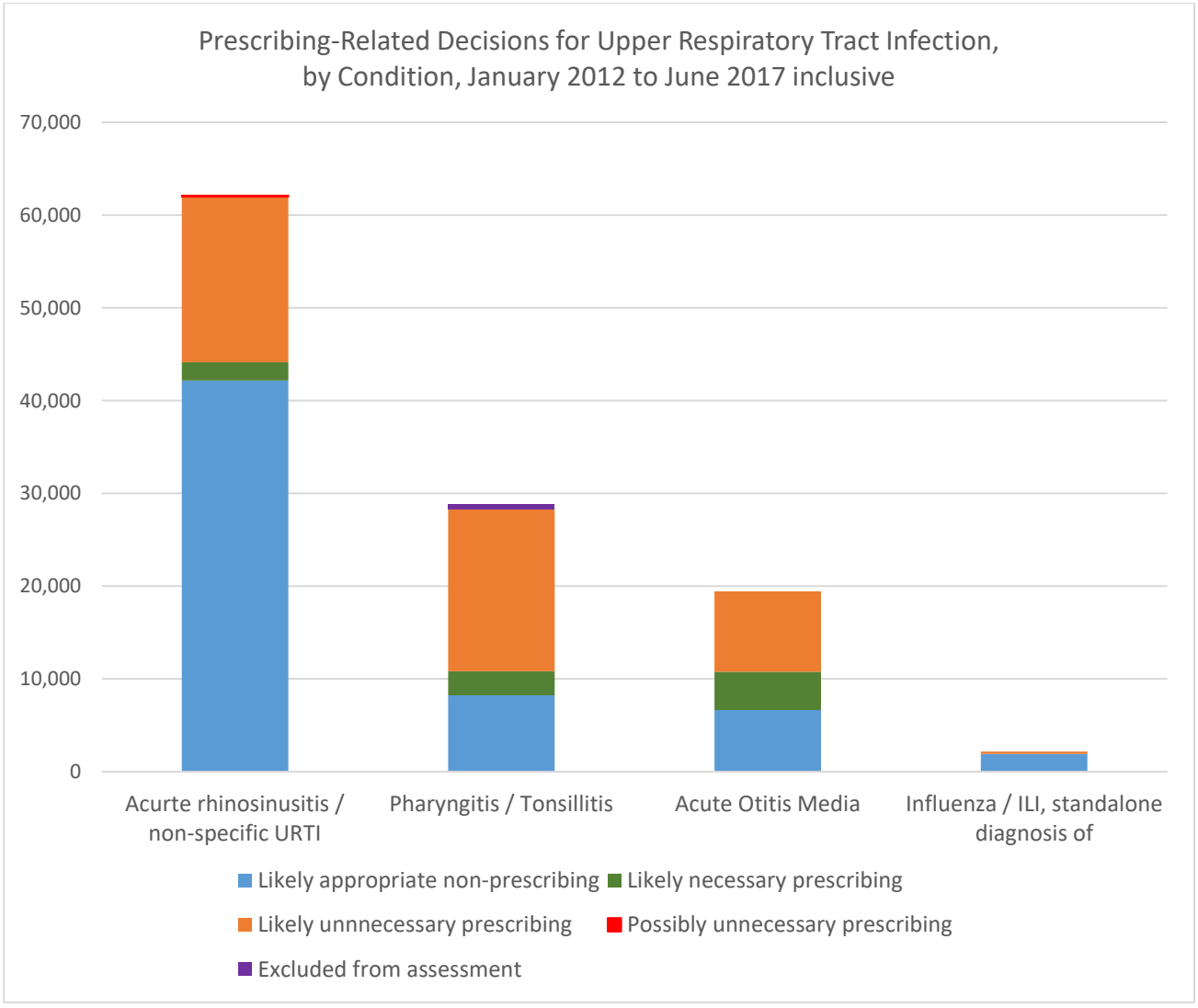


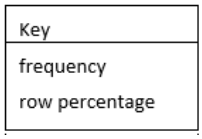
Figure 4-2: Bar graph of prescribing-related decisions for initial presentations of upper respiratory tract infection condition, graphed by upper respiratory tract infection condition

The strong majority of all 52,171 antibiotic prescriptions were unnecessary (85%). Of the 20,064 antibiotic prescriptions for acute rhinosinusitis / non-specific URTI, 89% were unnecessary and 10% were necessary (**Figure 4-2**). Prescribing for acute pharyngitis / tonsillitis was unnecessary in 85% of the total 20,500 prescribing situations, appropriate in 13%. The lowest proportion of unnecessary prescribing was for AOM, at 76% of the total 11,354 prescriptions for the condition. While insufficient information was available to assess under-prescribing, there was one notable diagnosis of tonsillitis with scarlet fever with no antibiotic prescribed.

Children aged 0-8 years had the lowest proportion of unnecessary prescriptions among all prescriptions per age group (69%). This was followed by 85% for the 9-21 year-old age group, 91% for patients 22-34 years, to a maximum of 94% for patients 35 years and over receiving unnecessary prescriptions among all antibiotic prescriptions (**Table 4-5**). Unnecessary prescribing increased proportionally with increasing age.

Table 4-5: Frequency table of patient age group by necessary / unnecessary antibiotic prescribing for initial presentations of upper respiratory tract infection

	Necessary Prescribing	Unnecessary Prescribing	Excluded	Total
Patient Age Group				
0-8 yrs	3,990	9,266	99	13,355
	29.88	69.38	0.74	100
9-21 yrs	1,226	7,633	149	9,008
	13.61	84.74	1.65	100
22-34 yrs	1,242	14,094	148	15,484
	8.02	91.02	0.96	100
35+ yrs	806	13,206	72	14,084
	5.72	93.77	0.51	100
Missing	0	2	238	240
	0	0.83	99.17	100
Total	7,264	44,201	706	52,171
	13.92	84.72	1.35	100



Among antibiotic prescriptions for these initial presentations of URTI, 60% were non-first-line. Rhinosinusitis had the highest proportion of non-first-line among all antibiotics prescribed per condition (68%), followed by pharyngitis / tonsillitis (58%), and AOM (53%) (**Figure 4-3**, **Table 4-6**). AOM was the only condition with the highest proportion of antibiotics being first-line, and the second-highest proportion being second-line, and so forth, in the order recommended in the guidelines (29).

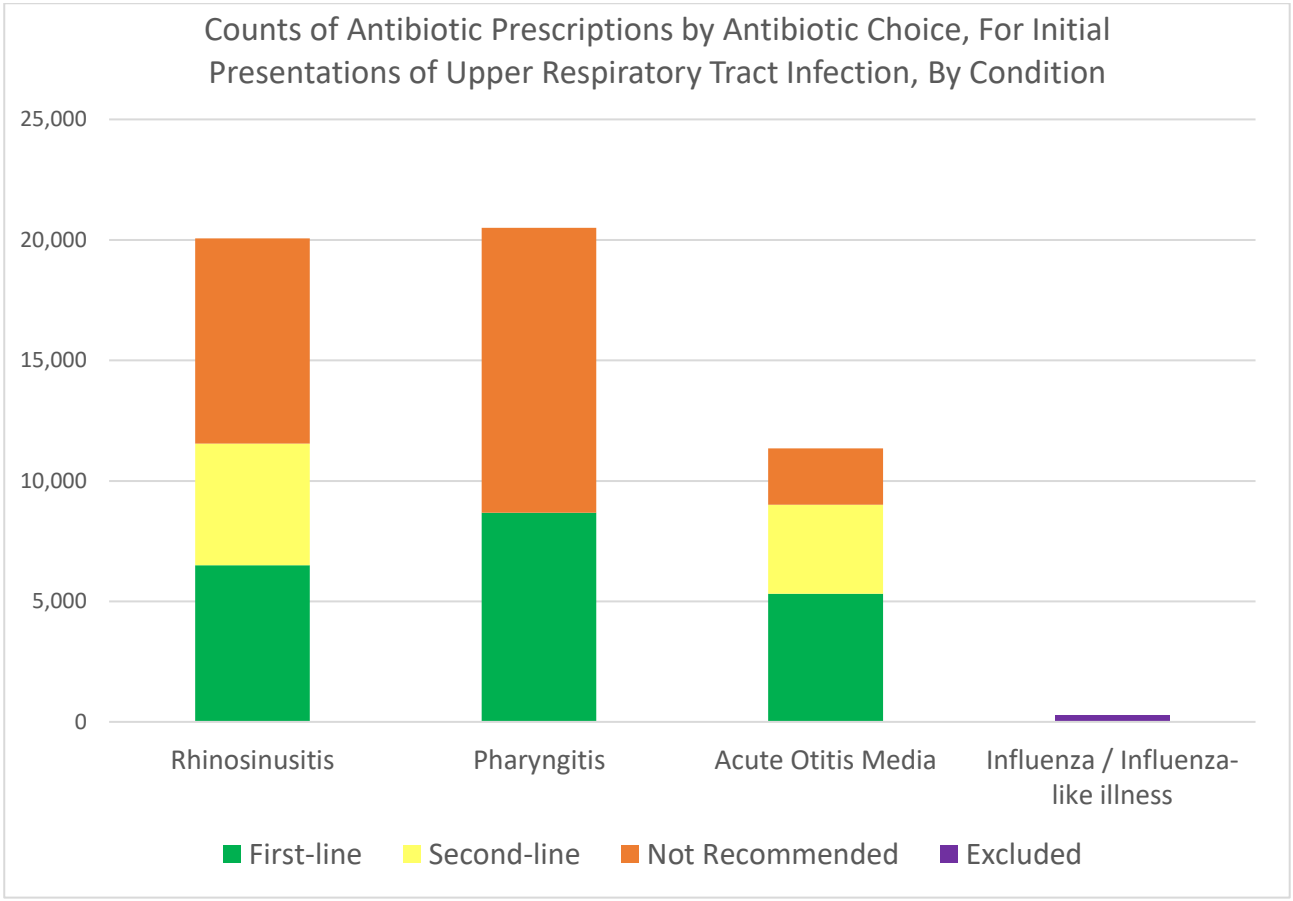


Figure 4-3: Bar graph of ordinal choice of antibiotic prescribed for initial diagnoses of upper respiratory tract infection, by condition

Table 4-6: Frequency table of first-line and non-first-line antibiotic prescriptions for initial presentations of upper respiratory tract infection, by upper respiratory tract infection condition

	First-line	Non-first-line	Excluded	Total
URTI Condition				
Rhinosinusitis	6,504	13,560	0	20,064
	32.42	67.58	0	100
Pharyngitis/Tonsillitis	8,683	11,817	0	20,500
	42.36	57.64	0	100
Acute Otitis Media	5,317	6,037	0	11,354
	46.83	53.17	0	100
Influenza/ILI	0	0	253	253
	0	0	100	100
Total	20,504	31,414	253	52,171
	39.3	60.21	0.48	100

Key
frequency
row percentage

Of antibiotics not recommended in the guidelines for each respective condition, macrolides, first-generation cephalosporins and penicillins dominated (**Appendix C.2: Table C-3**). Beta-lactamase inhibitors are not recommended for acute pharyngitis / tonsillitis but were commonly used. There were no prescriptions of higher generation cephalosporins.

With respect to ordered choice of antibiotic prescribed, first-line prescribing decreased with increasing patient age, meanwhile antibiotics not recommended in the guidelines (29) increased in proportion with increasing patient age (**Table 4-7**). Non-first-line antibiotic prescribing also increased with increasing age. Within necessary prescribing situations (n=7,264), 46% were first-line, 20% were second-line, and 33% were not recommended (**Table 4-8**). Within unnecessary prescribing (n=43,946), 43% were first-line, 17% second-line and 40% were not recommended (**Table 4-8**). For a summary of how the antibiotic prescribing for URTI analysed here compares with prominent quality indicators, please see **Appendix G.1**.

Table 4-7: Frequency table of ordinal choice of antibiotic prescribed, by patient age group, for patients with initial presentations of upper respiratory tract infection

	First-line	Second-line	Not Recommended	Excluded	Total
Patient Age Group					
0-8 yrs	6,443	2,110	4,781	21	13,355
	48.24	15.8	35.8	0.16	100
9-21 yrs	3,942	1,303	3,724	39	9,008
	43.76	14.46	41.34	0.43	100
22-34 yrs	5,917	2,159	7,338	70	15,484
	38.21	13.94	47.39	0.45	100
35+ yrs	4,092	3,142	6,727	123	14,084
	29.05	22.31	47.76	0.87	100
Missing	110	33	97	0	240
	45.83	13.75	40.42	0	100
Total	20,504	8,747	22,667	253	52,171
	39.3	16.77	43.45	0.48	100

Key
frequency
row percentage

Of all antibiotic prescriptions for URTI, 32% of these antibiotic prescriptions were issued with one or more repeats issued on them. Proportionally, repeats were most commonly issued on non-first-line prescriptions, to patients with comorbid conditions or mental health conditions, and most frequently to young children (**Appendix C.4.1**).

Table 4-8: Frequency table of unnecessary and necessary antibiotic prescribing for initial presentations of upper respiratory tract infection, by ordinal choice of antibiotic prescribed

Unnecessary / Necessary Prescribing	First-line	Second-line	Not Recommended	Total
Necessary Prescribing	3,368	1,485	2,411	7,264
	46.37	20.44	33.19	100
Unnecessary Prescribing	18,852	7,311	17,783	43,946
	42.9	16.64	40.47	100
Total	22,220	8,796	20,194	51,210
	43.39	17.18	39.43	100

Key
frequency
row percentage

Of the antibiotics commonly used for URTI, prescriptions for amoxicillin and amoxicillin with clavulanate represented over 60% of prescriptions issued with repeats (**Table 4-9**). For details regarding repeats being issued on antibiotic prescriptions for influenza / ILI, see **Appendix C.4.1: Table C-11**.

Table 4-9: Frequency table of active ingredients prescribed for initial presentations of URTI with repeats issued, excluding prescriptions for influenza / influenza-like illness.

Active Ingredient	Frequency	Percent	Cumulative Percent
Amoxicillin	3,792	22.63	22.63
Amoxicillin with clavulanate	6,397	38.18	60.8
Azithromycin	70	0.42	61.22
Benzathine benzylpenicillin	1	0.01	61.23
Cefaclor	499	2.98	64.21
Cefalexin	2,093	12.49	76.7
Cefuroxime	124	0.74	77.44
Ciprofloxacin	18	0.11	77.54
Clarithromycin	574	3.43	80.97
Clindamycin	13	0.08	81.05
Doxycycline	145	0.87	81.91
Erythromycin	506	3.02	84.93
Flucloxacillin	6	0.04	84.97
Minocycline	20	0.12	85.09
Nitrofurantoin	1	0.01	85.09
Norfloxacin	2	0.01	85.1
Phenoxymethylpenicillin	953	5.69	90.79
Procaine benzylpenicillin (procaine p..	73	0.44	91.23
Roxithromycin	1,285	7.67	98.9
Tobramycin	1	0.01	98.9
Trimethoprim	10	0.06	98.96
Trimethoprim with sulfamethoxazole	174	1.04	100
Total	16,757	100	

Cefalexin is the recommended antibiotic for penicillin hypersensitive patients with pharyngitis / tonsillitis. However, a repeat can be required to complete a single of cefalexin course due to manufacturer pack sizes. While 897 prescriptions for cefalexin were issued to patients with pharyngitis / tonsillitis, only 120 patients had a penicillin allergy label recorded (**Appendix C.4.2**). All but one of the 897 patients who received a repeat would have required one to complete a guideline-concordant course. Additionally, there was substantial variation in duration of treatment among cefalexin prescriptions, ranging from five to 28 days. Please see **Appendix C.4.2** for details.

4.3.1 Introduction to modelling - clustering considerations

Noting that the same patient may present multiple times to the same GP during the study period, multiple patients may attend the same GP / provider, and multiple GPs may work at the same practice, this violates the assumption of independence underpinning the basis of generalised linear regression with fixed effects (361,362). For URTI diagnoses, there were between 68 to 10,513 patients per practice, between five and 104 unique providers per practice. For antibiotic prescribing for URTI, there were between one and 2007 prescriptions per provider, and between 76 and 17,015 prescriptions per practice. The large variation between cluster sizes reinforces the need to allow, wherever possible, for non-independence. Model design was driven by variation in the size and numbers of clusters, with random intercepts for practice ID, and within practice level, the provider ID.

4.3.2 Model 0: predictors of inappropriate decisions (unnecessary prescribing versus necessary prescribing and appropriate non-prescribing)

Patient age group, gender, penicillin allergy label status, concession status, mental health condition status, socioeconomic disadvantage, weekend consultations, practice size, and patient's PHN were predictors of inappropriate decisions (**Table 4-10**, **Appendix C.5.1: Table C-20**). The following variables were insignificant in the multivariable model: other patient comorbid conditions, remoteness and accessibility, URTI condition, number of URTI episodes, and temperature recording status. Culture testing information were too few for inclusion.

Table 4-10: Mixed effects logit regression models of binary inappropriate decisions (Model 0) and binary unnecessary antibiotic prescribing (Model 1) for initial presentations of upper respiratory tract infection

Model	**Inappropriate Decision** (ref. Appropriate Decision, including Appropriate Non-Prescribing)		**Unnecessary Prescribing Among Prescriptions** (ref. Appropriate Prescribing)	
Independent Variable	**Adj. Odds Ratio**	**95% C.I.**	**Adj. Odds Ratio**	**95% C.I.**
Patient Age Group, (ref. 0-8 yrs)				
9-21 yrs	2.164***	[2.051,2.283]	3.344***	[3.077,3.634]
22-34 yrs	2.219***	[2.107,2.336]	4.691***	[4.279,5.143]
35+ yrs	2.056***	[1.958,2.160]	5.597***	[5.106,6.135]
Patient penicillin allergy label, (ref. Negative)				
Positive	1.421***	[1.341,1.506]	0.832**	[0.737,0.938]
Patient Concession (ref. Negative)				
Positive	1.041*	[1.003,1.080]	1.125**	[1.035,1.223]
Patient Mental Health Condition (ref. Negative)				
Positive	1.054*	[1.010,1.100]	1.297***	[1.156,1.455]
Missing	1.315	[0.857,2.017]	1.28	[0.687,2.387]
Patient gender, (ref. Female)				
Male	1.051*	[1.003,1.101]		
Age group # Gender (ref. Female # 0-8 yrs)				
9-21 yrs # Male	0.813***	[0.752,0.878]		
22-34 yrs # Male	0.848***	[0.787,0.914]		
35+ yrs # Male	0.908**	[0.847,0.973]		
URTI Condition, (ref. Rhinosinusitis)				
Pharyngitis / Tonsillitis			0.430***	[0.373,0.494]
AOM			0.254***	[0.221,0.292]
Ordinal Line Agent Prescribed, (ref. First-line)				
Second-line			0.612***	[0.522,0.718]
Not Recommended			0.763***	[0.656,0.886]
URTI Condition # Ordinal Line of Antibiotic,				
Pharyngitis # Not Recommended			1.697***	[1.413,2.039]
AOM # Second-line			2.643***	[2.176,3.210]
AOM # Not Recommended			1.769***	[1.446,2.166]
Disadvantaged Patient, (ref. No Disadvantage)				
Positive	1.063*	[1.000,1.130]		
Missing disadvantage status	0.922*	[0.861,0.986]		
Repeat on script, (ref. negative)				
Positive			0.903**	[0.838,0.974]
Multiple URTI episodes for patient, (ref. Negative)				
Positive			0.897**	[0.839,0.959]
Patient's Primary Health Network, (ref. Perth North)				
Perth South	0.954	[0.881,1.033]		
Country WA	1.034	[0.944,1.133]		
Interstate PHN	1.209*	[1.040,1.406]		
Patient's PHN Missing	1.134	[0.996,1.290]		
Practice size, (ref. Medium / Large)				
Small	1.678***	[1.300,2.166]		
Weekend (ref. Weekday)				
Positive	1.241***	[1.183,1.302]		

Model	**Inappropriate Decision** (ref. Appropriate Decision, including Appropriate Non-Prescribing)		**Unnecessary Prescribing Among Prescriptions** (ref. Appropriate Prescribing)	
Independent Variable	**Adj. Odds Ratio**	**95% C.I.**	**Adj. Odds**	**95% C.I.**
Seasonality allowed for in form of dummy variables for annual influenza seasons				
var(_cons[~c])	2.756***	[2.429,3.127]	4.282***	[3.359,5.458]
N	111848		51210	
AIC	131446.7		32977.7	
BIC	131706.6		33189.9	
ICC				
Level	ICC (S.E.)	[95% C.I.]	ICC (S.E.)	[95% C.I.]
unique provider ID & practice ID combination	0.236	[0.214,0.259]	0.307	[0.272,0.343]
Level	ICC (S.E.)	[95% C.I.]	ICC (S.E.)	[95% C.I.]

Note: SE in parentheses, *** p<0.01, ** p<0.05, * p<0.1.
Note #: STATA 16 does not calculate ICC (incl. SE and 95%CI for ordinal models. ICC calculated by the author.
Note: Direct application of adjusted odds ratios to estimate the effect of a single variable in the model is not valid without also allowing for multi-level clustering. As such, direct application of adjusted odds ratios is not recommended.

There was an interaction identified between patient age group and gender. When considered without patient gender, patients 22-34 years were at highest chance of receiving inappropriate decisions, at fourteen percentage points higher (0.141, p<0.001, 95%CI: 0.133, 0.149), while patients 9-21 years and patients 35 and over had thirteen percentage points higher chance of inappropriate decisions than young children (both p<0.001, see **Appendix C.5.1: Table C-20**). Without considering patient age, males were one percentage point less likely to receive inappropriate decisions than females (-0.010, p<0.001, -0.015, -0.004).

However, when, using MERs, patient age and gender are considered together, this is not the case. In this situation, relative to similar females, young male children were one percentage point more likely (0.009, p=0.035, 95%CI: 0.001, 0.018) while male patients 9-21 years were three percentage points less likely, and males 22-34 years were two percentage points less likely (both p<0.001, see **Appendix C.5.2**) to receive an inappropriate decision. There was no significant difference in gender for patients 35 years and over (-0.010, p=0.074, 95%CI: -0.020, 0.001). Regardless of patient gender, all other age groups were eleven to sixteen percentage points more likely to receive an inappropriate decision than young children 0-8 years (all p<0.001, see **Appendix C.5.3**). However, the CIs for the AMEs for the three older female age groups partially overlap, as do those for males, suggesting there is no substantial difference for patients of the same gender across the three older age groups. With other variables held constant at sample means, young children had a probability of 32-33% of receiving an inappropriate decision (0.328, p<0.001, 95%CI:

0.313, 0.344), (0.319, p<0.001, 95%CI: 0.304, 0.334). Under the same conditions, patients of either of the two adult female age groups had probabilities of 46-48% of receiving likely inappropriate decisions, while adult male groups had probabilities of 44-45% (see **Appendix C.5.4**).

4.3.2.1 Model 0: summary

Young children had lower probabilities of receiving inappropriate decisions than other age groups, and patients 22-34 years had the highest probability. There was an interaction between patient age and gender, with young male children having an increased likelihood of the outcome than young female children. However, females had a slightly higher chance of inappropriate decision than males for patients 9-21 and 22-34 years. Other than patient age and gender, it was practice size and penicillin allergy label status which had the highest magnitude of effect upon the outcome of inappropriate decisions. Other predictors of inappropriate decisions, which were identified but not presented in detail, included weekend consultation status and patient's PHN, and there were small effects for mental health condition status and government concession status (see **Table 4-10**, **Appendix C.5.1: Table C-20** for more detail). Of the variance not explained by fixed effects, the level consisting of the unique combination of individual provider and individual practice combination accounted for 24% (see **Table 4-10**). This suggests that the individual provider drives most of this variation among the two, as the provider represents the lower level of the two (and with notably higher membership) within the data hierarchy of patient-provider-practice structure.[7]

4.3.3 Model 1: predictors of unnecessary prescribing (versus necessary prescribing) among all antibiotic prescriptions

The predictors of unnecessary prescribing identified included patient age group, mental health condition status, patient concession status, patient penicillin allergy label status, URTI condition, number of URTI episodes, ordinal line of antibiotic prescribed and repeat prescription status (**Table 4-10**, **Appendix C.6.1: Table C-21**). The following variables were insignificant in the multivariable model: patient gender, patient-registered PHN, patient comorbid conditions status, patient remoteness and socioeconomic disadvantage indicators, and the dummy variable for cefalexin. Culture testing was too infrequent for

[7] A model with three, nested levels was not feasible for the data. As such, a two-level model with a level for the unique combination of the provider and practice IDs was used, in addition to the patient level.

inclusion and temperature recording status was excluded due to correlation with URTI condition.

The probability of receiving unnecessary prescribing increased with increasing age group, regardless of the URTI condition. One may note in **Figure 4-4** below, the notable step between the probability for young children and the remaining age groups for all conditions. Relative to children 0-8 years: the probability of unnecessary prescribing for patients 9-21 years increased by twelve percentage points (0.117, p<0.001, 95%CI: 0.107, 0.127), for patients 22-34 years the probability increased by thirteen to fourteen percentage points, and for patients 35 years and over, it increased by fourteen percentage points (0.137, p<0.001, 95%CI: 0.126, 0.148), and by fifteen percentage points for patients aged 35 years and over (0.146, p<0.001, 95%CI: 0.135, 0.157).

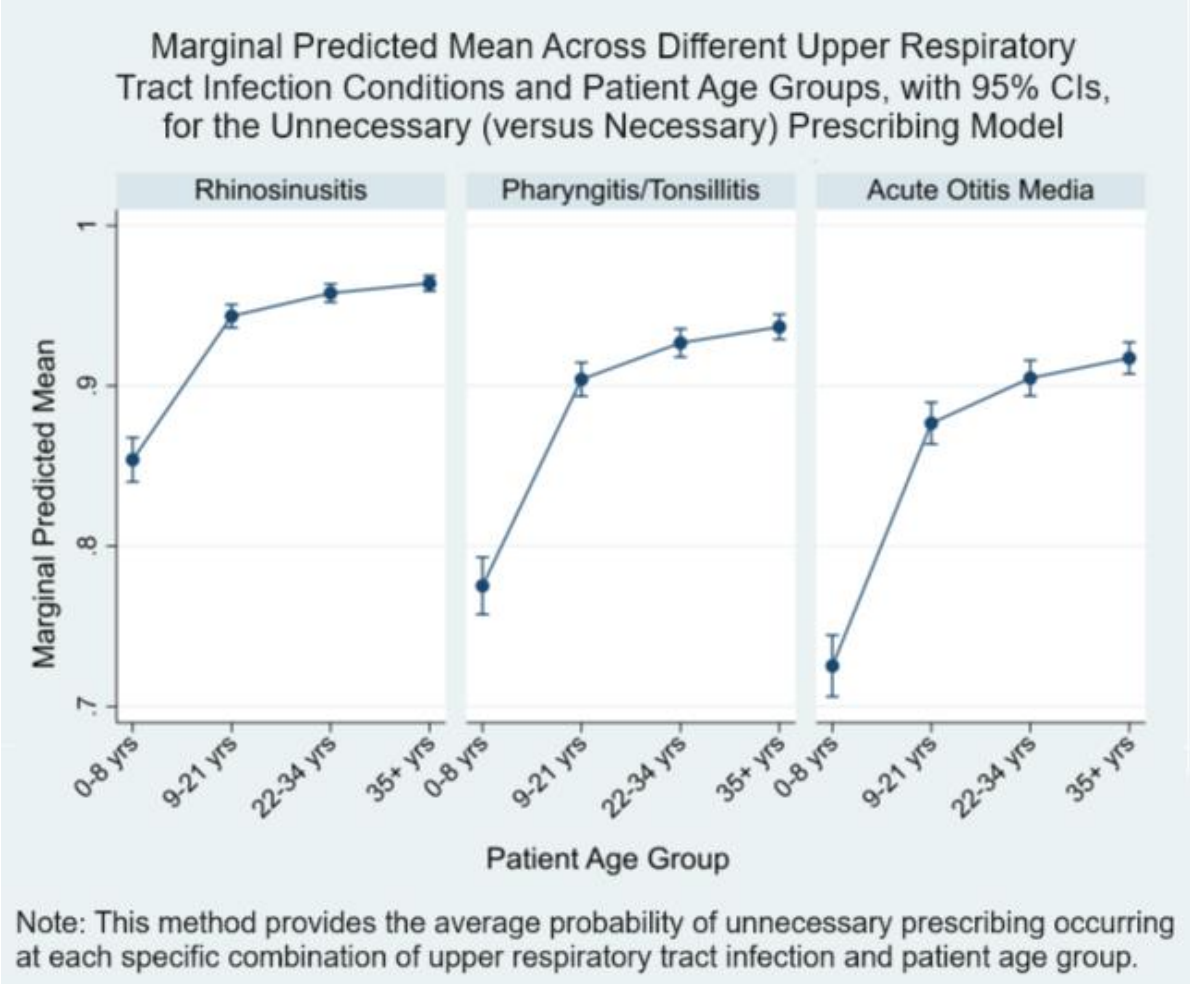


Figure 4-4: Plots of the marginal predicted mean of the outcome of unnecessary antibiotic prescribing occurring, across different upper respiratory tract infection conditions and different patient age groups, by condition

When URTI condition was considered independently, rhinosinusitis had the highest probability of receiving unnecessary prescriptions, followed by pharyngitis / tonsillitis, then AOM (**Table 4-10**, **Appendix C.6.1: Table C-21**). However, there was an interaction identified between URTI condition and choice of antibiotic prescribed. With other covariates held constant at sample means (**Appendix C.6.4**), the probability of receiving unnecessary prescriptions with first-line antibiotics was 94% for rhinosinusitis (0.945, p<0.001, 95%CI: 0.937, 0.953), 89% for pharyngitis (0.890, p<0.001, 95%CI: 0.879, 0.901), and 84% for AOM (0.838, p<0.001, 0.823, 0.853). When second-line antibiotics were prescribed, the chance of unnecessary prescribing dropped to 92% for rhinosinusitis (0.917, p<0.001, 95%CI: 0.906, 0.927) and 84% for pharyngitis (0.842, p<0.001, 95%CI: 0.820, 0.865) but rose to 89% for AOM (0.886, p<0.001, 95%CI: 0.873, 0.899). For not recommended antibiotics, the probability of unnecessary prescriptions was 93% for rhinosinusitis (0.931, p<0.001, 95%CI: 0.922, 0.939), rising to a maximum of 91% for pharyngitis (0.910, p<0.001, 95%CI: 0.900, 0.920) and 87% for AOM (0.870, p<0.001, 95%CI: 0.854, 0.886). By condition and antibiotic choice, the probability of unnecessary prescribing was highest for patients with: rhinosinusitis receiving first-line, pharyngitis receiving not recommended, and AOM receiving second-line antibiotics. However, the probability of unnecessary prescribing remained higher for rhinosinusitis than any other condition regardless of antibiotic choice.

Patients with mental health conditions had a probability of receiving likely unnecessary prescriptions of two percentage points higher (0.020, p<0.001, 95%CI: 0.011, 0.028) than patients without mental health conditions. There was no significant difference for patients with missing mental health condition status (0.019, p=0.407, 95%CI: -0.026, 0.063). Patients with penicillin allergy labels had a two percentage point decrease in chance of receiving an unnecessary prescription (-0.015, p=0.004, 95%CI: -0.026, -0.005) than patients without these allergy label. Please see **Appendix C.6** for more details.

4.3.3.1 Model 1: summary

The probability of unnecessary prescribing increased with increasing age. By condition and choice of antibiotic, the probability of unnecessary prescribing was highest for rhinosinusitis receiving first-line, pharyngitis receiving not recommended, and AOM receiving second-line. However, the likelihood of this outcome remained higher for rhinosinusitis than any other condition regardless of the choice of antibiotic prescribed. Patients with penicillin allergy labels and repeats issued on prescriptions were linked to lower chance of receiving unnecessary prescriptions. Of the variance not explained by fixed effects, the unique

provider accounted for 31% of remaining variation (**Table 4-10**). When the same model is calculated but with three, nested levels, the provider accounts for 31% while practice accounts for 5%. In both models, as the provider level is responsible for the higher percentages of variance unexplained by fixed effects than the practice level, this suggests that the individual provider drives the majority of this variation.

4.3.4 Model 2: predictors of increasing choice of antibiotic prescribed

The final model for increasing line of agent includes age group, prescribing reason recorded, URTI condition, multiple URTI episodes status, patient comorbid conditions, patient disadvantaged status, practice size, as well as unnecessary versus necessary prescribing status and repeat prescription status (**Table 4-11, Appendix C.7.1: Table C-22**). The following variables were insignificant in the multivariable model: patient gender, mental health conditions, temperature recording status, patient remoteness and accessibility, concession status, PHN, penicillin allergy label status, and private prescription status.

There was an effect modification between patient age group and URTI condition. When patient age group is considered with URTI condition using MERS, the interaction is apparent for patients with pharyngitis receiving first-line and not recommended antibiotics (**Figure 4-5**, **Appendix C.7.2**). Relative to patients with rhinosinusitis: patients with pharyngitis aged 0-8 years were eight percentage points less likely to receive first-line antibiotics (-0.081, p<0.001, 95%CI: -0.097, -0.066), and seven percentage points more likely to receive not recommended antibiotics (0.073, p<0.001, 95%CI: 0.059, 0.087). Meanwhile, patients with pharyngitis aged 9-21 years and 22-34 years were linked to a two (0.018, p=0.046, 95%CI: 0.0002, 0.0351) and a three (0.0274, p=0.001, 95%CI: 0.011, 0.044) percentage point increase, respectively, in the chance of receiving first-line antibiotics, compared to patients with rhinosinusitis. There were no significant differences between patients with pharyngitis aged 35 years and over and those with rhinosinusitis (all p>0.06, **Appendix C.7.2**). Compared to patients with rhinosinusitis, patients with AOM were eight percentage points more likely to receive first-line antibiotics (all p<0.001, **Appendix C.7.2**), and seven to eight percentage points less likely to receive not recommended antibiotics (all p<0.001, **Appendix C.7.2**).

Table 4-11: Mixed effects logit regression models of choice of antibiotic (Model 2) and binary non-first-line antibiotic prescribing (Model 3) for upper respiratory tract infection

Model	**Ordinal Line of Antibiotic Prescribed (ref. First-line)**		**Binary Non-first-line Prescribing (ref. First-line)**	
Independent Variable	**Adj. Odds Ratio**	**95% C.I.**	**Adj. Odds Ratio**	**95% C.I.**
Patient Age Group, ref 0-8 yrs				
9-21 yrs	1.207***	[1.111,1.310]	1.491***	[1.354,1.642]
22-34 yrs	1.330***	[1.227,1.440]	2.041***	[1.853,2.248]
35+ yrs	1.665***	[1.550,1.788]	2.845***	[2.608,3.104]
Prescribing Decision, (ref Appropriate)				
Inappropriate	1.124***	[1.063,1.188]	0.636***	[0.550,0.736]
URTI Condition (ref Rhinosinusitis)				
Pharyngitis / Tonsillitis	1.519***	[1.404,1.643]	0.422***	[0.354,0.502]
AOM	0.646***	[0.612,0.682]	0.485***	[0.409,0.574]
Age Group # Pharynigitis (ref 0-8 yrs# Pharyngitis)				
9-21 yrs # Pharynigitis	0.601***	[0.538,0.671]	0.500***	[0.440,0.568]
22-34 yrs # Pharynigitis	0.570***	[0.511,0.636]	0.383***	[0.337,0.436]
35+ yrs # Pharynigitis	0.711***	[0.640,0.791]	0.387***	[0.341,0.438]
Patient Comorbid Conditions (ref Negative)				
Positive	1.151***	[1.094,1.211]	1.137***	[1.068,1.211]
Missing Status	1.228	[0.738,2.044]	1.031	[0.596,1.783]
Repeat on Prescription (ref Negative)				
Positive	1.140***	[1.061,1.225]	1.431***	[1.312,1.561]
Age Group # Repeat Status (ref 0-8yrs # Repeat)				
9-21 yrs # Repeat Positive	1.481***	[1.326,1.654]	1.798***	[1.568,2.061]
22-34 yrs # Repeat Positive	1.941***	[1.737,2.170]	3.067***	[2.651,3.548]
35+ yrs # Repeat Positive	1.345***	[1.220,1.484]	2.320***	[2.038,2.640]
Disadvantaged Patient, (ref No Disadvantage)				
Positive	0.903*	[0.832,0.981]	0.914	[0.828,1.009]
Missing status	0.872***	[0.805,0.944]	0.845***	[0.770,0.928]
Multiple URTI episodes per Patient, (ref Negative)				
Positive	0.933**	[0.893,0.976]	0.905***	[0.858,0.955]
Practice size, (ref medium / large)				
Small	1.783***	[1.319,2.409]	1.791***	[1.294,2.481]
Prescribing Reason Recorded (ref Negative)				
Positive	0.681***	[0.591,0.784]	0.686***	[0.587,0.801]
Condition # Decision (ref Rhinosinusitis # Appropriate Decision)				
Pharyngitis / Tonsillitis # Inappropriate Decision			2.419***	[2.025,2.890]
AOM # Inappropriate Decision			1.768***	[1.480,2.111]
Patient Gender (ref Female)				
Male			1.092***	[1.045,1.141]
Seasonality allowed for in form of dummy variables for annual influenza seasons				
cut1	0.370 (0.06765)	[0.237, 0.502]		
cut2	1.252 (0.06788)	[1.119, 1.385]		
var(_cons)	0.323 (0.09242)	[1.153, 1.517]	1.488 (0.10379)	[1.298, 1.706]
N	51210		51210	
AIC	93253.7		52719.6	
BIC	93510.2		52993.8	
ICC Level	ICC	95% C.I.	ICC	95% C.I.
Unique combination of provider ID & practice ID	0.28673092 #	#	0.311 (0.01496)	[0.283, 0.342]

Note: SE in parentheses, *** p<0.01, ** p<0.05, * p<0.1.
Note #: STATA 16 does not calculate ICC (incl. SE and 95%CI for ordinal models. ICC calculated by the author.
Note: Direct application of adjusted odds ratios to estimate the effect of a single variable in the model is not valid without also allowing for multi-level clustering. As such, direct application of adjusted odds ratios is not recommended.

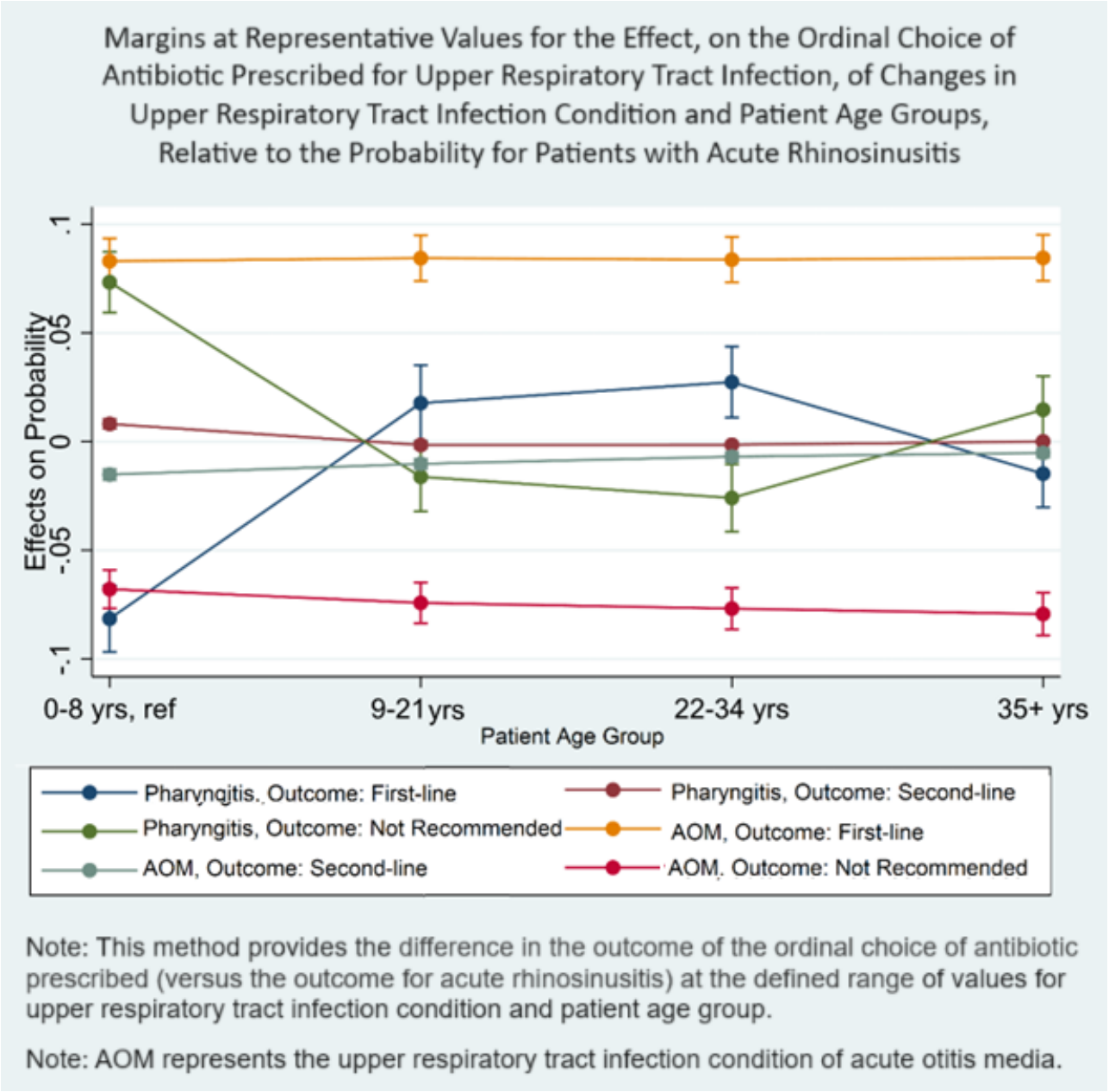


Figure 4-5: Plot of margins at representative values for the effect on the probability of various levels of ordinal choice of antibiotic prescribed, with change in condition, across different patient age groups, relative to patients with rhinosinusitis

There was also an effect modification between patient age group and repeat prescription status. When repeat status was considered with age group using MERs, the increase in probability of receiving not recommended antibiotics mirrored a similar and opposite decrease in the probability of receiving first-line antibiotics (**Figure 4-6**, **Appendix C.7.3**). Relative to patients receiving prescriptions with no repeats, patients aged 0-8 years with a repeat on the prescription were three percentage points less likely to receive first-line (-0.025, p<0.001, 95%CI: -0.039, -0.011) and two percentage points more likely to receive a not recommended antibiotic (0.022, p<0.001, 95%CI: 0.010, 0.034) (**Appendix C.7.3**).

Relative to patients receiving prescriptions without a repeat, patients 9-21 years receiving a repeat were ten percentage points less likely to receive first-line (-0.101, p<0.001, 95%CI: -0.119, -0.083) and nine percentage points more likely to receive not recommended antibiotics (0.093, p<0.001, 95%CI: 0.076, 0.110). This effect was maximum for patients 22-34 years receiving repeats on prescriptions. Compared to prescriptions with no repeats, patients 22-34 years were fifteen percentage points less likely to receive first-line antibiotics (-0.152, p<0.001, 95%CI: -0.170, -0.134), and fifteen percentage points more likely to receive not recommended antibiotics (0.146, p<0.001, 95%CI: 0.128, 0.164). When compared to prescriptions without repeats, patients aged 35 years and over receiving repeats were eight percentage points less likely to receive a first-line antibiotic (-0.081, p<0.001, 95%CI: -0.095, -0.067) and eight percentage points more likely to receive a not recommended antibiotic (0.080, p<0.001, 95%CI: 0.066, 0.094). **Figure 4-6** also highlights the fact that second-line antibiotics featured little in the choice of antibiotic prescribed (see **Appendix C.7.3**).

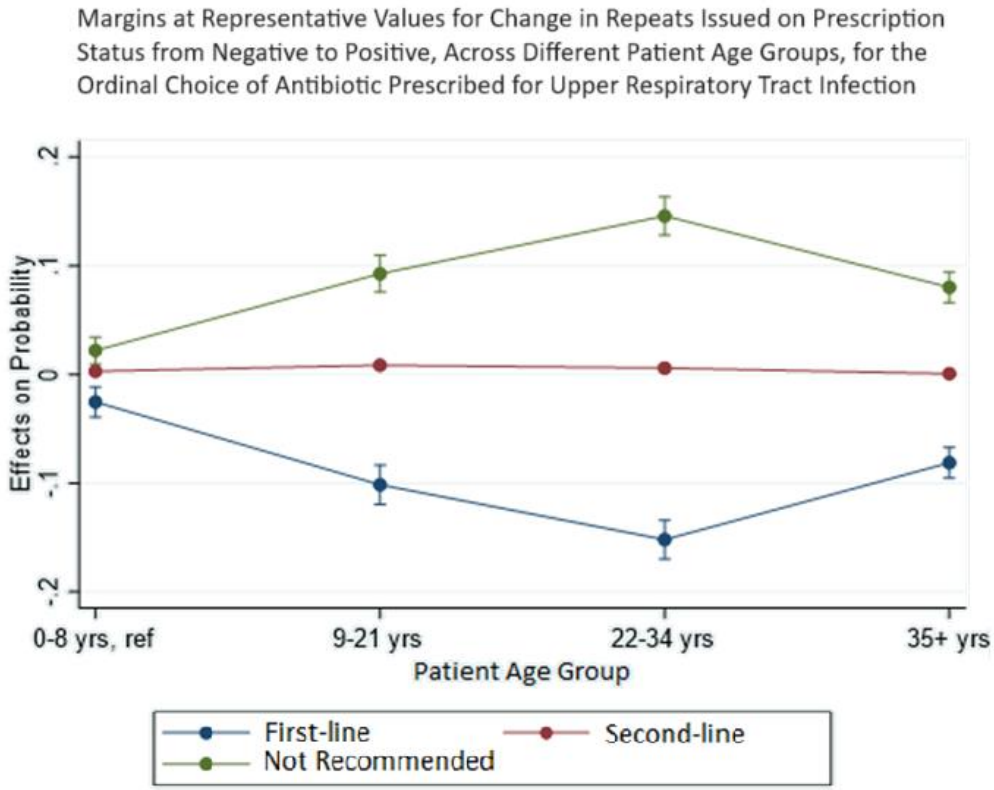


Figure 4-6: Plot of margins at representative values for the effect on the probability of the ordinal choice of antibiotic being prescribed, with change in whether repeats were issued on the prescription from negative to positive, across different patient age groups, relative to prescriptions without repeats issued on them

Compared to medium / large GP practices, small practice size was linked to an eleven percentage point decrease in the chance of receiving a first-line antibiotic (-0.110, p<0.001, 95%CI: -0.166, -0.054), and an equivalent eleven percentage point increase in the chance of receiving a not recommended antibiotic (0.105, p<0.001, 95%CI: 0.049, 0.161, **Appendix C.7.1: Table C-22**). The reason for prescribing field being completed resulted in a seven percentage point increase in probability of first-line antibiotics (0.074, p<0.001, 95%CI: 0.047, 0.100), and a six percentage point reduction in the chances of receiving not recommended antibiotics (-0.065, p<0.001, 95%CI: -0.088, -0.042), compared to the probability when the reason for prescribing was not completed. Likely unnecessary prescribing reduced the probability of first-line antibiotics by two percentage points (-0.022, p<0.001, 95%CI: -0.033, -0.012), and a corresponding two percentage point increase in the probability of receiving not recommended antibiotics (0.020, p<0.001, 95%CI: 0.011, 0.030), relative to likely necessary prescriptions (**Appendix C.7.1: Table C-22**).

Relative to patients without comorbid conditions, patients with comorbid conditions were three percentage points less likely to receive first-line antibiotics (-0.027, p<0.001, 95%CI: -0.037, -0.017) and two percentage points more likely to receive not recommended antibiotics (0.025, p<0.001, 95%CI: 0.016, 0.034). However, there was no significant difference for patients with missing comorbid condition status (all p>0.250, **Appendix C.7.1: Table C-22**) compared to patients without comorbid conditions. Relative to patients without socioeconomic disadvantage, patients with socioeconomic disadvantage were two percentage points more likely to receive a first-line antibiotic (0.019, p=0.015, 95%CI: 0.004, 0.035) and two percentage points less likely to receive an antibiotic not recommended in the guidelines (-0.018, p=0.014, 95%CI: -0.032, -0.004), (**Appendix C.7.1: Table C-22**). Meanwhile, patients with missing socioeconomic disadvantage status were linked to a two percentage point increase in first-line (0.026, p=0.001, 95%CI: 0.011, 0.041) and a two percentage point decrease in not recommended (-0.024, p=0.001, 95%CI: -0.037, 0.010) antibiotics, when compared to patients without socioeconomic disadvantage. Please see **Appendix C.7** for more details.

4.3.4.1 Model 2: summary

Patient age and repeats issued on prescription status had substantial effects on the ordinal choice of antibiotic prescribed. Patients aged 22-34 years were least likely to receive first-line antibiotics, and most likely to receive not recommended antibiotics. Second-line antibiotics barely featured in the results, with the main effects being any decrease in first-

line antibiotics was met with similar magnitude in increase in not recommended antibiotics, and vice versa.

Prescriptions classified as unnecessary were associated with increased probability of non-first-line choice of agent than for necessary prescriptions.

Binary equivalent models for non-first-line prescribing versus first-line prescribing were also developed (Model 3), with the same denominator of all antibiotics prescribed for URTI (**Table 4-11**, **Appendix C.8: Table C-23**). The results of this model are similar to model 2, and are therefore not covered in detail here.

Common to both models 2 and 3 was the fact that individual provider was responsible for much more variation than individual practice, of variation otherwise unexplained by fixed effects. Of the variance not explained by fixed effects, the unique provider within unique practice combination accounted for 29% and 31% of variation in Models 2 and 3, respectively (see **Table 4-11**).

4.3.5 Comparing mixed effects models with fixed effects models

All outcomes were modelled with fixed effects using multivariable logistic regression for comparison with the results of the mixed effects models. Varying results were obtained using models with fixed effects only, and for all outcomes, additional variables became significant (**Appendix C.10: Table C-26**). This highlights that different, likely misleading, results can arise when important unobserved heterogeneity has been (erroneously) ignored. The model for unecessary prescribing with fixed effects had an additional four variables, including PHN. When the ordinal choice of antibiotic was modelled using fixed effects, the PHN also became significant, as well as two other variables. When inappropriate decisions were modelled using fixed effects, additional variables became significant, and scrutiny was placed on different PHNs and not interstate.[8]

When the same modelling process was followed for unnecessary prescribing but without allowing for individual provider within practice, the final model also included patient PHN and patient comorbid condition status. This would put undue scrutiny on PHNs (AOR =0.81 for

[8] Please see the Appendix to this chapter for more details.

Perth South, and AOR=1.60 for Country WA, versus Perth North PHN) and potentially spurious association with patient comorbid conditions (AOR=1.19 for comorbid condition positive). This highlights a methodological advantage of using mixed-effects models for primary care data, despite the added complexity in both modelling and interpretation. This is a substantial advantage of this research over international studies which do not allow as accurately (or at all) for clustering.

4.3.6 Residual variance unexplained by fixed effects

It was of substantial interest whether individual practices or individual providers were responsible for more of the remaining variance unexplained by fixed effects in each model, which will be termed '*residual variance'* for ease of reference. The intention was to calculate between-level intra-class correlations (ICCs) in three-level models for each outcome in order to gain insight regarding the contribution to residual variance by each of the practice and provider levels (380,382).

However, the final *mixed-effects models* developed utilised a two-level model including the patient level within a level comprising a unique combination of individual provider and individual practice IDs (365), this structure was unsuited to calculating between-level ICC for providers and practices. Further hierarchical mixed models were therefore developed to address this question, using the same variables as had been identified in the *mixed-effects models* but with different *random-effects* structure. This was performed using three-level models where possible, and separate two-level models, using patient individual level and either unique provider ID or practice ID as the second level, for comparing ICC.

A three-level model of patient within provider within practice levels for unnecessary prescribing was developed, and the practice level is responsible for 5% while the provider level accounts for 31% of residual variance. A three-level model was not feasible for ordinal choice of antibiotic. However, an equivalent two-level model of patient within provider level had an ICC of 29% for the provider level, while a two-level model for patient within practice level demonstrated that 7% of residual variance was attributable to the practice level.

Consistent to all models was the fact that unique provider levels were responsible for the largest variance from random effects, and substantially more than the practice levels in each model or comparison model.

4.4 Summary

It is apparent, based on the guidelines, that inappropriate prescribing of systemic antibiotics is occurring frequently for initial episodes of care for URTI in WA general practice, and in multiple forms: inappropriate decisions among diagnoses, unnecessary prescriptions among antibiotic prescriptions, non-first-line antibiotics being prescribed for initial consultations, and repeats being issued on prescriptions without justification (29). Thirty-nine percent of patients received inappropriate decisions among all initial presentations of URTI. Among all antibiotic prescriptions for URTI, 85% of antibiotic prescriptions were found to be unnecessary, 68% of antibiotic prescriptions were non-first-line, for these initial presentations of URTI. Both figures are concerning.

Among all antibiotics prescribed for each condition, non-first-line prescribing occurred in 68% of occasions for acute rhinosinusitis, notably higher than for other conditions, while non-first-line antibiotics comprised 58% of prescriptions for pharyngitis / tonsillitis, and 53% prescribing situations for AOM. All three other patient age groups had notably higher probabilities of receiving inappropriate decisions than patients 0-8 years. Unnecessary prescribing increased with increasing patient age, regardless of the URTI condition. Pharyngitis was the condition with proportionally the most inappropriate decisions and the lowest appropriate non-prescribing rate. However, rhinosinusitis was the condition with the highest likelihood of unnecessary prescribing among antibiotics received for URTI.

There are other notable factors in discord with the guidelines (29). Second-line antibiotics featured little in the results of any model. Instead, the majority of results demonstrate that if first-line antibiotics were not prescribed, not recommended agents were prescribed, and vice versa. Additionally, based on the low numbers of pathology results available, it is clear that few laboratory culture and sensitivity tests are both being requested by GPs and the testing being performed by patients.

The fact that the unique provider levels demonstrated the largest variance from random effects, and substantially more than the practice levels in each model, suggests that individual providers have much more influence on inappropriate prescribing than individual practices.

Inappropriate decisions, unnecessary prescribing, the choice of antibiotic when prescribed, non-first-line antibiotic prescribing, and repeat prescribing are five different measures of inappropriate prescribing with different predictors, albeit with commonalities. Patient age group was significant in all models, while patient remoteness was consistently insignificant. Of the three outcomes of unnecessary, ordinal choice and repeat prescribing (not presented), these outcomes were all found to predict each other. Patient age and URTI condition were significant predictors in all three models.

Second to patient age, it was small practice size and weekend consultations, and the reason for prescribing being recorded that substantially increased the probability of patients receiving an inappropriate decision. Patient age and URTI condition had notable impact on the likelihood of unnecessary prescribing and non-first-line antibiotics being prescribed. This analysis demonstrates that patient factors of age, gender, comorbid conditions, mental health conditions, government concessions and penicillin allergy label status, do influence inappropriate antibiotic prescribing.

There were effect modifiers identified between patient age and gender in the likely inappropriate decision model, and between age and URTI condition in both the ordinal choice and the repeat positive prescribing models. Effect modification was also identified between choice of antibiotic and URTI condition in the likely unnecessary prescribing model, as well as between age and repeat prescription status in the ordinal choice model.

Repeat positive prescribing was associated with necessary prescribing. Conversely, necessary prescribing was more likely to occur with repeats issued on the prescription. It is feasible that GPs may tend to prescribe antibiotics with repeats on the prescription for the most seriously unwell patients in need of treatment, such as, necessary prescribing situations. Receiving repeats on prescriptions was also linked to increased rates of non-first-line prescribing in adults but was linked to lower chance of non-first-line choice for children. This may reflect that GPs may be more cautious with choice of antibiotic and whether to prescribe repeats when dealing with children. GPs may also be more comfortable issuing repeats for lower-line agents for children.

Having a penicillin allergy label was linked to patients receiving inappropriate decisions but it was also associated with necessary prescribing. This may be explained by the difference in denominators for both outcomes.

The large proportions of beta-lactamase inhibitors and second-generation cephalosporins issued with repeats supports the recent PBAC decision to amend the requirements for repeat prescriptions (127,128). The newly restricted agents represented 82% of repeats issued for initial presentations of URTI in this dataset. It is hopeful that PBAC may also consider extending the requirements to agents including phenoxymethylpenicillin, clindamycin and erythromycin, which were used frequently for URTI and were commonly issued repeats when likely not required.

CHAPTER 5 PREDICTORS OF INAPPROPRIATE PRESCRIBING FOR URINARY TRACT INFECTION

5.1 Introduction

UTI encompasses the condition acute cystitis (29). High rates of non-first-line prescribing for initial presentations of UTI are a common problem internationally, particularly in developed countries (119,122,335,400-403). In Australia, non-first-line prescribing occurs for UTI more frequently than it feasibly should (15,17,48). Antibiotic prescribing by GPs for initial presentations of UTI was therefore a focus of this project. Antibiotics are prescribed for UTIs more frequently than in any other presenting group in Australian primary care, second only to URTI (15).

The nationally agreed guidelines, called Therapeutic Guidelines: Antibiotic (the guidelines) recommend that (empirical) prescribing for UTI is appropriate (29). Research indicates that approximately 80% of adult females diagnosed with UTI require antibiotics (258,404). The guidelines for acute cystitis were developed to direct diagnosis and pathology testing to obtain aetiology, recommend effective antibiotics, minimise antibiotic resistance, and limit side effects (29). Reducing unnecessary use of antibiotics for UTI is considered crucial to lessening the spread of antibiotic resistance (6,16) and improving the quality of primary care.

The aim of this study was to quantify inappropriate, guideline non-conforming prescribing of systemic antibiotics in Australian general practice. The focus was on patients presenting with initial presentations of UTI, the choice of antibiotic prescribed, and any likely unnecessary repeat positive antibiotic prescriptions. The aim was also to elucidate patient-, practice- or consultation-related predictors of various levels of inappropriate antibiotic prescribing for patients presenting with UTI. The point of the study was to determine if there were any associations of inappropriate prescribing with patient factors such as age, comorbid conditions, SES, and remoteness / accessibility to health care.

5.2 Specific methods

Non-initial and / or chronic consultations were excluded, including consultations occurring within fourteen days of a previous UTI consultation for the same patient, and any mention of chronic, recurrent, resistant infections. Inappropriate prescribing was defined to include

non-first-line antibiotic prescribing for these initial presentations of UTI, as well as the issuing of repeats on prescriptions without justification. A graphical depiction of the variables and models developed follows in **Figure 5-1**.

As depicted in **Table 5-1**, the guidelines for treatment of initial presentations of UTI were utilised to classify recommended antibiotics into an ordinal variable termed choice based on the order of their recommendation in the guidelines (29), by patient group: women, men and children under 16 years of age.[9] The antibiotic choice prescribed to each patient group was the numerator and the denominator was all antibiotics prescribed to that patient group.

Table 5-1: Antibiotic classifications for the ordered choice variable for acute cystitis, based on the order of antibiotics recommended in Therapeutic Guidelines: Antibiotic (29), by patient group

Choice	Non-pregnant Women	Men	Children >= 1 month
First-line	trimethoprim	trimethoprim	trimethoprim
Second-line	cefalexin	cefalexin	cefalexin
Third-line	amoxicillin + clavulanate	amoxicillin + clavulanate	amoxicillin + clavulanate
Third-line	nitrofurantoin	nitrofurantoin	
Last resort	norfloxacin	Norfloxacin	norfloxacin

Note: A first-line option should be the antibiotic prescribed at initial consultations.
Third-line and last resort options were combined into the third ordinal level for analysis.
Where the antibiotic prescribed is not listed as an option for the condition diagnosed, the prescription was classified as 'not recommended'.
For more information, please refer to the Methods chapter.

While quantitative research using analytic methods to elucidate predictors of inappropriate, non-first-line prescribing for UTI in primary care has been undertaken internationally (122,296,323,353,405-407), Australia lags behind. Despite the existing research on antibiotic prescribing, resistance and its current surveillance within the Australian health system occurring at several levels (14,17), this is to the best of the author's knowledge the first Australian research using quantitative methods to identify predictors of inappropriate prescribing for UTI in primary care.

[9] For more information, please refer to the Methods chapter (Chapter 3).

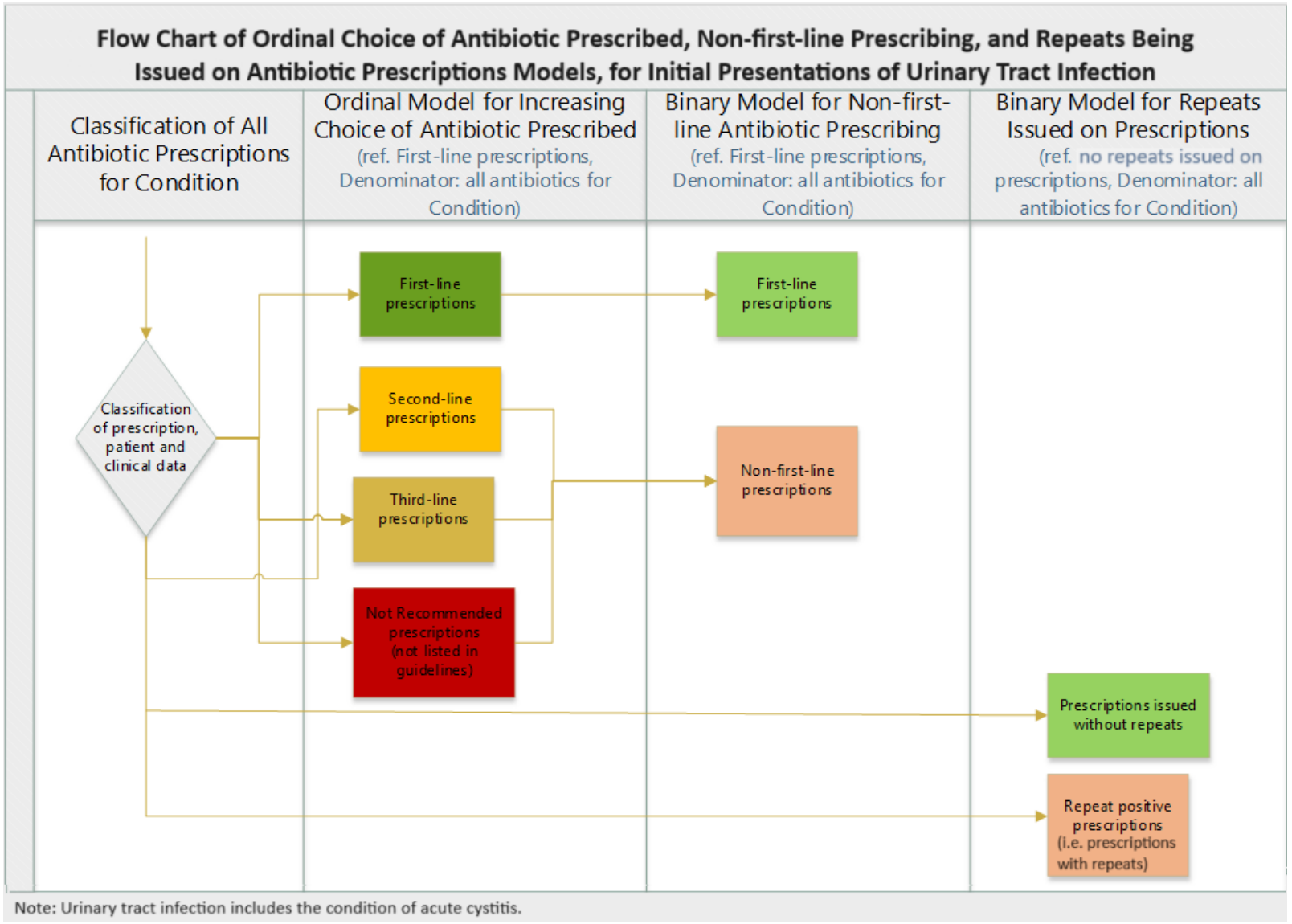


Figure 5-1: Depiction of the main outcome variables utilised in this analysis for initial presentations of urinary tract infection

5.3 Results

Initial descriptive analyses found that there were 21,205 initial episodes of care for UTI identified, of which 40% were to female patients aged 16-44 years (**Table 5-2, Table 5-3**). There were 17,973 systemic antibiotics issued, and the strong majority (81%) were prescribed to females at least sixteen years of age (Appendix D.1). The prescribing rate of prescriptions among diagnoses per patient group, was 85% for all patients, 87% for women, and 78% for men and 75% for children, respectively (**Appendix D.1**). Of patients with UTI, 18% presented with multiple, independent occurrences of UTI. The reason for prescribing field was completed in eighteen percent of antibiotic prescriptions.

First-generation cephalosporins were the most common class of antibiotic prescribed, followed by trimethoprim and derivatives. First-line cefalexin was the most commonly prescribed active ingredient (41%), followed by first-line trimethoprim (38%), and third-line amoxicillin with clavulanate (8%) (**Table 5-4**). Among antibiotics not recommended in the guidelines for the patients receiving them were nitrofurantoin (40%), amoxicillin without clavulanate (33%), and trimethoprim with sulfamethoxazole (12%) (**Appendix D.1**). There were 68 fluoroquinolones and one third-generation cephalosporin prescribed.

Table 5-4: Frequency table to all active ingredients for systemic antibiotics prescribed for initial presentations of urinary tract infection

Active Ingredient	Frequency	Percent	Cumulative Percent
Amoxicillin	510	2.84	2.84
Amoxicillin with clavulanate	1,402	7.8	10.64
Ampicillin	1	0.01	10.64
Azithromycin	11	0.06	10.7
Cefaclor	83	0.46	11.17
Cefalexin	7,374	41.03	52.19
Ceftriaxone	1	0.01	52.2
Cefuroxime	11	0.06	52.26
Ciprofloxacin	68	0.38	52.64
Clarithromycin	10	0.06	52.7
Clindamycin	3	0.02	52.71
Doxycycline	17	0.09	52.81
Erythromycin	16	0.09	52.9
Flucloxacillin	5	0.03	52.92
Nitrofurantoin	702	3.91	56.83
Norfloxacin	430	2.39	59.22
Phenoxymethylpenicillin	8	0.04	59.27
Roxithromycin	9	0.05	59.32
Trimethoprim	6,976	38.81	98.13
Trimethoprim with sulfamethoxazole	336	1.87	100
Total	17,973	100	

Table 5-2: Frequency table of patient characteristics for all patients, and patients with initial episodes of care for urinary tract infection (column percentage)

	All patients	All visits	Initial care episode UTI	Antibiotic Prescribed for UTI	No antibiotic prescribed for UTI
Characteristic	n=791,280	n=1,925,985	n=21,205	n=17,793	n=3,232
Patient					
Female gender, %	52.8	59.1	88.4	89.6	81.3
Mean age, years (s.d.)	38.1 (22.07)	48.0 (23.69)	45.3 (23.83)	45.3 (23.06)	45.6 (27.72)
Patient's Primary Health Network, %					
Country WA	12.9	32.8	27.4	26.2	33.9
Perth South	33.1	33.5	32.2	32.4	31.0
Perth North	34.8	31.8	37.5	38.5	32.2
Interstate	2.2	0.5	1.2	1.3	1.0
Missing	1.5	1.3	1.7	1.7	2.0
Patient concession status positive, %	34.1	35.6	33.9	33.0	39.1
Comorbid condition, %	1.9	10.2	20.6	19.6	26.0
Missing	3.4	2.5	2.8	2.0	2.0
Mental health condition, %	12.9	28.7	25.9	25.9	26.2
Missing	3.4	2.5	2.8	2.9	2.0
Patient remote, % (remote & very remote Australia, ARIA)	6.0	4.4	5.8	5.9	5.5
Missing	1.1	1.0			
Patient disadvantaged, % (top 40% percentiles of most disadvantage, SEIFA IRSD)	11.7	10.3	1.0	1.0	1.2
Missing	1.5	1.3	10.8	10.5	12.4
Multiple UTIs per patient, %			17.6	16.8	21.9
Consultation					
Temperature recorded, %, (% of which fever positive >=37.5C)			15.9 (12)	16.3 (11)	13.8 (15)
Urine dipstick tested, %, (% of which positive result)			95.5 (93)	95.5 (93)	96.0 (92)
Culture performed, %, (% of which had positive growth for any pathogen)			2.8 (100)	3.1 (99)	1.3 (100)
Sensitivity performed, %			0.0	0.0	0.0
Weekend consult, %			8.9	9.2	7.3
Prescription					
Repeat issued on prescription, %				28.4	
Reason for prescribing entered, %				17.8	

Table 5-3: Frequency table of patient, consultations and prescription characteristics for patients prescribed an antibiotic for urinary tract infection (column percentage)

	Any Antibiotic Prescribed for UTI	First-line Agent Prescribed	Second-line Agent Prescribed	Third-line Agent Prescribed	Not Recommended Agent Prescribed
Characteristic	n=17,793 (100%)	n=7,127 (40.0%)	n=7,374 (41.0%)	n=1,906 (10.6%)	n=1,556 (8.7%)
Patient					
Female gender, %	89.6	36.6	36.9	8.2	7.9
Mean age, years (s.d.)	45.3 (23.06)	48.3 (21.74)	42.8 (23.61)	45.6 (24.66)	42.8 (22.62)
Patient's Primary Health Network, %					
Country WA	26.2	36.5	38.0	41.3	46.2
Perth South	32.4	33.9	30.1	34.2	34.2
Perth North	38.5	26.7	28.8	21.3	17.2
Interstate	1.3	1.3	1.5	1.1	0.4
Missing	1.7	1.6	1.6	2.1	2.0
Patient concession status positive, %	33.0	34.8	31.8	33.7	29.0
Comorbid condition positive, %	19.6	20.1	18.2	23.8	18.7
Missing	2.0	1.6	3.8	2.9	4.3
Mental health condition positive, %	25.9	28.2	23.5	26.1	26.3
Missing	2.9	1.6	3.8	2.9	4.3
Patient remote positive, % (remote & very remote Australia, ARIA)	5.9	4.7	7.5	5.0	4.5
Missing	1.0	1.0	1.0	1.1	0.8
Patient disadvantaged positive, % (top 40% percentiles of most disadvantage, SEIFA IRSD)	10.5	10.1	11.6	8.2	9.8
Missing	16.8	18.0	16.6	15.8	14.1
Multiple UTIs per patient, %	17.0	17.7	15.6	19.1	17.7
Consultation					
Temperature recorded, %, (% of which fever positive >=37.5C)	16.3 (11)	16.1 (6)	16.9 (13)	16.6 (23)	14.6 (11)
Urine dipstick tested, %, (% of which positive result)	95.5 (93)	5.5 (92)	3.8 (95)	2.8 (91)	5.8 (93)
Culture performed, %, (% of which had positive growth for any pathogen)	3.1 (99)	3.9 (100)	2.6 (100)	2.3 (95)	2.8 (100)
Sensitivity performed, %	0.0	0.0	0.0	0.0	0.0
Weekend consult, %	9.2	9.2	9.6	8.2	8.6
Prescription					
Repeat issued on prescription, %	28.4	22.0	30.7	48.2	22.0
Reason for prescribing entered, %	17.8	21.7	21.8	19.7	15.4

1

As seen in **Figure 5-2**, there were notable changes in the proportions of antibiotic lines prescribed across patient age groups. Children had much higher ratios of non-first-line to first-line prescriptions than adult age groups, by a factor of 3.6-6.4 (**Appendix D.3: Table D-4**). The proportions of second-line and not recommended antibiotic prescriptions increased with decreasing age (**Appendix D.3: Table D-5**).

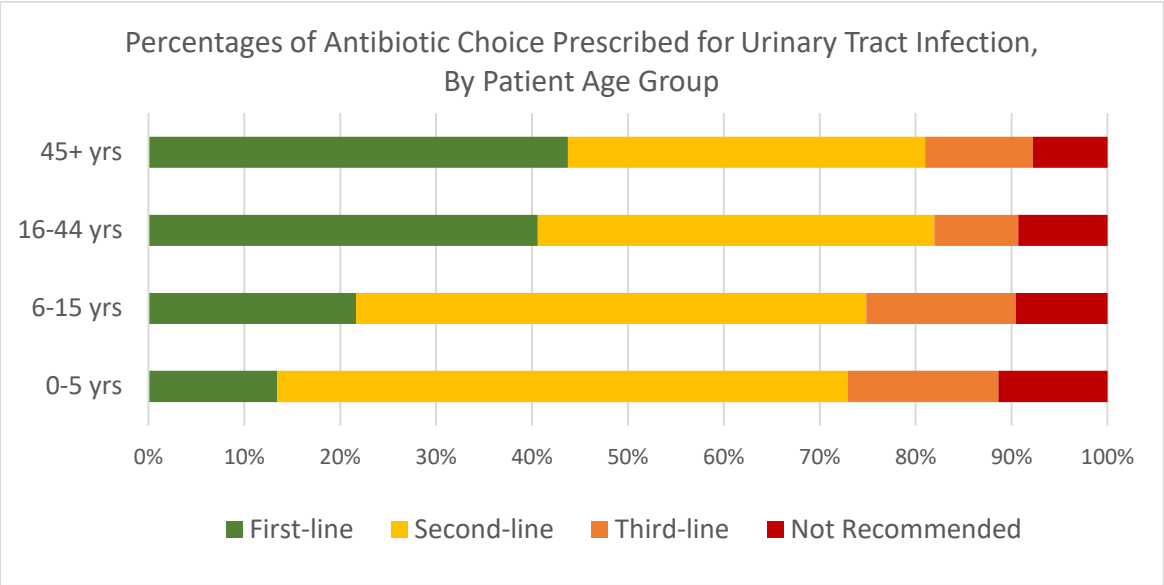


Figure 5-2: Bar graph of ordinal choice / line of antibiotic prescribed for initial presentations of urinary tract infection, by patient group

Among all antibiotic prescriptions issued for each patient group, 57% of women, 68% men and 82% children under sixteen received antibiotic prescriptions other than first-line (**Table 5-5**). While the proportions of first-line and second-line agents prescribed for women appeared in order in which they appear in the guidelines (29), both men and children received higher proportions of second-line than first-line antibiotics (**Figure 5-3**). Children under sixteen years received second-line (56%) more than three times as often as first-line antibiotics (18%).

Table 5-5: Frequency table of first-line and non-first-line antibiotics prescribed for initial episodes of urinary tract infection, by patient group

	First-line	Non-first-line	Total
Women	6,290	8,238	14,528
	43.3	56.7	100
Men	504	1,068	1,572
	32.06	68	100
Children under 16yrs	333	1,540	1,873
	18	82	100
Total	7,127	10,846	17,973
	39.65	60.35	100

Key
frequency
row percentage

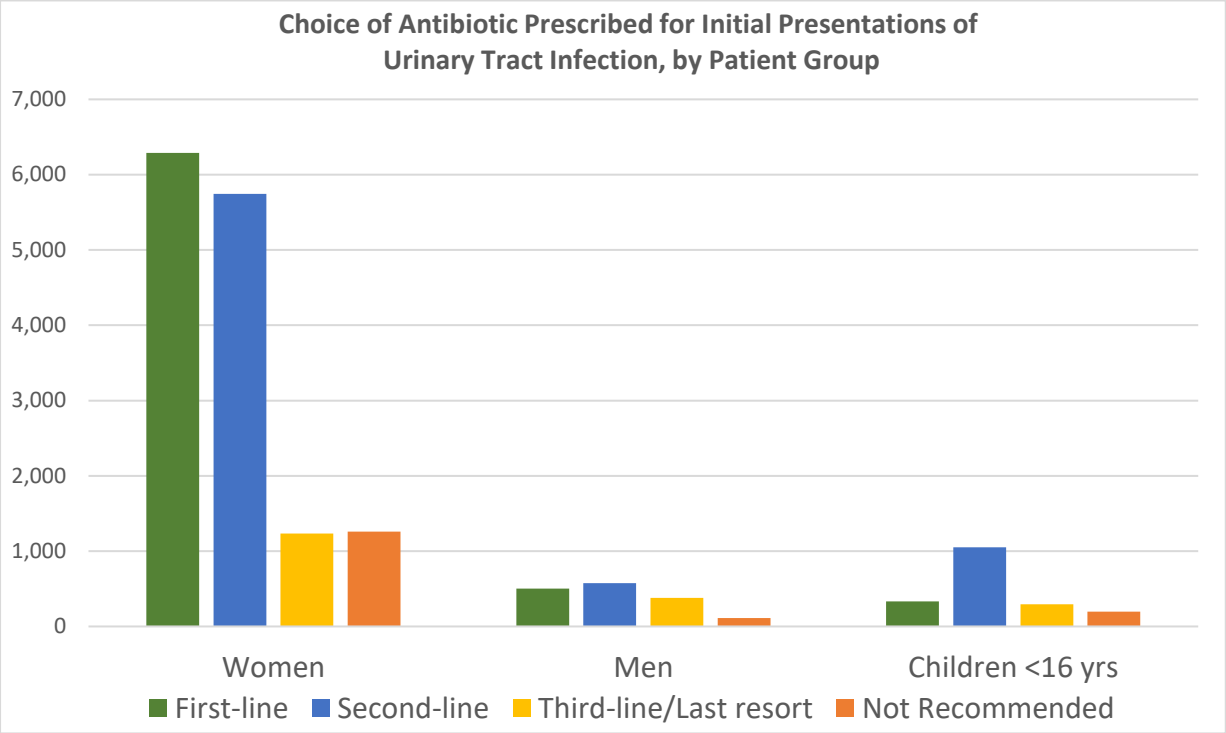


Figure 5-3: Bar graph of counts of ordinal choice of antibiotic prescribed for initial presentations of urinary tract infection, by patient group

Despite guideline recommendations stating that both children and men should receive both culture and sensitivity testing (29), no children or adult males receiving prescriptions for initial UTI received both forms of testing. Among all UTI diagnoses for each patient group, culture testing occurred for 2% children, 3% of women and 3% of men. There were no sensitivity testing results available for patients presenting with initial UTI, although there were sensitivity results present for other conditions, and, despite guideline recommendations, there were no sensitivity test results available for all 430 norfloxacin prescriptions issued (29). Urine dipstick testing was recorded in 96% consultations (**Table 5-2**). For a summary of how the antibiotic prescribing for UTI analysed here compares with prominent quality indicators, please see **Appendix G.2**.

A repeat was issued on 28% prescriptions for UTI, and 99% of these were for one repeat. While a repeat can be required to provide a guideline-concordant course for cefalexin, 56% prescriptions with repeats issued were for antibiotic agents other than cefalexin, and for which a repeat is typically not required. Other than cefalexin, repeats were numerically most common for trimethoprim and amoxicillin with clavulanate (**Table 5-6**). Proportionally, however, repeats on prescription were much more common among third-line / last resort antibiotics (48%) than first-line (21%), or second-line cefalexin

(31%) (**Appendix D.4**). The antibiotics restricted by PBAC in 2020 account for 60% of repeats issued for initial UTI in this dataset (127,128). By age group, children 6-15 years received the highest proportion of repeats issued, and adults 16-24 years received the lowest (**Table 5-7**).

Table 5-6: Frequency table of antibiotic prescriptions issued with repeats for initial presentations of urinary tract infection, by active ingredient

Active ingredient	Repeat Negative	Repeat Positive	Total
Amoxicillin	396	114	510
Amoxicillin with clavulanate	725	677	1,402
Ampicillin	1	0	1
Azithromycin	11	0	11
Cefaclor	72	11	83
Cefalexin	5,108	2,266	7,374
Ceftriaxone	1	0	1
Cefuroxime	8	3	11
Ciprofloxacin	60	8	68
Clarithromycin	8	2	10
Clindamycin	2	1	3
Doxycycline	12	5	17
Erythromycin	10	6	16
Flucloxacillin	5	0	5
Nitrofurantoin	572	130	702
Norfloxacin	214	216	430
Phenoxymethylpenicillin	8	0	8
Roxithromycin	5	4	9
Trimethoprim	5,455	1,521	6,976
Trimethoprim with sulfamethoxazole	202	134	336
Total	12,875	5,098	17,973

Table 5-7: Frequency table of whether repeats were issued on antibiotic prescriptions (negative or positive) for initial presentations of urinary tract infection, by patient age group

Patient Age Group	Repeat Negative	Repeat Positive	Total (count, row %)
45+ yrs, ref	5,701	2,446	8,147
	69.98	30.02	100
16-44 yrs	5,947	2,006	7,953
	74.78	25.22	100
6-15 yrs	630	364	994
	63.38	36.62	100
0-5 yrs	597	282	879
	67.92	32.08	100
Total	12,875	5,098	17,973

Key
frequency
row percentage

While cefalexin is typically the recommended antibiotic for patients with penicillin sensitivity (29), it was prescribed in 7,374 situations when only 5% of these patients had any record of a penicillin allergy label (**Appendix D.4.2**). Of cefalexin prescriptions with repeats, 0% men (n=5), 0% women at least 18 years of age, 53% (n=10) patients 16-17yrs, and 99% children (n=294) likely required a repeat for a full course (**Appendix D.4.**2). While over 99% repeats were likely unnecessary for adults over seventeen, 99% were potentially necessary for children. For patients at least sixteen years, the duration of cefalexin prescription was variable, most commonly five or seven days and up to fourteen days. Over-treatment was common for women receiving cefalexin prescriptions with repeats, however, under- and over-treatment were common for men. For children under sixteen years, the duration varied between three and fourteen days, and most commonly five days. Please see **Appendix D.4.2** for details.

5.3.1 Modelling introduction - clustering considerations

Noting that multiple patients may attend the same provider / GP, and multiple GPs may work at the same practice, this violates the assumption of independence underpinning the basis of generalised linear regression with allowance for unobserved heterogenous effects (362). With respect to antibiotics prescribed for initial UTI, there were for example between 46 to 1,929 patients per practice, and between five and eight unique providers per practice. Model design was driven by these clusters, and it was possible to include a random intercept to allow for unobserved heterogeneity at both the practice level, and within practice, the provider level for these data (408).

Following experimentation, the final model consisted of patient age group and gender with an interaction term. A three-level hierarchical model of patient level, within provider level, within practice level was developed, including random intercepts for individual practice ID and individual provider ID within their respective levels (409,410).[10]

[10] Recall that AMEs are used to summarise effects unless otherwise stated.

5.3.2 Model 1: ordinal choice of antibiotic prescribed

The ordinal model of choice of antibiotic prescribed (Model 1) and the equivalent, binary model of non-first-line prescribing (Model 2) are similar outcomes. As Model 1 utilises more information, the focus of discussions will be Model 1, and Model 2 will not be discussed in detail.

Patient age, gender, repeat prescription status, and patient comorbid condition status, urine dipstick testing and culture testing status were identified as predictors of non-first-line prescribing (**Table 5-8**, **Appendix D.5**). When considered independently, male gender, young patient age, prescriptions with repeats, and comorbid conditions were linked to non-first-line prescribing. Female gender, older patient age, prescriptions without repeats, urine dipstick testing and culture testing were independently associated with first-line prescribing, and were less likely to receive non-first-line prescribing. The following variables were insignificant in the multivariable model: patient PHN, patient measures of remoteness and socioeconomic disadvantage, concession status, patient mental health condition status, temperature recording status, day of the week, and whether a reason for prescribing was recorded.

Two effect modifiers were identified in the ordinal model for antibiotic choice: repeat prescription status and patient gender, both of which were found to independently interact with patient age. There first effect modification was between patient age group and gender. Increasing patient age was independently associated with decreasing probability of non-first-line antibiotic. However, when patient gender is allowed for, males had an increased probability of non-first-line prescribing for adults, compared to females, and the magnitude of effect increased with increasing age.

Table 5-8: Mixed effects models for initial presentations of urinary tract infection

Model	**Ordinal Line Prescribed** ref. First-line		**Binary Non-first-line** ref. First-line		**Repeat Positive Prescribing** ref. Prescriptions without Repeats	
Independent Variable	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.
Patient Age group, (ref 45+yrs)						
16-44 yrs	1.180***	[1.099,1.268]	1.294***	[1.188,1.410]	0.886*	[0.799,0.983]
6-15 yrs	2.191***	[1.904,2.520]	3.724***	[3.063,4.526]	1.670***	[1.363,2.047]
0-5 yrs	2.839***	[2.443,3.300]	7.433***	[5.791,9.540]	1.158	[0.923,1.453]
Patient gender, (ref Female)						
Male	1.791***	[1.581,2.029]	1.825***	[1.559,2.137]	2.114***	[1.775,2.516]
Age group # Gender						
16-44 yrs # Male	0.877	[0.696,1.105]	0.809	[0.600,1.090]	0.967	[0.699,1.339]
6-15 yrs # Male	0.759	[0.528,1.091]	0.838	[0.487,1.442]	0.405***	[0.238,0.690]
0-5 yrs # Male	0.596**	[0.422,0.844]	0.596	[0.336,1.057]	0.343***	[0.200,0.588]
Repeat on script, (ref. negative)						
Positive	1.627***	[1.501,1.763]	2.088***	[1.880,2.319]		
Comorbid condition positive, (ref. negative)						
Positive	1.215***	[1.117,1.322]	1.262***	[1.143,1.394]		
Missing	1.649	[0.899,3.024]	1.65	[0.779,3.493]		
Culture tested, (ref. negative)						
Positive	0.740**	[0.609,0.900]	0.749*	[0.599,0.938]	1.472**	[1.116,1.943]
Dipstick tested, (ref. negative)						
Positive	0.710**	[0.576,0.875]	0.676**	[0.532,0.860]	0.661*	[0.474,0.921]
Ordinal Line Prescribed, (ref First-line)						
Second-line					1.910***	[1.702,2.144]
Third-line / Last resort					4.112***	[3.522,4.801]
Not Recommended					1.103	[0.915,1.329]
Temperature recorded, (ref negative)						
Positive					1.186*	[1.023,1.375]
Multiple UTI episodes for patient, (ref negative)						
Positive					1.556***	[1.378,1.758]
Potential changes in prescribing behaviours allowed for over time by inclusion of continuous variable for year of consultation in all models.						
cut1	55.1715	[4.729,105.614]				
cut2	57.47025	[7.027,107.913]				
cut3	58.53822	[8.095,108.981]				

Variable	**Ordinal Line Prescribed** ref. First-line		**Binary Non-first-line** ref. First-line		**Repeat Positive Prescribing** ref. Prescriptions without Repeats	
	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.
var(cons[practice id)	1.064	[0.987,1.147]	1.075	[0.964,1.200]	1.568**	[1.115,2.204]
var(cons[practice id> provider id]	2.923***	[2.460,3.473]	5.803***	[4.311,7.810]	35.00***	[19.17,63.89]
Observations	17973		17973		17973	
Information Criterion						
AIC	38670.8		19842.5		14537.1	
BIC	38811.1		19967.3		14677.4	
ICC Level	ICC	[95% C.I.]	ICC	[95% C.I.]	ICC	[95% C.I.]
Practice	0.014		0.014	[0.003,0.061]	0.062	[0.030,0.124]
Provider within practice	0.257		0.358	[0.321,0.395]	0.549	[0.507,0.590]

Note: Exponentiated coefficients; 95% confidence intervals in brackets: * p<0.05, ** p<0.01, *** p<0.001

As depicted in **Figure 5-4**, older men are eleven percentage points less likely to receive first-line antibiotics (-0.109, p<0.001, 95%CI: -0.132, -0.086), four percentage points more likely to receive third-line or not recommended antibiotics (both p<0.001, see **Appendix D.5.2**) than similarly aged women. Relative to young adult females, young adult men were eight percentage points less likely to receive first-line (-0.083, p<0.001, -0.118, -0.047), and three percentage points more likely to receive third-line or not recommended antibiotics (both p<0.001, see **Appendix D.5.2**). For children, there was no significant difference between genders in the probability of receiving first-line antibiotics (both p>0.064, see **Appendix D.5.2**), or for non-first-line choices (all p>0.05, see **Appendix D.5.2**).

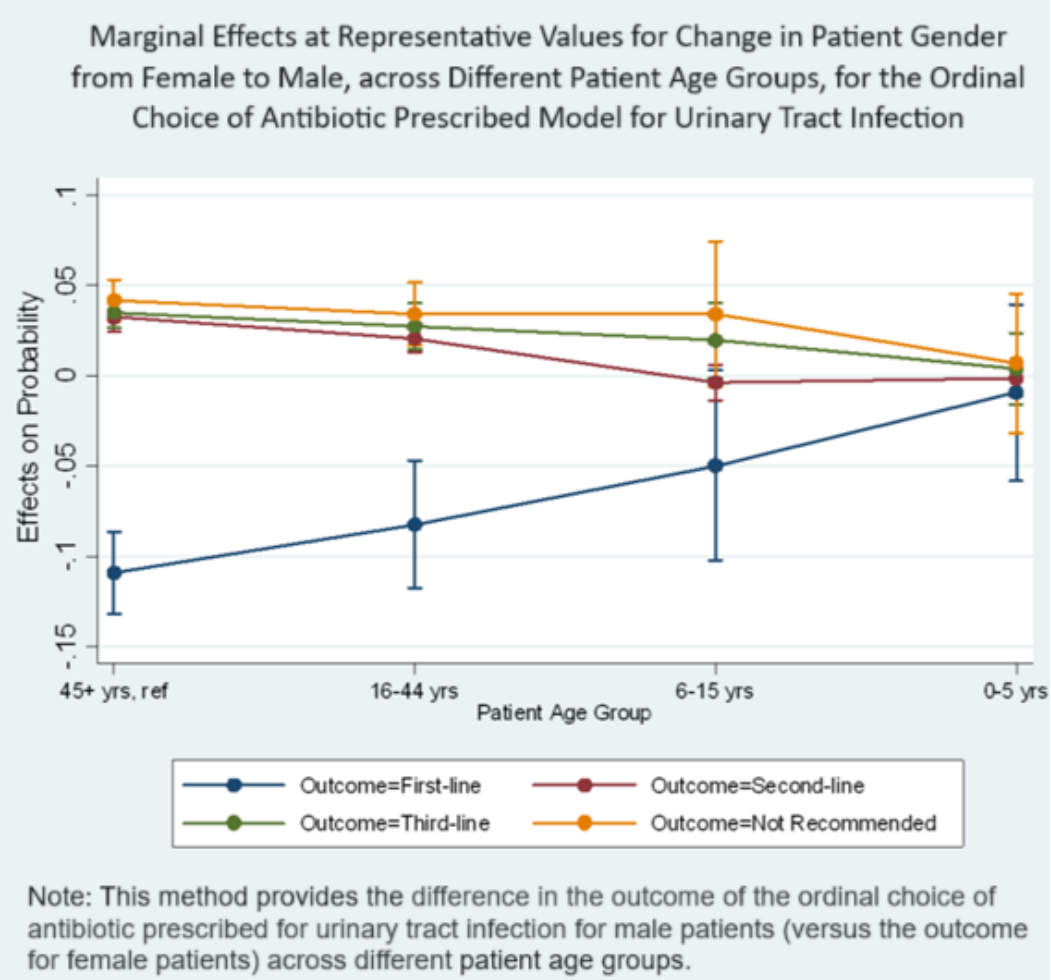


Figure 5-4: Plot of marginal effects at representative values for change in patient gender from female to male, at different patient age groups for model 1 (ordinal line of antibiotic prescribed) for initial presentations of urinary tract infection

The second effect modification was between patient age group and repeat prescription status. Recall that increasing patient age was independently associated with decreasing probability of receiving a non-first-line antibiotic. When repeat prescription status is taken into account, however, a repeat being present decreased the probability of first-line antibiotics and increased the probability of non-first-line prescribing for adult age groups. Compared to the patients receiving prescriptions without repeats, adults with a repeat issued on the prescription were eleven percentage points less likely to receive first-line antibiotics (both p<0.001, see **Appendix D.5.4**), and three to four percentage points more likely to receive a non-first-line antibiotic (all p<0.001, see **Appendix D.5.4**), (**Figure 5-5**). With a repeat present, there was no significant difference in the antibiotic received for children (all p>0.10, see **Appendix D.5.4**). There was no three-way effect modification present between patient age, gender and repeat prescription status.

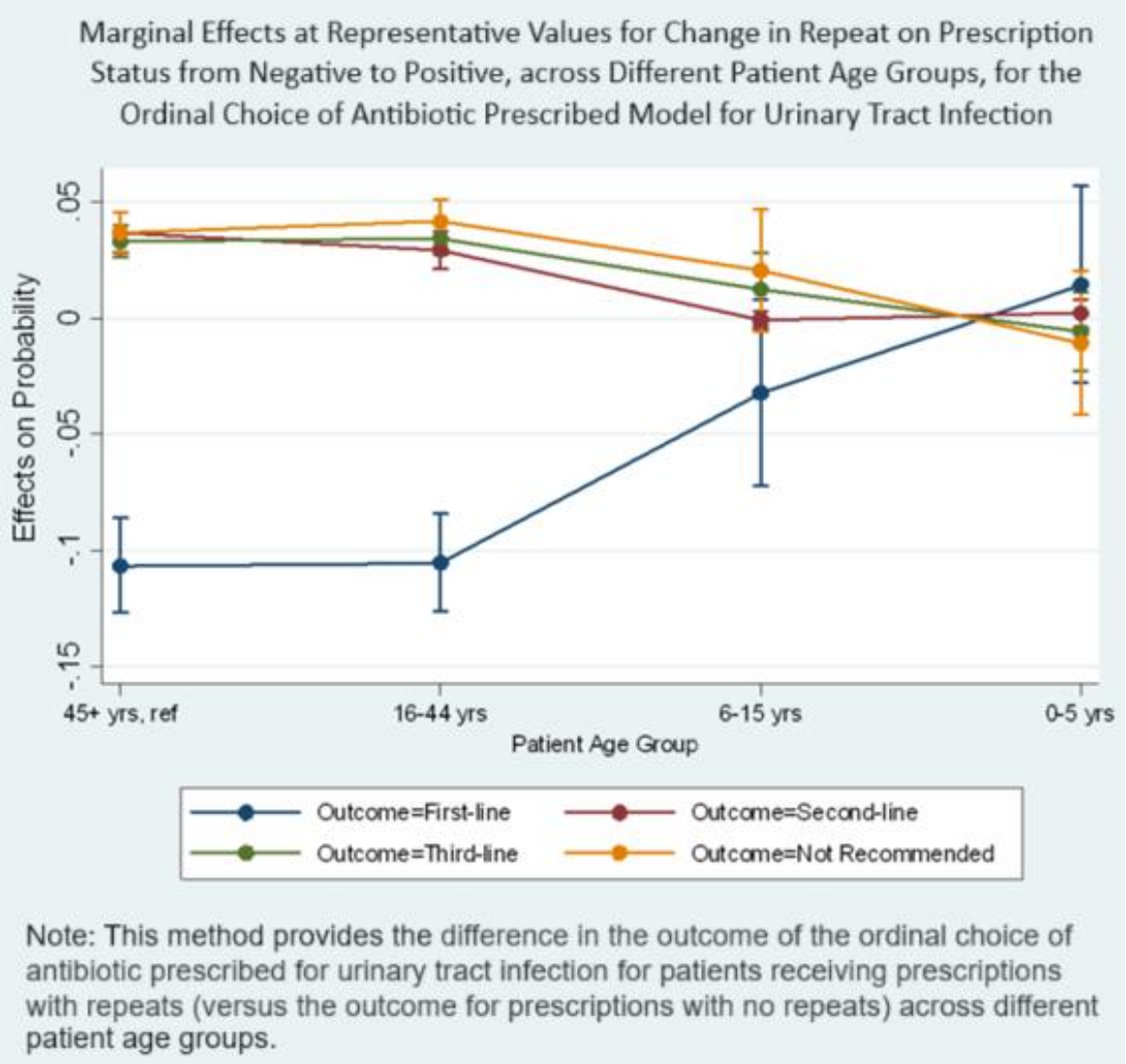


Figure 5-5: Plot of marginal effects at representative values for change in repeat on prescription status from negative to positive by patient age group for model 1 (ordinal line of antibiotic prescribed) for urinary tract infection

With all other covariates held constant at the sample means, depending upon patient gender and repeat status, adults had a 26-47% chance of receiving a first-line antibiotic, while for older children this was 22-30% and 23-26% for young children (all p<0.001, see **Appendix D.5.5**). Young children had the lowest probability of receiving first-line antibiotics, while adult patient groups had the highest.

Again, with all other covariates held constant at the sample means, women 45 years and over receiving a prescription without a repeat had a 47% chance of receiving a first-line antibiotic (0.471, p<0.001, 95%CI: 0.445, 0.498), while with a repeat this dropped to 36% (0.363, p<0.001, 95%CI: 0.334, 0.392). For women 16-44 years, the probability of receiving a first-line antibiotic was 44% without a repeat (0.438, p<0.001, 95%CI:

0.412, 0.465) but dropped to 33% with a repeat (0.331, p<0.001, 95%CI: 0.303, 0.360). Women aged at least 45 years and 16-44 years had probabilities of 39-43%, and 40-43%, respectively, of receiving second-line antibiotics, regardless of repeat prescription status (all p<0.001, see **Appendix D.5.5**). With other covariates held at sample means, for men the highest probability outcome (of 43-44%) was a second-line antibiotic, regardless of their adult age group, or repeat prescription status (all p<0.001, see **Appendix D.5.5**). Similarly, the most likely outcome for children was second-line antibiotics (at 43-44%), regardless of the age group, gender, or repeat status (all p<0.001, see **Appendix D.5.5**).

Relative to patients not receiving dipstick testing, across all age groups, patients who received urine dipstick testing were seven percentage points more likely to receive first-line (0.065, p=0.002, 95% CI: 0.024, 0.107), and two percentage points less likely to receive second-line (-0.025, p=0.008, 95% CI: -0.043, -0.007), third-line (-0.019, p=0.001, 95% CI: -0.031, -0.008) or not recommended antibiotics (-0.021, p=0.001, 95% CI: -0.0332, -0.009), (**Appendix D.5.1: Table D-21**). Compared to patients not receiving culture testing, patients receiving culture testing were six percentage points more likely to receive first-line antibiotics (0.060, p=0.002, 95%CI: 0.021, 0.098), and two percentage points less likely to receive any non-first-line antibiotic option (all p<0.009, see **Appendix D.5.1: Table D-21**).

Patients with a comorbid condition were four percentage points less likely to receive first-line (-0.037, p<0.001, 95%CI: -0.053, -0.021), and one percentage point more likely to receive second-line (0.011, p<0.001, 95%CI: 0.006, 0.016), third-line (0.012, p<0.001, 95%CI: 0.007, 0.017) or not recommended (0.014, p<0.001, 95%CI: 0.008, 0.021) antibiotics than patients without chronic conditions. Patients with missing comorbid condition status were two percentage points more likely to receive second-line antibiotics (0.022, p=0.002, 95% CI: 0.008, 0.036) than patients without comorbid conditions (see **Appendix D.5.1: Table D-21**).

As can be seen in **Table 5-8**, the ICC for practice level in Model 1 for ordinal choice was 0.014 while the ICC for provider level was 0.257. ICC can be interpreted as the remaining variance unexplained by observed heterogeneous effects in the model. Therefore, of the variance not explained by observed heterogenous effects in Model 1,

the provider level was responsible for 26% of variance compared to only 1% for practice level.

5.3.3 Model 3: predictors of repeat positive prescribing

The predictors of a repeat being issued on the antibiotic prescription in Model 3 were identified as patient age, gender, ordinal choice of antibiotic prescribed, whether the patient had multiple UTI episodes, temperature recording, culture testing and urine dipstick testing status (**Table 5-7, Appendix D.6**). The probability of receiving a repeat on prescription was linked to both third-line prescribing and second-line prescribing. There was an effect modification between patient age group and gender. The following variables were insignificant in the multivariable model: day of the week of the consultation, patient concession status, measures of patient remoteness and socioeconomic disadvantage, mental health conditions status and comorbid condition status.

Patients receiving third-line prescriptions were nineteen percentage points more likely (0.187, p<0.001, 95%CI: 0.163, 0.211), and patients receiving second-line antibiotics were eight percentage points more likely (0.080, p<0.001, 95%CI: 0.064, 0.095), to receive a repeat than patients receiving first-line antibiotics. There was no significant difference between patients receiving not recommended antibiotics (0.011, p=0.310, 95%CI: -0.010, 0.033) (**Appendix D.6.1: Table D-22**).

When patient age group and gender are considered together using MERs, there is a significant difference for adults between the effect of gender on the chance of receiving a repeat (**Appendix D.6.2**). Men 45 years and over were ten percentage points (0.100, p<0.001, 95%CI: 0.075, 0.124) and men 16-44 years were nine percentage points (0.093, p<0.001, 95%CI: 0.054, 0.131) more likely to receive a repeat on their prescription than equivalent women. There was no significant difference in the effect of gender on children (-0.021, p=0.543, 95%CI: -0.089, 0.047), (-0.040, p=0.205, 95%CI: -0.101, 0.022).

As one may see in **Figure 5-6**, when all other covariates are kept at sample means, the adjusted probability of receiving a repeat on the prescription is highest for men 45 years and over at 38% (0.377, p<0.001, 95%CI: 0.335, 0.419). For women of equivalent age,

the chance of receiving a repeat was ten percentage points less (0.276, p<0.001, 95%CI: 0.243, 0.309). Men aged 16-44 years had a 36% chance of receiving a repeat (0.355, p<0.001, 95%CI: 0.303, 0.407), and again this was ten percentage points lower for similar women (0.261, p<0.001, 95%CI: 0.229, 0.293). Female children 6-15 years had a probability of 34% (0.344, p<0.001, 95%CI: 0.300, 0.387) of receiving a repeat, while this was two percentage points lower (0.322, p<0.001, 95%CI: 0.250, 0.395) for equivalent males, albeit noting the 95% CIs partly overlap. Young female children had a 29% probability of receiving a repeat (0.295, p<0.001, 95%CI: 0.252, 0.337), while similar males had the lowest probability at 25% (0.254, p<0.001, 95%CI: 0.191, 0.318), again noting the partial overlap of CIs. Please see **Appendix D.6.3** for more detail.

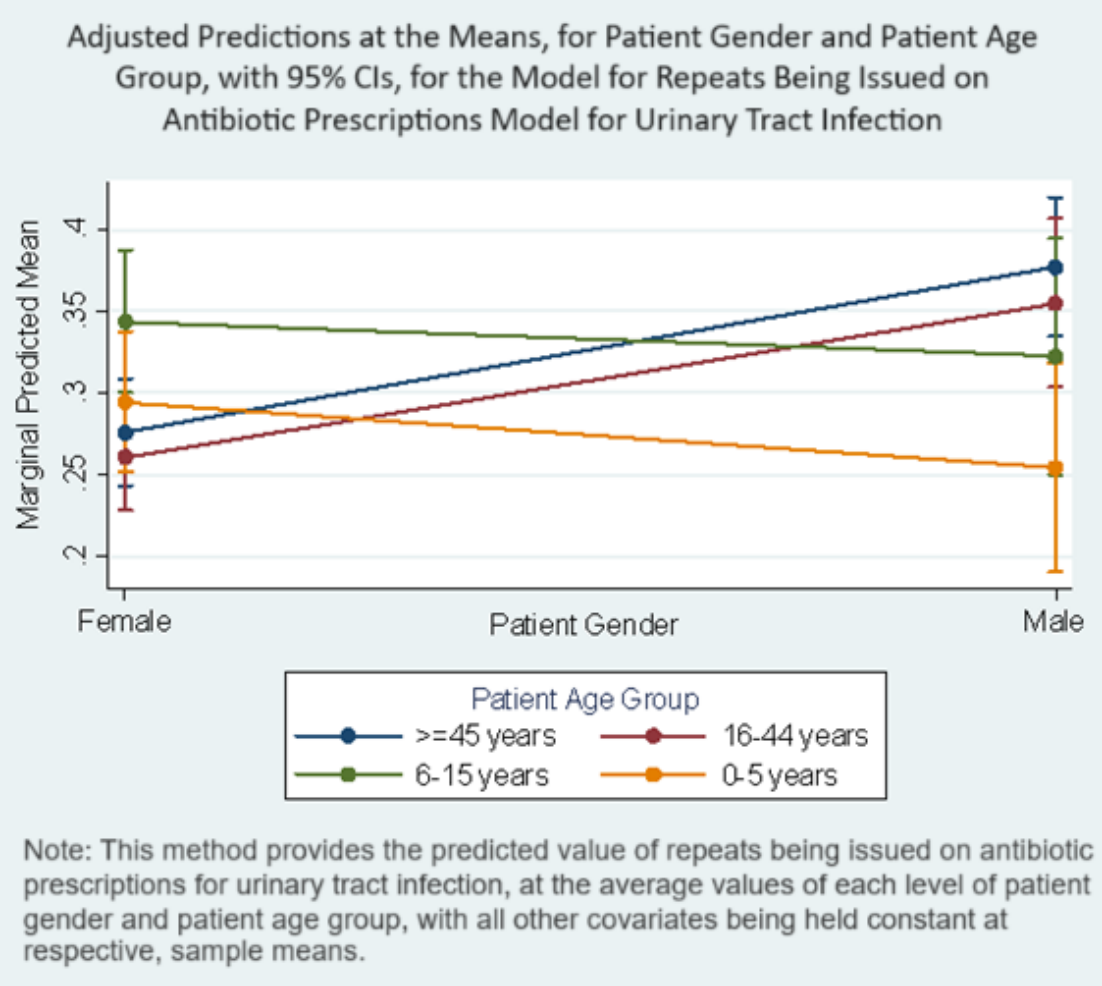


Figure 5-6: Graph of adjusted predictions at the means for model 3 (repeats present on antibiotic prescription) at differing values of patient gender and age group, keeping all other covariates in the model constant at their sample means

Patients with multiple, separate UTI episodes were six percentage points more likely to receive a repeat on the prescription than patients with a single episode (0.057, p<0.001, 95%CI: 0.040, 0.073). Patients receiving urine dipstick testing were five percentage

points less likely to receive a repeat than patients without dipstick testing (-0.049, p=0.011, 95%CI: -0.087, -0.012). Meanwhile, patients receiving culture testing were five percentage points more likely to receive a repeat than patients who did not receive culture testing (0.050, p=0.008, 95%CI: 0.013, 0.087). Regardless of patient age, patients receiving temperature testing were two percentage points more likely to receive a repeat than patients who did not have their temperature tested (0.022, p=0.026, 95%CI: 0.003, 0.040). (Please see **Appendix D.6.1: Table D-22**).

The ICC for the practice level was found to be 0.062 (95% CI: 0.030, 0.124), whereas the ICC for the provider level was 0.549, (95% CI: 0.507, 0.590). As such, the provider level was responsible for 55% of variance compared to only 6% for practice level, of variance not explained by homogenous effects in Model 3 (see **Table 5-8**).

5.3.4 Modelling considerations

For the purposes of comparison, the same modelling process was performed without allowance for unobserved heterogeneity, using logit and ordered logit models, in addition to trialling a dummy variable for practice ID number (in lieu of a random intercept for practice). With no allowance for unobserved heterogeneity, the ordinal logistic model for choice of antibiotic included patient remoteness status, day of the week and patient's PHN also become significant predictors in addition to those identified from the mixed effects models. This represents nine of the total fourteen variables tested. For the model repeat prescribing, with observed heterogeneity only, eleven of the total fourteen variables became significant, including day of the week, reason recording status, and patient PHN. Without allowance for unobserved heterogenous effects, the models included more variables and tended to have lower AORs, for the most part, for the variables in both models (see **Appendix D.8**). This highlights that different, likely misleading, results are obtained when using fixed models which do not allow for unobserved heterogeneity as achieved by using mixed models.

Likelihood ratio testing demonstrated that the adult male and child samples were insufficient samples to use in separate models (376). Brant testing indicated that the distances between first-line, second-line and not recommended antibiotics are not the same (378,411).

5.4 Summary

This research offers new insights regarding the complex nature of antibiotic prescribing for UTI in Australian general practice. It demonstrates that there is substantial, unjustifiably non-first-line antibiotic prescribing occurring for patients with initial presentations of UTI in Australian general practice, and repeats frequently issued on prescription without justification. Sixty percent of patients received non-first-line prescriptions for initial episodes of care for UTI: children under sixteen (82%) and men (68%) and women (57%). Culture testing was low, results were present for 2% children, 3% of women and 3% of men, and sensitivity testing results were absent. Children and men were prone to receiving non-first-line antibiotics and frequently lacking both culture and sensitivity testing (29).

The predictors of increasing line of antibiotic prescribed were identified as patient age group, patient gender, comorbid condition status, repeat prescription status, urine dipstick-testing, culture testing. Predictors of repeat prescribing included patient age group, ordinal choice of antibiotic, urine dipstick testing, temperature recording, multiple episodes. Day of the week, practice size, patient concession, remoteness, and disadvantage status, mental health condition and cefalexin prescription status were insignificant in all models. It is also apparent that non-first-line prescribing and repeat positive prescribing are linked, due to each variable's presence in the model for the other.

From the model of ordinal choice of antibiotic, repeat negative and female gender are linked to lower probability of higher line prescribing in adults. Young children were least likely to receive first-line antibiotics, followed by older children, then adults. Children and men were most likely to receive second-line antibiotics. Urine dipstick and culture testing being performed were associated with lowered chance of non-first-line prescribing. Patients with comorbid conditions were found to be at increased probability of non-first-line prescribing compared to patients without comorbid conditions.

Repeats being issued on prescriptions appears strongly linked to third-line, and to a lesser extent, to second-line antibiotic prescribing. Adult males had a notably higher probability of receiving repeats on antibiotic prescriptions than adult females. Patients with multiple, separate UTI episodes during the study period were six percentage points

more likely to receive a repeat than patients with only a single UTI episode. Urine dipstick testing being performed was linked to lower likelihood of repeat positive prescribing, while culture and temperature testing being performed increased the probability of repeat positive prescribing.

Patient age and gender are the most pressing drivers of inappropriate prescribing for UTI, and it is clear that there are differences in the patient groups as is expected given different guidelines for different patient groups (29). By virtue of the fact that UTI in men and children may be considered complicated as opposed to uncomplicated infection in women (412,413), it is unsurprising that men and children have increased probabilities for non-first-line prescribing and repeat positive prescribing than adult women.

While attempting to clarify whether predominantly patient-specific factors might be driving inappropriate UTI prescribing, several of the predictors identified are also, consultation- or prescription-related. Measures of patient remoteness and socioeconomic disadvantage were hypothesised as potential predictors of inappropriate prescribing but this does not appear to be the case for UTI. Similarly, patient comorbid and mental health conditions were considered potentially relevant to inappropriate prescribing, however, only comorbid condition status emerged as a predictor for UTI.

Of the variance not explained by observed heterogenous effects in Model 1 for ordinal choice of antibiotic, the provider level was responsible for 26% of variance compared to only 1% for practice level, as detailed earlier. Of variance not explained by observed heterogenous effects in Model 3 for repeat positive prescribing, the provider level was responsible for 55% of variance compared to only 6% for practice level.

Conditional upon the homogenous effects, we find that all outcomes of all models for UTI are minimally correlated within the same practice, however, they are moderately correlated within the same provider and practice. This can be interpreted as the provider level being predominantly responsible for the remaining variance unexplained by observed heterogenous effects in all models, rather than the practice level which is responsible for little residual variance. This suggests that the individual provider has substantially more effect on choice of antibiotic than variation by practice.

A comparison of results obtained from the mixed effects models allowing for unobserved heterogeneity and those without unobserved heterogeneous effects highlights that there are notable differences in the results. For example, the inclusion of PHN as a predictor of non-first-line prescribing in the ordinal logit model for ordinal prescribing would likely place pressure on PHNs, which may be unfounded.

CHAPTER 6 ANALYSIS OF CHANGES IN ANTIBIOTIC PRESCRIBING FOR UPPER RESPIRATORY TRACT INFECTION CONDITIONS OVER TIME

6.1 Background to trends analyses for upper respiratory tract infection and urinary tract infection

There were 19,5 million encounters by 791,280 patients, of which 53% were female, and the mean patient age was 38 years. The strong majority (97%) of patients had residential addresses listed as in WA. By PHN for WA-listed patients, 30% patients had residential addresses within the Country WA PHN, 34% in Perth North PHN, 35% in Perth South PHN, and 1% were missing PHN information (42). By accessibility and remoteness index (34,35). these correspond to 66% in major cities of Australia, 5% in remote, 1% in very remote, and 1% were missing PHN information.

Over the study period of 1 January 2012 to 30 June 2017, inclusive, there were fluctuations in involvement of individual GPs, as well as to a lesser degree, individual general practices, with a small number of practices opening and closing. **Figure 6-1** depicts the proportion of practices located within each PHN over time, including interstate PHNs.

Multiple steps were taken to limit the dataset to initial presentations for both condition groups, URTI and UTI. Some of these steps included the removal of diagnoses of UTI/URTI containing various terms to describe either chronic/recurrent UTI/URTI or follow-up consultation from the dataset. Furthermore, any UTI/URTI diagnoses with another presentation for the same condition group occurring within fourteen days prior to the diagnosis of interest were considered the same episode of UTI/URTI and were therefore excluded. Diagnoses containing a definitive pathogen, which would have required laboratory pathology to ascertain, were also excluded, as these are unlikely to represent initial consultations.

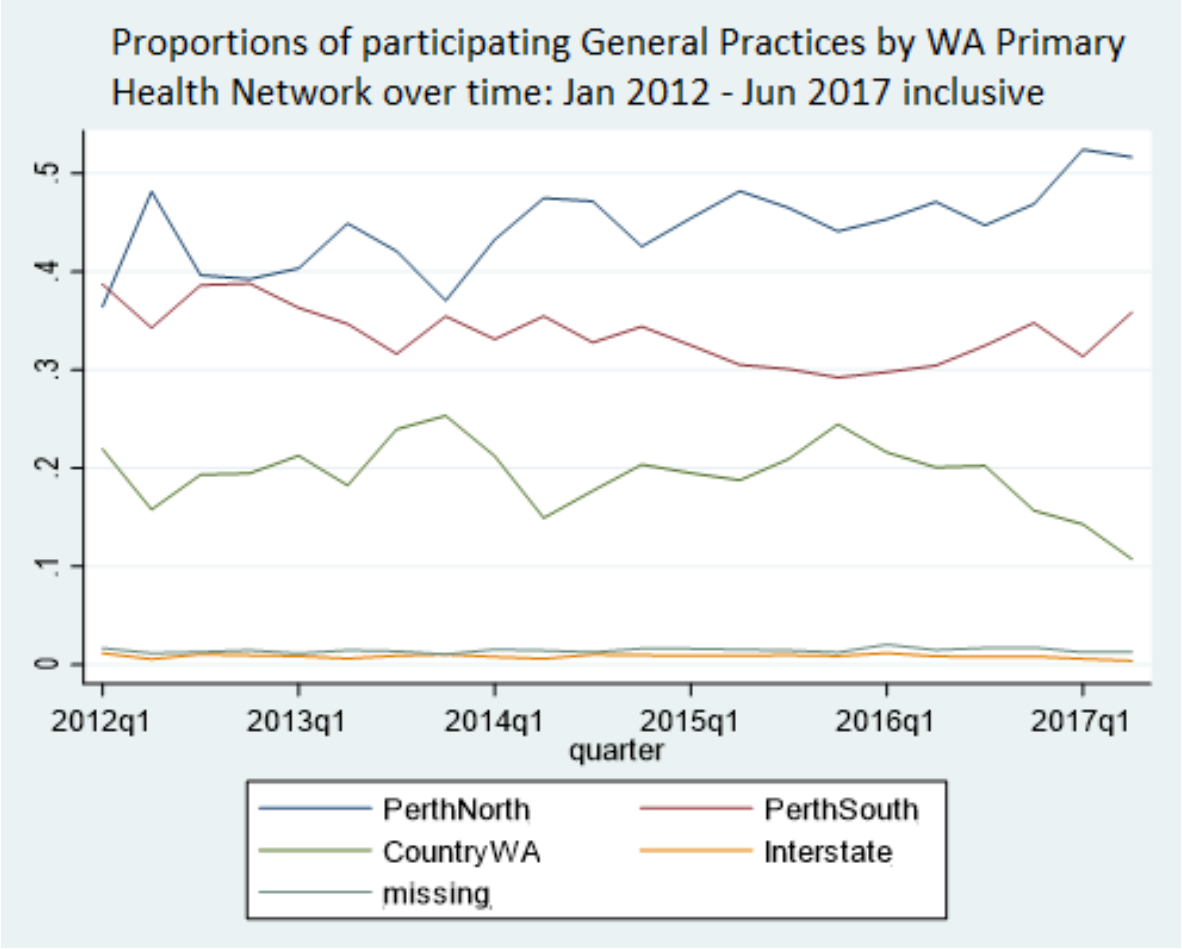


Figure 6-1: Plots for proportions of participating general practices by Western Australian primary health network, January 2012 to June 2017, inclusive, by quarter

There were 145,889 initial episodes of care for URTI and 21,206 for UTI during the study period. For URTI there was an antibiotic prescribing rate of 36%, and the frequency of consultation and antibiotic prescribing peaked at approximately six years. For UTI, there were 17,974 systemic antibiotics issued, and the strong majority of these (81%) were prescribed to females at least sixteen years of age.

6.2 Introduction to trends analyses for upper respiratory tract infection

The objective of this analysis was to explore trends in antibiotic prescribing for patients with initial presentations with URTI conditions over time. Inappropriate prescribing is frequently reported for URTI presentations to primary care, ranging from prescribing when not indicated (210,270,272-274,332), to using non-first-line antibiotics without initially treating with first-line antibiotics (270,271,275-277,280,282,284,295,297,321,322,329,332). As antibiotic prescribing is typically not

indicated for initial episodes of care for URTI (29), it was primarily of interest to establish whether there were notable changes over time in unnecessary antibiotic prescribing to patients at these initial episodes of care for URTI. Secondary questions included whether there were substantial changes over time in the proportion of patients receiving antibiotic prescriptions for initial diagnoses of URTI conditions, and the proportion of patients receiving non-first-line antibiotics among all prescribed antibiotics.

While the local epidemiology of these URTI conditions is not expected to change meaningfully over a relatively short period of time, there may be changes to antibiotic prescribing behaviours in light of growing antibiotic resistance (12,14,18), as well as increasing publicity regarding antibiotic resistance and antibiotic stewardship initiatives as described in the Background chapter. Due to these factors, one would hope that inappropriate antibiotic prescribing may be decreasing. Therefore, it was of interest to establish whether or not antibiotic prescribing was decreasing and, if so, by how much. Favourable changes would include decreasing rates of likely unnecessary prescribing over time, for all URTI conditions, and reducing proportions of non-first-line antibiotics among all antibiotics prescribed for these conditions (275).

Previously defined outcome variables were used in this analysis, as described in the Methods chapter (Chapter 3). For ease of reference, visual depictions of how these outcomes were previously defined and obtained are included below (**Figure 6-2** and **Figure 6-3**). These diagrams also contain details regarding the denominator for each outcome variable. Recall that non-initial and / or repeat consultations were excluded for URTI, including the exclusion of consultations occurring within fourteen days of a previous URTI consultation for the same patient. URTI was defined to include uncomplicated URTIs, acute rhinosinusitis including the common cold and non-specific URTI, acute pharyngitis and / or tonsillitis, and AOM, influenza and ILI, in accordance with the Therapeutic Guidelines: Antibiotic (the guidelines) (29).

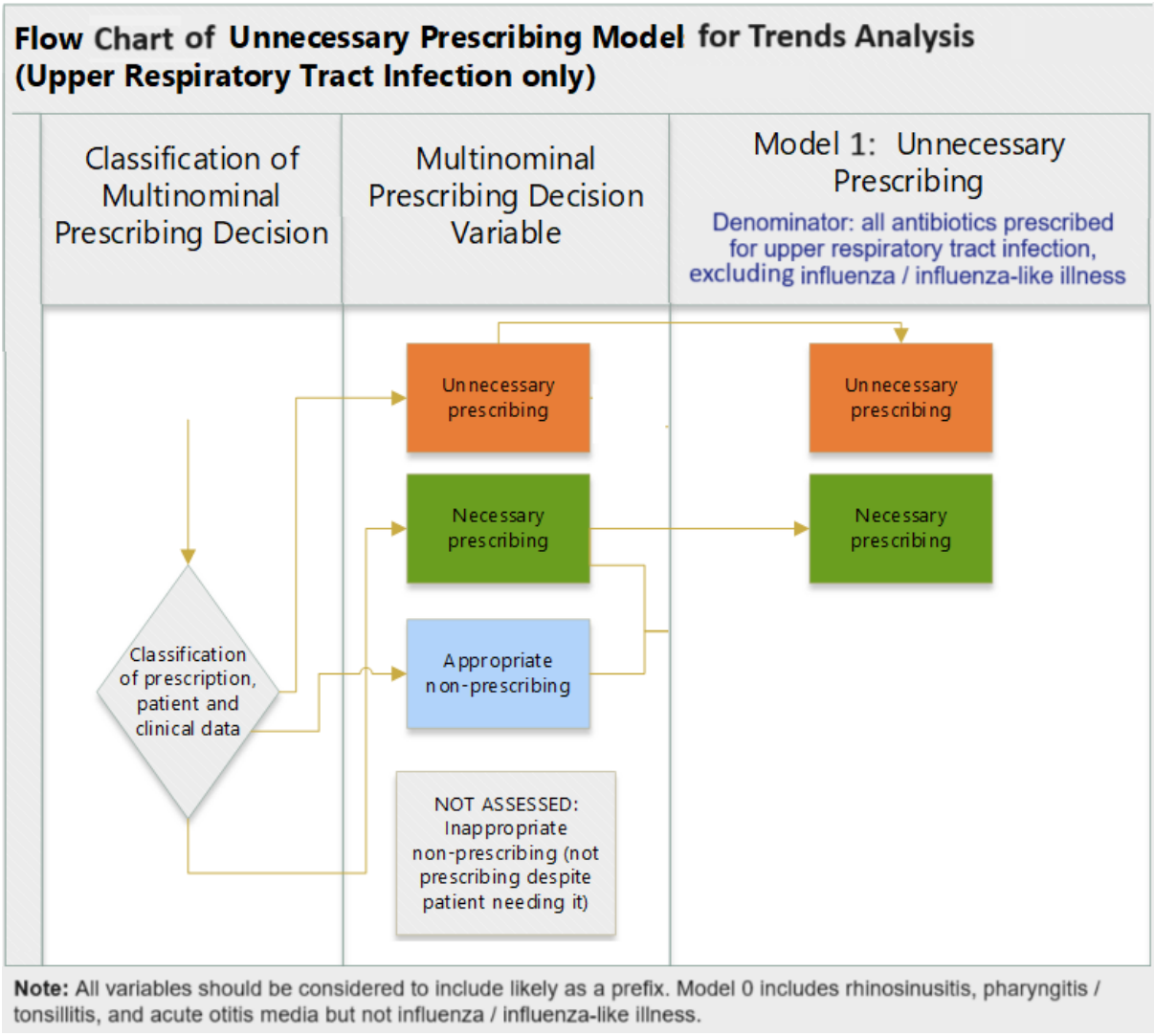


Figure 6-2: Depiction of the main outcome variables utilised in this trends analysis, and previous analyses for initial presentations of upper respiratory tract infection

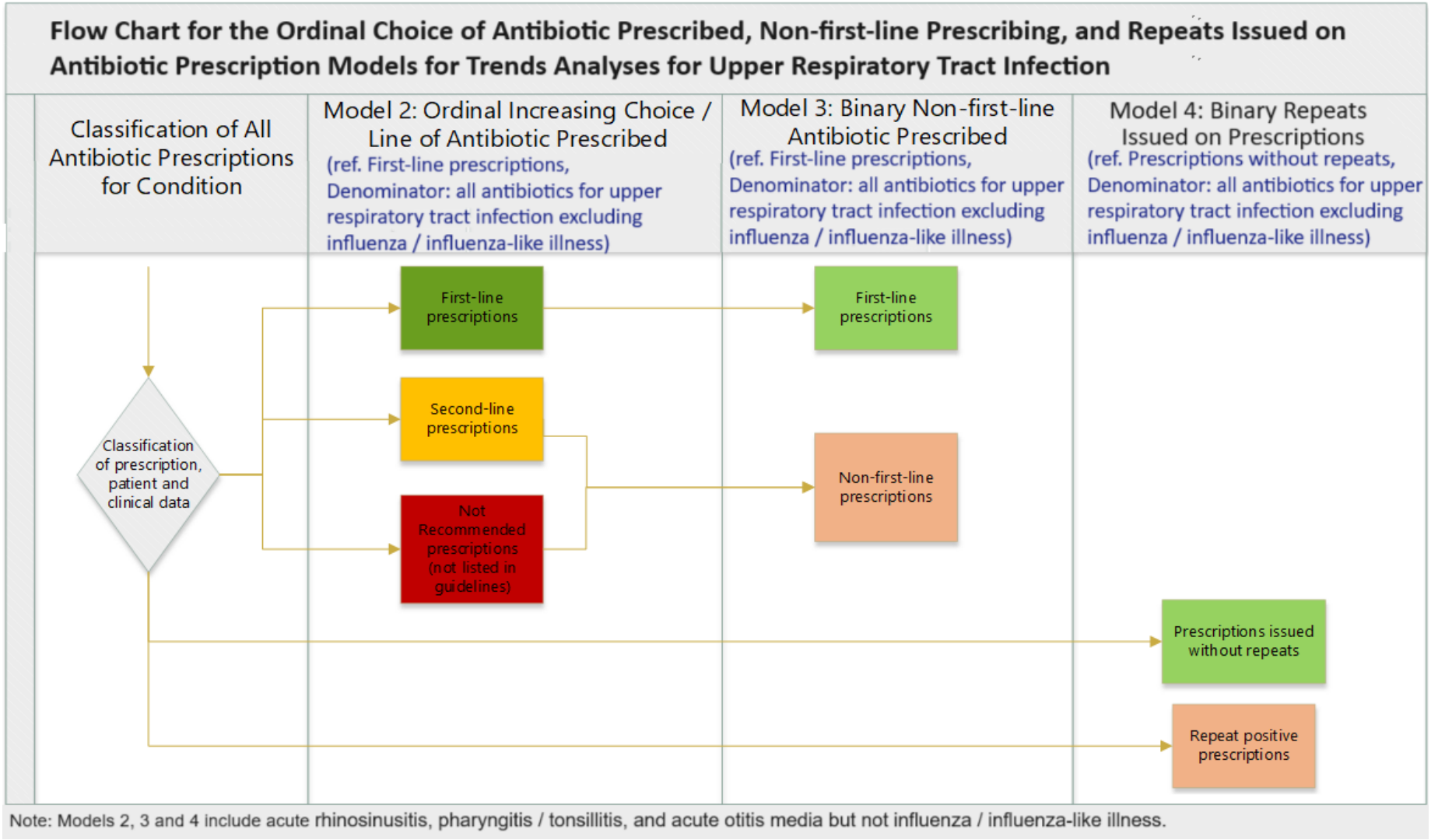


Figure 6-3: Depiction of the main response variables used in this trends analysis, and previous analyses for, initial presentations of upper respiratory tract infection, continued

Table 6-1 serves as a reminder of the guideline recommendations (29) for antibiotic treatment of for initial presentations of URTI conditions as were applied in the analysis, by classifying individual antibiotic agents into an ordered choice based on the order of their recommendation in the guidelines for each condition. Penicillin hypersensitivities were allowed for (332), and suitable alternative antibiotics were also classified as first-line choices where the patient had a recorded allergy label for penicillin. Antibiotics which were prescribed but are not listed in this table were classified as not recommended, as were situations in which penicillin hypersensitivity options were utilised despite the patient having no record of a penicillin allergy label.

Table 6-1: Choice of antibiotic for upper respiratory tract infection conditions, by condition, and by allergy label, as per Therapeutic Guidelines: Antibiotic (29)

Condition	Line / Choice	No penicillin hypersensitivity	Penicillin non-immediate hypersensitivity	Penicillin immediate hypersensitivity
Acute rhinosinusitis	**First-line**	amoxicillin	cefuroxime	doxycycline
	Second-line	amoxicillin + clavulanate	doxycycline	
Acute pharyngitis / tonsillitis	**First-line**	phenoxymethylpenicillin	cefalexin	azithromycin
	Second-line	benzathine penicillin		
Acute otitis media	**First-line**	amoxicillin	cefuroxime	trimethoprim + sulfamethoxazole
	Second-line	amoxicillin + clavulanate	trimethoprim + sulfamethoxazole	

Note: A first-line antibiotic should be prescribed at initial consultations where prescribing is indicated. Where the antibiotic prescribed is not listed as an option for the condition diagnosed, the prescription was classified as 'not recommended'.

By virtue of its definition, any reduction in unnecessary prescribing would coincide with a reduction in overall antibiotic prescribing (within a static epidemiological setting). This would represent a significant increase in compliance with the guidelines (29), as to when to prescribe antibiotics to patients presenting with initial episodes of URTI, as well as secondary improvements in the choice of antibiotic by clinicians in situations when antibiotics are prescribed.

Although there were many outcomes analysed, for all patients with initial presentations of URTI, as well as for each specific URTI condition, only the most pertinent results are presented here. For additional results from this analysis, please see **Appendix E**.

Please note that the linear trend models utilise smoothed, five-month moving average, data for each outcome, which were used to calculate mean monthly rates (414). Note that percentage point difference reported for each outcome uses the difference between the predicted values of these linear models at the commencement of the study in January 2012 and its conclusion in June 2017. For more details, please refer to the **Methods chapter (Chapter 3)**.

6.3 Results

Throughout the study period from January 2012 to June 2017 inclusive, children of eight years and under accounted for 25 to 44% of the URTI patient population, by month. The proportion of patients diagnosed with acute rhinosinusitis / non-specific URTI ranged between 33 and 68% of URTI diagnoses per month, whereas pharyngitis / tonsillitis represented 17 to 40% of URTI diagnoses (**Figure 6-4**). Each month, AOM diagnoses ranged from 10 to 27% of URTI diagnoses, and influenza / ILI (with no mention of bacterial superinfection) represented 0 to 6% of all URTI diagnoses.

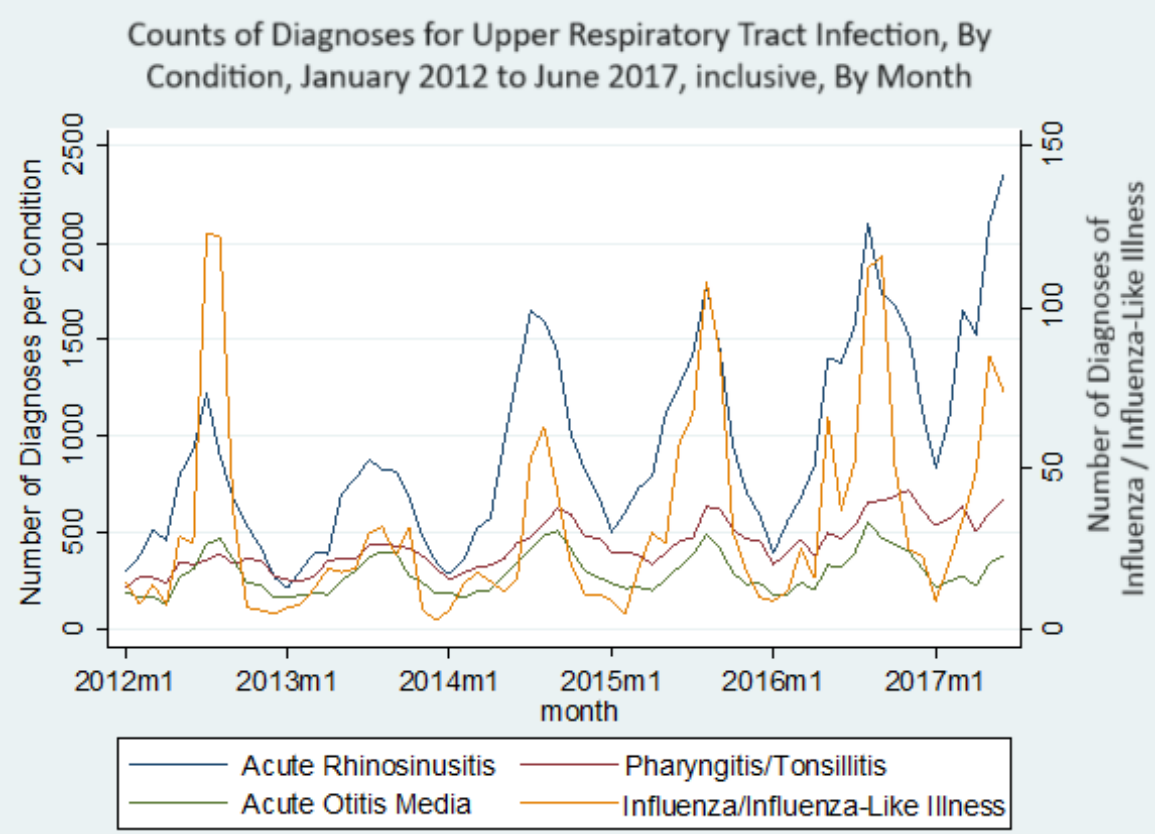


Figure 6-4: Plot of counts of diagnoses, by upper respiratory tract infection condition, from January 2012 to June 2017, inclusive, by month

Note: Influenza / influenza-like illness included purely for the purposes of observing seasonality, also noting the different scale used for influenza / influenza-like illness diagnoses

6.3.1 *All upper respiratory tract infection conditions altogether*

For all patients with initial presentations of URTI, there was a significant, downward trend in antibiotic prescribing of -0.0023 per month over the study period January 2012 to June 2017 inclusive (-0.0023, p<0.001, 95%CI: -0.0025, -0.0022). Although the raw coefficients from these linear regression models of the monthly aggregate data (**Table 6-2**) appear 'small', it is important to note that these represents unit changes per month. For example, the linear regression coefficient of -0.0023 unit increase per month for antibiotic prescribing extrapolates to a three percentage point decrease per year, and a fifteen percentage point reduction in antibiotic prescribing the over the five-and-a-half year study period. This was a notable reduction in antibiotic prescribing, from 56 to 41%, (**Figure 6-5**). One will note that the linear trend line in **Figure 6-5** varies from the smoothed prescribing rate data at various points on visual inspection, such as a peak in late 2013, as well as a calculated R-squared of 93%. Despite this, the linear trend line provides a reasonable estimate of the overall downward trend which can be clearly seen in antibiotic prescribing for rhinosinusitis (**Figure 6-5**).

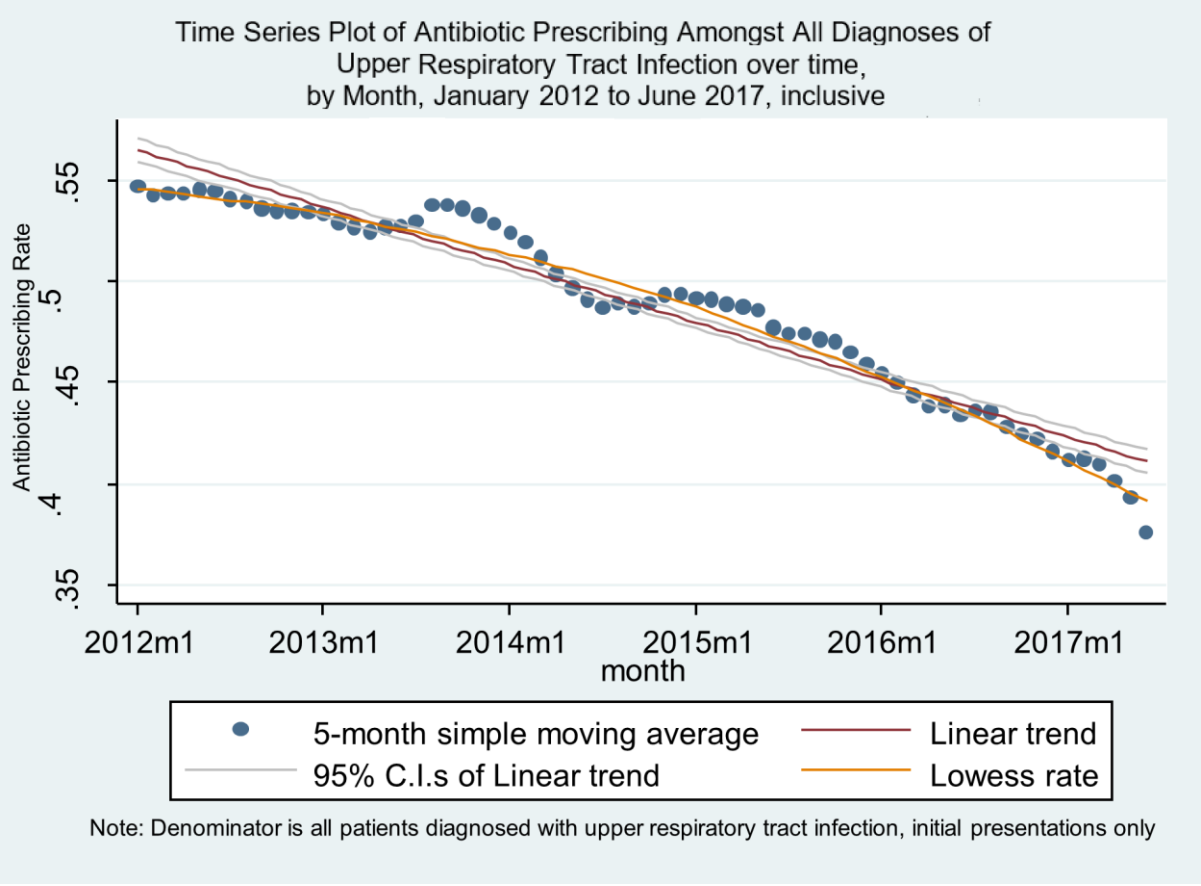


Figure 6-5: Time series plot for antibiotic prescribing rate among initial presentations of upper respiratory tract infection, January 2012 to June 2017, inclusive, by month

There was a significant, downward trend in unnecessary antibiotic prescribing by -0.00092 per month (-0.0009, p<0.001, 95%CI: -0.0010, -0.0008) (**Table 6-2**). This corresponds to a six percentage point reduction, from 89 to 83% of antibiotic prescriptions for initial presentations of URTI. There was also a downward trend in the not recommended prescribing (-0.0014, p<0.001, 95%CI: -0.0015, -0.0012), which reduced by nine percentage points, from 44 to 35% of all antibiotics (**Table 6-2**). There was also a significant, increasing trend in second-line antibiotic prescribing (0.0011, p<0.001, 95%CI: 0.1251, 0.1991), which increased from thirteen to twenty percent of all antibiotics prescribed for initial presentations. However, there was no significant trend for non-first-line prescribing (-0.0002, p=0.178, 95%CI: 0.5658, 0.5502) among all antibiotics prescribed for all patients with URTI (**Table 6-2**). See **Appendix E** for more detail.

It is important to note that patients with acute rhinosinusitis comprise the majority of patients with URTI, and as such, the results for all URTI and rhinosinusitis are similar.

6.3.2 By individual upper respiratory tract infection condition

After considering overall trends for all URTI conditions, the focus is now on the individual component conditions, which is important as they have different treatment guidelines, disease patterns, and risks of serious sequalae (29).[11]

6.3.2.1 Acute rhinosinusitis

For acute rhinosinusitis (and non-specific URTI), there was a significant, downward trend in antibiotic prescribing (-0.0020, p<0.001, 95%CI: -0.0023, -0.0018), involving a thirteen percentage point reduction from 40% to 27% (**Table 6-2**). Unnecessary antibiotic prescribing also reduced significantly from 97% to 85% (-0.0019, p<0.001, 95%CI: -0.0020, -0.0017) (**Table 6-2**). However, significant upward trends were found for both second-line prescribing (0.0031, p<0.001, 95%CI: 0.0028, 0.0033) and non-first-line prescribing (0.0028, p<0.001, 95%CI: 0.0024, 0.0033). As can be seen in **Figure 6-6**, second-line prescribing increased by twenty percentage points, from 14 to 34% of antibiotic prescriptions for rhinosinusitis. The "fit" of this linear trend model varies, with several peaks and troughs about the linear trend line upon visual

[11] Due to the small sample size for antibiotics prescribed for initial presentations of influenza/ILI (n=253), trends analyses for this condition are not presented here. Please see the Appendix E for more details.

inspection in **Figure 6-6**. One also notes a calculated R-squared of 88% (**Table 6-2**). Although a strict linear trend does not appear particularly appropriate here, there is a clear upward trend, and the linear trend model intends to provide an estimate of this trend. There was a significant, eighteen percentage point, increase in non-first-line prescribing from 58 to 76%. There was no significant trend over time for prescribing of antibiotics not recommended in the guidelines (-0.0003, p=0.056, 95%CI: -0.0005, 6.6E-06), which occurred at a mean monthly rate of 43% of all antibiotic prescriptions for rhinosinusitis (**Table 6-2**).

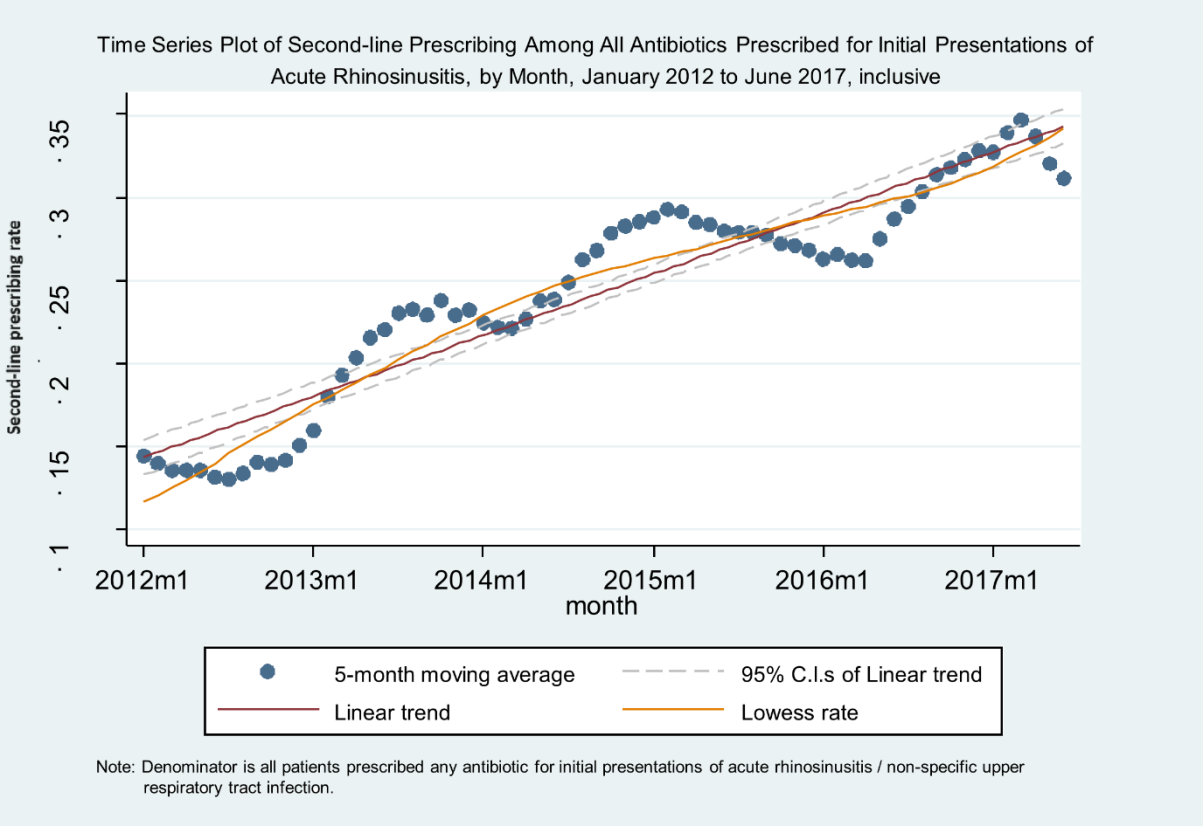


Figure 6-6: Time series plot of prescribing rates for second-line antibiotics for initial presentations of acute rhinosinusitis, January 2012 to June 2017 inclusive, by month

When examining specific antibiotics prescribed for initial presentations of rhinosinusitis, there was a significant downward trend for amoxicillin (-0.0028, p<0.001, 95%CI: -0.0033, -0.0024), and a significant upward trend for amoxicillin with clavulanate (0.0030, p<0.001, 95%CI: 0.0027, 0.0033) (**Table 6-3**). Amoxicillin use decreased from 42 to 23%, while the use of amoxicillin with clavulanate increased from 14 to 34% of all antibiotics prescribed for the condition (**Figure 6-7**). As seen in **Figure 6-7**, the increases in second-line amoxicillin with clavulanate use appear to correspond to similar decreases in the use of first-line amoxicillin. Trends in these two antibiotics

agents are likely to be relevant to the increases in second-line and therefore non-first-line prescribing for initial presentations for rhinosinusitis over the study period.

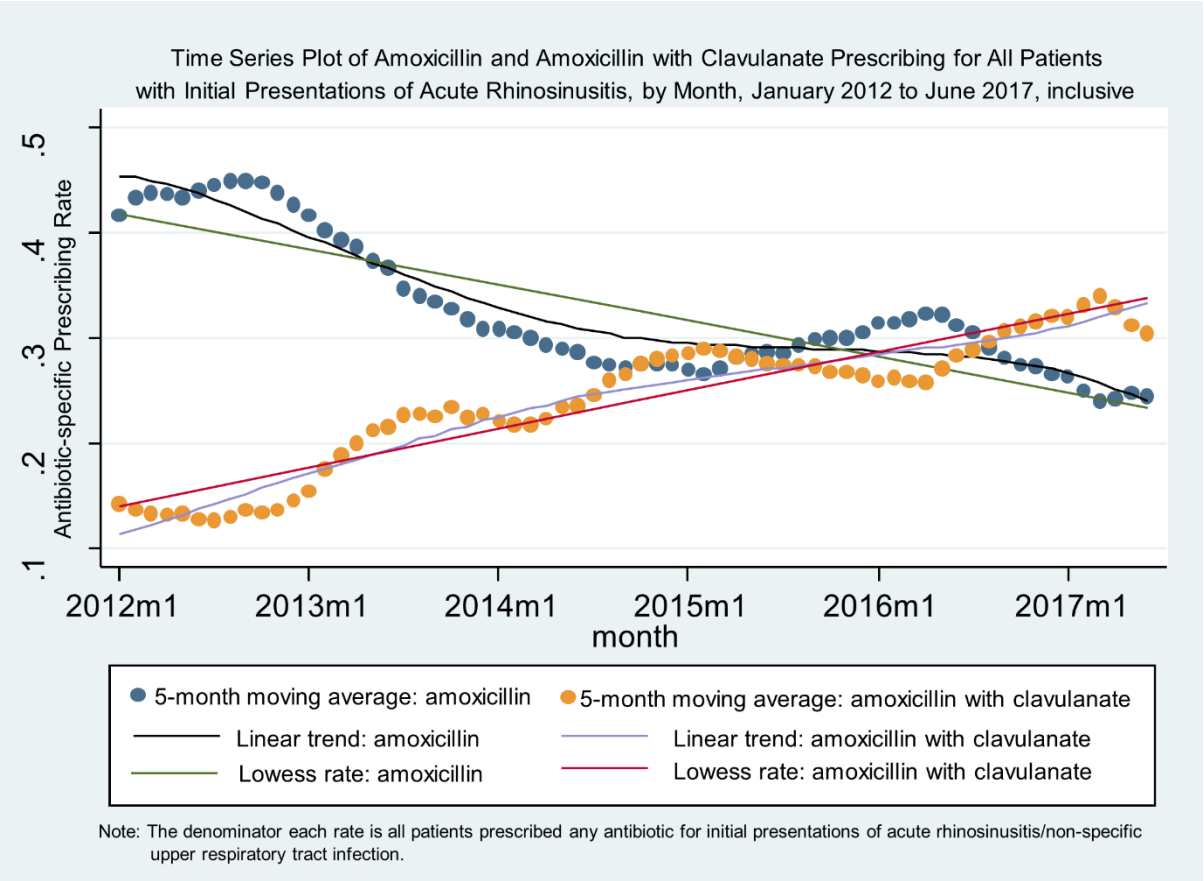


Figure 6-7: Time series plot of amoxicillin and amoxicillin with clavulanate prescribing rates for initial presentations of acute rhinosinusitis, January 2012 to June 2017, inclusive, by month

Table 6-2: Prescribing outcomes for patients with initial presentations of upper respiratory tract infection, by condition group

Prescribing Outcomes for All Patients with initial presentations of URTI												
URTI Condition	**Dependent Variable**	**a) Descriptive Statistics (Moving Average Data)**			**b) Linear Regression Model for Trend**							
	Prescribing Outcome Monthly Rate	**Mean prop.**	**January 2012 prop.**	**June 2017 prop.**	**Coefficient (unit increase per month)**	**[95% Conf.**	**Interval]**	**p-value**	**R-squared**	**January 2012 predicted**	**June 2017 predicted value**	**Percentage Point Difference ***
All URTI	**Unnecessary Antibiotic Prescribing**	0.86	0.90	0.84	-0.00092	-0.001041	-0.000803	0.0000	0.7899	0.885750	0.825816	-6
	Overall Antibiotic Prescribing +	0.48	0.54	0.39	-0.00232	-0.002478	-0.002165	0.0000	0.9320	0.556847	0.405952	-15
	Prescribing of Second-line antibiotic	0.16	0.10	0.18	0.001139	0.0008867	0.0013912	0.0000	0.5597	0.125075	0.199103	7
	Prescribing of antibiotic Not Recommended in guidelines	0.4	0.45	0.36	-0.00138	-0.001527	-0.001231	0.0000	0.8447	0.440770	0.351132	-9
	Non-first-line (non-first-line) antibiotic prescribing	0.56	0.54	0.54	-0.00024	-0.000592	0.0001121	0.1780	0.0282	0.565844	0.550236	-2
Acute Rhinosinusitis	**Unnecessary Antibiotic Prescribing**	0.91	0.98	0.85	-0.00185	-0.001984	-0.00172	0.0000	0.9244	0.969503	0.849124	-12
	Overall Antibiotic Prescribing +	0.34	0.40	0.26	-0.00200	-0.00225	-0.001753	0.0000	0.8018	0.4013533	0.2712579	-13
	Prescribing of Second-line antibiotic	0.67	0.55	0.76	0.003066	0.0027845	0.0033484	0.0000	0.8806	0.143700	0.343019	20
	Prescribing of Not Recommended antibiotic	0.24	0.12	0.34	-0.00025	-0.000513	6.61E-06	0.0559	0.0559	0.437753	0.421293	-2
	Non-first-line (non-first-line) antibiotic prescribing	0.43	0.43	0.42	0.002813	0.0023695	0.0032569	0.0000	0.7149	0.581453	0.764312	18

URTI Condition	Prescribing Outcome Monthly Rate	Mean prop.	Jan 2012 prop.	Jun 2017 prop.	Coefficient (unit increase per month)	[95% Conf.	Interval]	p-value	R-squared	Jan 2012 predicted value	Jun 2017 predicted value	Percentage Point Difference *
Acute Pharyngitis / Tonsillitis	**Unnecessary Antibiotic Prescribing**	0.86	0.90	0.84	-0.00118	-0.001368	-0.001001	0.0000	0.7223	0.893786	0.816808	-8
	Overall Antibiotic Prescribing +	0.71	0.75	0.69	-0.00064	-0.000774	-0.000503	0.0000	0.5795	0.732203	0.690698	-4
	Prescribing of Second-line antibiotic	-	-	-	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Prescribing of antibiotic Not Recommended in guidelines	0.48	0.62	0.36	-0.00425	-0.004463	-0.00404	0.0000	0.9618	0.619348	0.343029	-28
	Non-first-line (non-first-line) antibiotic prescribing	0.48	0.62	0.36	-0.00425	-0.004463	-0.00404	0.0000	0.9618	0.619348	0.343029	-28
Acute Otitis Media	**Unnecessary Antibiotic Prescribing**	0.77	0.81	0.78	0.000168	-6.04E-05	0.0003958	0.1468	0.0326	0.765647	0.776547	1
	Overall Antibiotic Prescribing +	0.59	0.68	0.50	-0.00265	-0.002741	-0.002555	0.0000	0.9805	0.673169	0.501051	-17
	Prescribing of Second-line antibiotic	0.53	0.44	0.53	0.001456	0.0008301	0.0020819	0.0000	0.2523	0.280424	0.375064	9
	Prescribing of antibiotic Not Recommended in guidelines	0.33	0.21	0.31	0.000114	-0.00013	0.0003571	0.3547	0.0134	0.203054	0.210439	1
	Non-first-line (non-first-line) antibiotic prescribing	0.21	0.23	0.22	0.00157	0.0010925	0.0020467	0.0000	0.4029	0.483478	0.585502	10

Note: The rate calculation for each particular prescribing outcome (excluding overall antibiotic prescribing) was calculated with the numerator being all patients with initial presentations of acute otitis media, who were prescribed an antibiotic classified as being part of the particular outcome. The denominator is all patients with initial presentations of acute otitis media who were prescribed an antibiotic.
Note +: The rate calculation for overall antibiotic prescribing was calculated with the numerator being all patients with initial presentations of the specific condition or the condition group, who were prescribed an antibiotic. The denominator is all patients with initial presentations of the specific condition or the condition group.
Note *: The percentage point difference uses predicted values for first and last months of the study period, January 2012 to June 2017 inclusive.

Table 6-3: Individual antibiotic agents prescribed for upper respiratory tract infection conditions: two antibiotics with the highest magnitude of statistically significant change

Prescribing Rates for Individual Antibiotic Agents for Patients with initial presentations of Acute Rhinosinusitis / non-specific URTI												
	Dependent Variable	**a) Descriptive Statistics (Moving Average Data)**			**b) Linear Regression Model for Trend**							
URTI condition	**Prescribing Outcome Monthly Rate**	**Mean prop.**	**January 2012 prop.**	**June 2017 prop.**	**Coefficient (unit increase per month)**	**[95% Conf.**	**Interval]**	**p-value**	**R-squared**	**January 2012 predicted value**	**June 2017 predicted value**	**Percentage Point Difference***
Acute Rhinosinusitis	**amoxicillin**	0.33	0.45	0.24	-0.002824	-0.003273	-0.002375	0.0000	0.7117	0.418076	0.234534	-19
	amoxicillin with clavulanate	0.24	0.11	0.33	0.003009	0.002723	0.003295	0.0000	0.8734	0.141548	0.337153	20
Acute Pharyngitis / Tonsillitis	**amoxicillin**	0.16	0.30	0.09	-0.003214	-0.003517	-0.002911	0.0000	0.8751	0.260872	0.051951	-21
	phenoxymethyl-penicillin	0.40	0.26	0.50	0.003621	0.003438	0.003803	0.0000	0.9608	0.284396	0.519731	24
Acute Otitis Media	**amoxicillin**	0.46	0.56	0.46	-0.001656	-0.002131	-0.001182	0.0000	0.4315	0.515498	0.407845	-11
	amoxicillin with clavulanate	0.32	0.20	0.30	0.001402	0.000772	0.002032	0.0000	0.2358	0.278309	0.369422	9

Note: The rate calculation for each particular antibiotic agent was calculated with the numerator being all patients with initial presentations of the specific condition who were prescribed the particular antibiotic. The denominator is all patients with initial presentations of the same specific condition who were prescribed any antibiotic agent.
Note *: The percentage point difference uses predicted values for first and last months of the study period, January 2012 to June 2017 inclusive.

6.3.2.2 Acute pharyngitis / tonsillitis

There were two prescriptions for the second-line antibiotic recommended for pharyngitis, benzathine penicillin, occurring over duration of the study period. Second-line prescriptions were therefore considered negligible and too few to model so they were excluded from the analyses. The antibiotic choices for pharyngitis were therefore either first-line or not recommended (comprising non-first-line) agents. For initial presentations of pharyngitis, there were significant downward trends in likely unnecessary prescribing (-0.0012, p<0.001, 95%CI: -0.0014, -0.0010) and overall antibiotic prescribing (-0.0006, p<0.001, 95%CI: -0.0008, -0.0005) over the study period (**Table 6-2**). Antibiotic prescribing decreased from 73 to 69% among all pharyngitis diagnoses, while unnecessary prescribing reduced from 89 to 82% of all antibiotic prescriptions for the condition (**Table 6-2**).

There was also a significant downward trend in the prescribing of antibiotics not recommended in the guidelines for pharyngitis (-0.0043, p<0.001, 95%CI: -0.0045, -0.0040), which is the same as non-first-line antibiotic prescribing for this condition (**Table 6-2**). As depicted in **Figure 6-8**), the prescribing of not recommended antibiotics decreased notably from 62 to 34% of all antibiotics prescribed for initial presentations of pharyngitis. On visual inspection of **Figure 6-8**), one will note that a small peak in mid-2014 and a small trough in early 2016 are notable variations of the linear trend model from the smoothed data series for not recommended prescribing for pharyngitis. Also, the R-squared of the linear model was calculated at 96% (**Table 6-2**). Despite variations, there is an apparent downward trend in not recommended prescribing (**Figure 6-8**), which the linear model approximates.

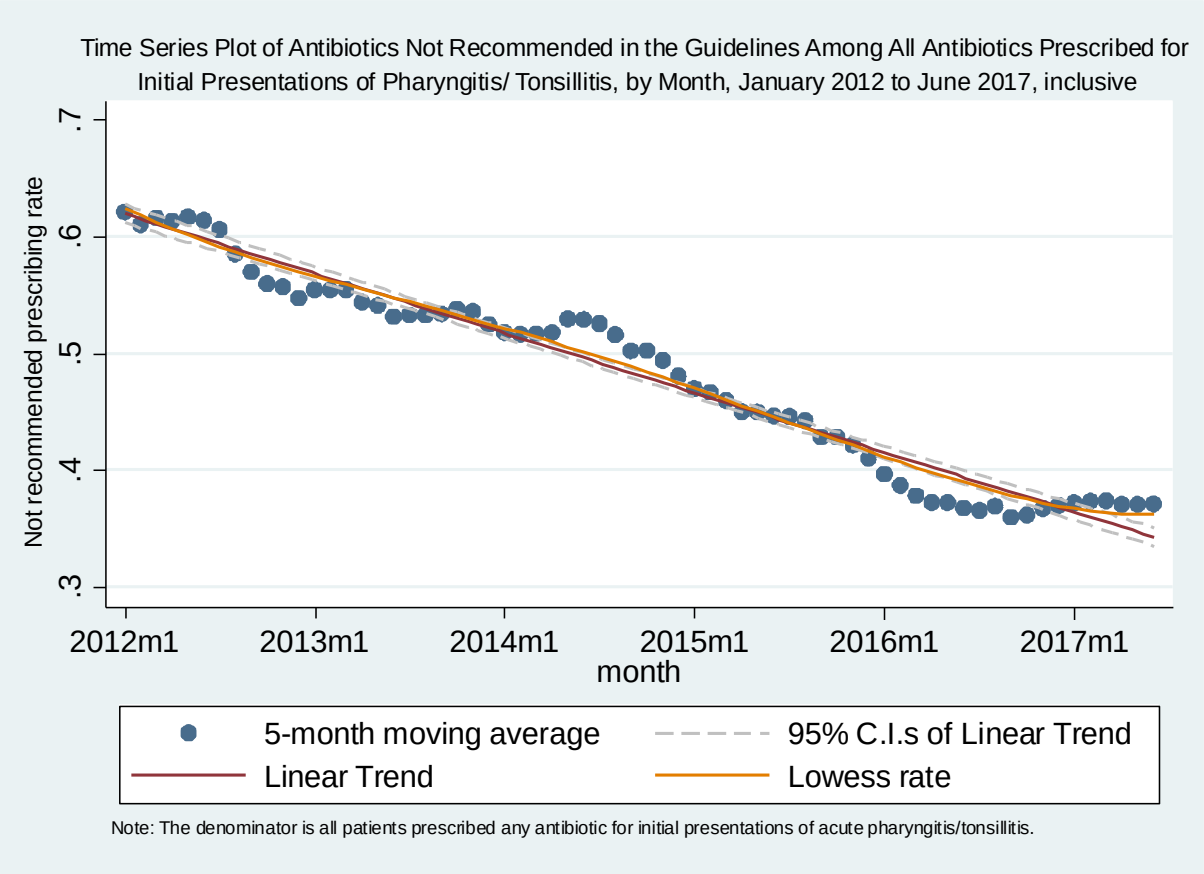


Figure 6-8: Time series plot of antibiotics not recommended in the guidelines for initial presentations of acute pharyngitis / tonsillitis, January 2012 to June 2017 inclusive, by month

For initial presentations of pharyngitis, there was a significant upward trend in phenoxy-methylpenicillin use (0.0036, p<0.001, 95%CI: 0.0034, 0.0038) and a significant downward trend for amoxicillin without clavulanate (-0.0032, p<0.001, 95%CI: -0.0035, -0.0029) (**Table 6-3**). First-line phenoxymethylpenicillin prescribing increased from 28 to 52% of all antibiotics prescribed for pharyngitis, while the use of not recommended amoxicillin without clavulanate decreased from 26 to 6% of all antibiotics for the condition (**Table 6-3**). The graphical depiction of both follows below (**Figure 6-9**) suggests that there has been a downward shift in the use of amoxicillin in exchange for phenoxymethylpenicillin.

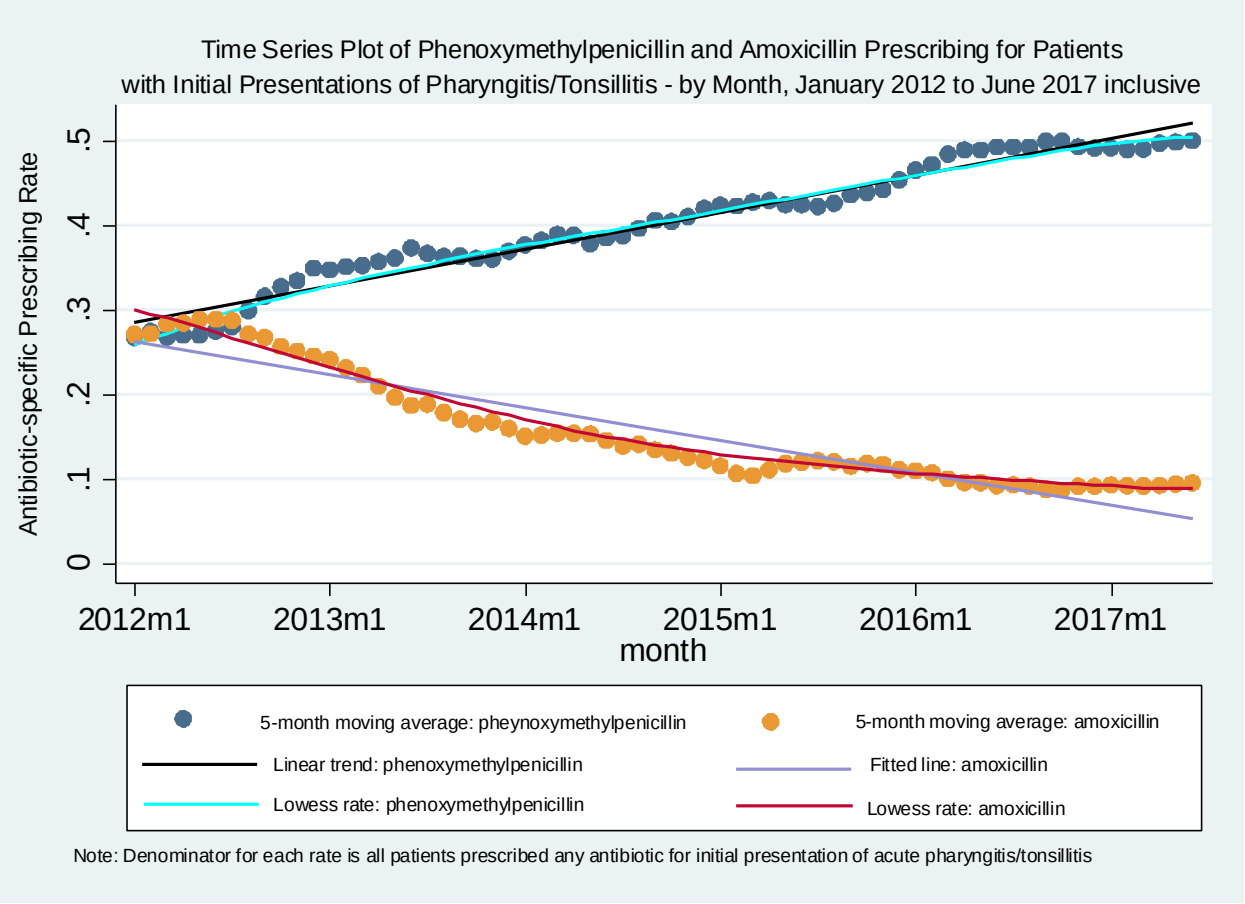


Figure 6-9: Time series plot for phenoxymethylpenicillin and amoxicillin prescribing rates for initial presentations of acute pharyngitis / tonsillitis, January 2012 to June 2017 inclusive, by month

6.3.2.3 Acute otitis media

For patients with initial presentations of AOM, there were significant, upward trends in antibiotic prescribing (-0.0027, p<0.001, 95%CI: -0.0027, -0.0026), second-line prescribing (0.0015, p<0.001, 95%CI: 0.0008, 0.0021), and non-first-line prescribing (0.0016, p<0.001, 95%CI: 0.0011, 0.0020) during the study period (**Table 6-2**). However, there was no notable change in unnecessary antibiotic prescribing for initial presentations of AOM over time, (0.0027, p=0.147, 95%CI: -6.0E-05, 0.0004), which remained at a mean monthly rate of 77% of all antibiotic prescriptions for AOM. Similarly, the prescribing of not recommended antibiotic agents was also insignificant (0.0001, p=0.355, 95%CI: -0.0001, 0.0004), with a mean monthly rate of 21% of all antibiotics for AOM (**Table 6-2**).

The percentage of antibiotic prescriptions among diagnoses of AOM decreased by seventeen percentage points from 67% to 50% (**Figure 6-10, Table 6-2**) There are several variations between the smoothed data series for antibiotic prescribing for AOM and the linear trend model. A small trough in the second half of 2014 and a small peak in the second half of 2015 are notable variations from the linear trend line clearly visible in **Figure 6-10**, and R-squared for the linear model was 98% (**Table 6-2**). Despite variations, there is an apparent downward trend in antibiotic prescribing for AOM (**Figure 6-10**). The linear model goes some way to summarizing this trend.

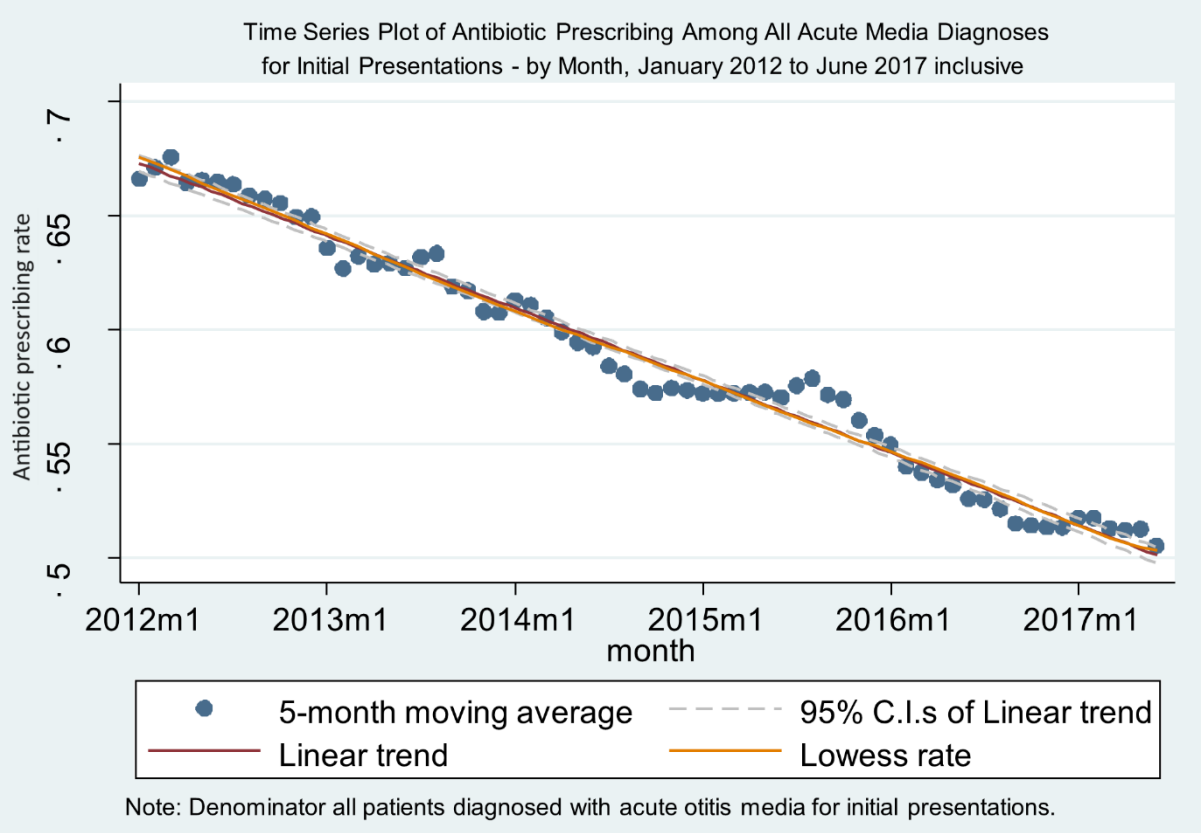


Figure 6-10: Time series plot of antibiotic prescribing rate among initial presentations of acute otitis media, January 2012 to June 2017, inclusive, by month

There was an increase in second-line prescribing for AOM, from 28 to 38% of all antibiotics for initial AOM (**Table 6-2**). Non-first-line prescriptions also increased from 48 to 59% of all antibiotic prescriptions for initial presentations of AOM, however, it is important to note that non-first-line prescribing appears to peak at over 60% in early 2015 then decrease again (**Appendix E.2.1.3**).

When examining individual antibiotic prescribed for initial presentations of AOM, there was a significant downward trend in the prescribing of first-line amoxicillin (-0.0017, p<0.001, 95%CI: -0.0021, -0.0012), and a significant upward trend in the use of second-line amoxicillin with clavulanate (0.0014, p<0.001, 95%CI: 0.0008, 0.0020) (**Table 6-3**). As seen in **Figure 6-11**, the use of amoxicillin decreased from 52 to 41% of all antibiotics prescribed for AOM, while amoxicillin with clavulanate use increased from 28 to 40% of all antibiotic prescriptions for the condition (**Table 6-3**). The peak in amoxicillin with clavulanate prescribing also appears to correlate reasonably in time with the peak seen in non-first-line prescribing and may be relevant to this change. For additional results from this analysis, please see **Appendix E**.

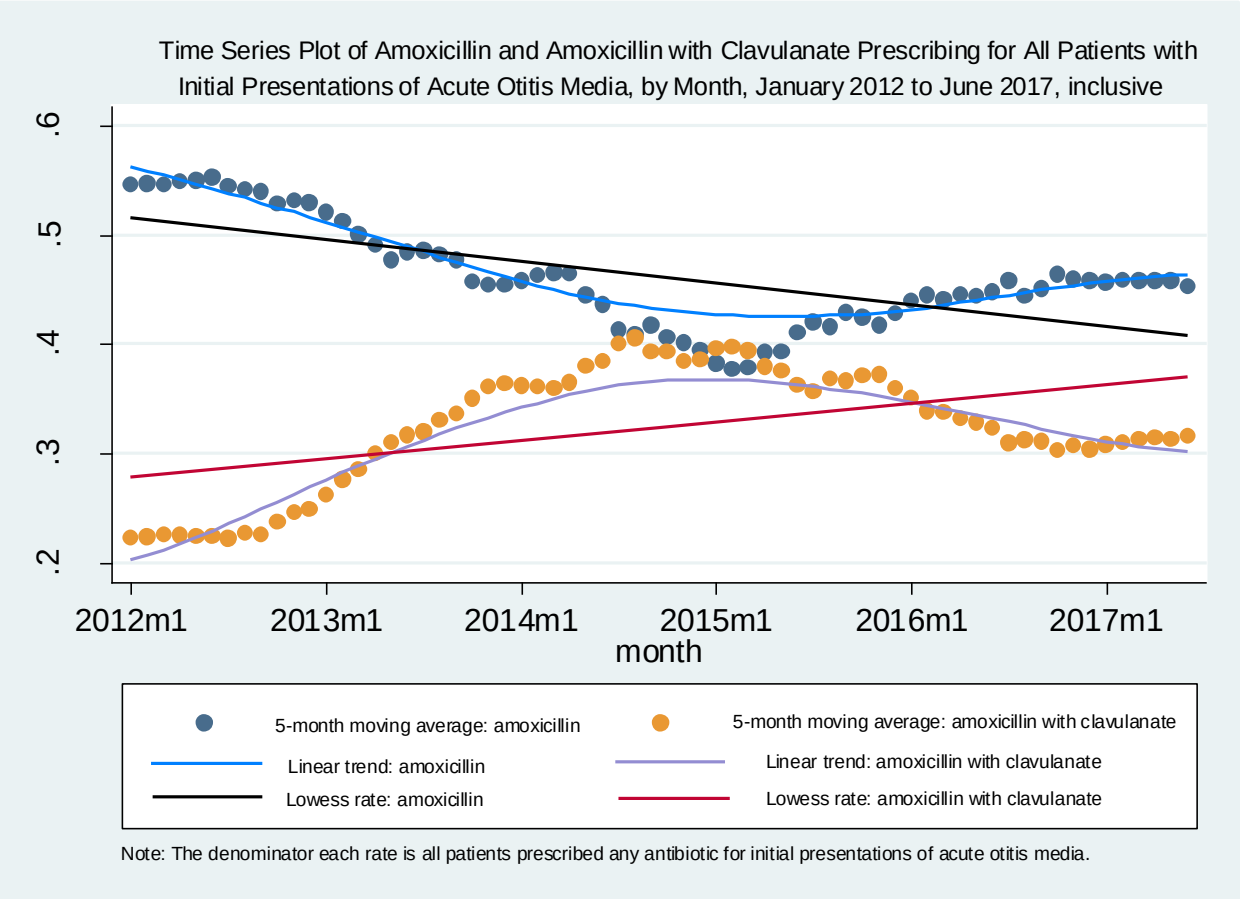


Figure 6-11: Time series plot for amoxicillin and amoxicillin with clavulanate prescribing for initial presentations of acute otitis media, January 2012 to June 2017, inclusive, by month

6.3 Summary

There was a common trend to all URTI conditions: the significant reduction in rates of antibiotic prescribing among initial presentations of URTI. There were significant reductions in the rate of unnecessary prescribing for rhinosinusitis and pharyngitis but not AOM. For both rhinosinusitis and AOM, there were increases in second-line prescribing and decreases in first-line prescribing. There were notable increases in second-line amoxicillin with clavulanate usage and decreases in first-line agent amoxicillin, for both rhinosinusitis and AOM. For pharyngitis, however, there was an increase in first-line usage and a decrease in the use of antibiotics not recommended in the guidelines. This correlates to an increase in first-line phenoxymethylpenicillin and a decrease in not recommended antibiotic amoxicillin for pharyngitis.

There were significant decreases in the rates of unnecessary prescribing for both rhinosinusitis and pharyngitis. Pharyngitis was the only condition, however, with decreases in both unnecessary prescribing and non-first-line antibiotic prescribing. Despite a decreasing trend for antibiotic prescribing for AOM, there was no significant change in unnecessary prescribing, and there was also an increase in non-first-line antibiotic use. For both rhinosinusitis and AOM, there were increases in second-line and non-first-line antibiotic prescribing. There was a dramatic increase in the use of second-line antibiotics for rhinosinusitis.

While the largest reduction in unnecessary prescribing was for rhinosinusitis, this was accompanied by increasing non-first-line prescribing. The mean monthly rate of unnecessary prescribing was 91% among all antibiotic prescriptions for patients with rhinosinusitis, which was the highest among all URTI conditions. For pharyngitis, there were reductions in the three most prominent outcomes: overall antibiotic prescribing, unnecessary prescribing, and non-first-line antibiotic prescribing. It is on this basis one might consider there being consistent reductions in prominent outcomes for pharyngitis.

To this end, for AOM, there was no significant change in unnecessary prescribing ($p=0.1468$), as well as increasing non-first-line prescribing. The mean monthly rate of unnecessary prescribing was 0.77 among all antibiotic prescriptions for patients with initial AOM. This is noteworthy, given that AOM does not usually require an antibiotic

prescription in most circumstances (29). However, an alternate perspective is that AOM also had the lowest mean rates for both unnecessary prescribing and non-first-line prescribing, and also represents the smallest cohort, and may therefore be in less need of change.

For patients with acute rhinosinusitis, the magnitude of change was similar for overall antibiotic prescribing and unnecessary prescribing, which were thirteen percentage points and twelve percentage points, respectively. However, for patients with pharyngitis / tonsillitis, the reduction of unnecessary prescribing of eight percentage points was twice that of the decrease in antibiotic prescribing of four percentage points. For rhinosinusitis, the magnitude of change was also similar for second-line and non-first-line prescribing for rhinosinusitis, with increases of twenty and eighteen percentage points, respectively. There was a 28 percentage point reduction for not recommended / non-first-line antibiotic prescribing for pharyngitis. Meanwhile, for AOM, there were increases in second-line and non-first-line prescribing, of nine and ten percentage points, respectively. With regard to antibiotic prescribing, the seventeen percentage point reduction for AOM outweighs that of rhinosinusitis with a thirteen percentage point decrease and a four percentage point reduction for pharyngitis. However, this notable reduction in antibiotic prescribing for AOM must be considered in balance with no significant reduction in unnecessary prescribing for this condition.

Regardless of the perspective taken, it is apparent that there are meaningful changes occurring in prescribing behaviours among all URTI conditions over the study period, and that many avenues for improvement can be identified from these results.

CHAPTER 7 ANALYSIS OF CHANGES IN ANTIBIOTIC PRESCRIBING FOR URINARY TRACT INFECTION OVER TIME

7.1 Introduction

The objective of this analysis was to explore antibiotic prescribing for patients with initial presentations of UTI / acute cystitis over time. As empirical antibiotic prescribing is accepted for initial episodes of UTI (29,123), the main question is not so much whether prescribing occurs but rather what specific antibiotics are being prescribed. Inappropriate antibiotic prescribing is commonly reported from primary care internationally for UTIs (15,17,29,48,119-122,278,283,285,296,305,323,336,387,415,416). While the local epidemiology of UTI is not expected to change substantially over a relatively short period of time, it is possible that antibiotic prescribing behaviour may vary. This is particularly given growing antibiotic resistance among UTI pathogens nationally (12,14,18,167,417), as well as increasing publicity regarding antibiotic resistance and antibiotic stewardship, as detailed in the Background chapter. In light of these factors, one would hope that decreases in non-first-line prescribing for UTI was occurring over time, which would represent favourable changes in the antibiotic prescribing (275).

It was therefore of interest to establish whether there were notable reductions in the proportions of non-first-line antibiotics being prescribed to patients with initial presentations for UTI over the study period, and, if so, by how much. It was also a focus to identify any substantial changes in the use of specific antibiotics over this time, and particularly in light of local reports of changing antibiotic use (12,14,18,167). The objective was to explore these factors for all patients with initial presentations of UTI, and also for independent patient groups defined in the Therapeutic Guidelines: Antibiotic (the guidelines). These patient groups were men, non-pregnant women, and children (29).

Previously defined datasets and outcome variables, as described in the Methods chapter, were used in this analysis (**Figure 7-1**). UTI was defined to include acute cystitis (29). In order to accurately evaluate the antibiotic prescribing at initial presentations for UTI, non-initial and chronic / recurrent consultations were excluded, by removing consultations occurring within fourteen days of a previous UTI consultation for the same patient.

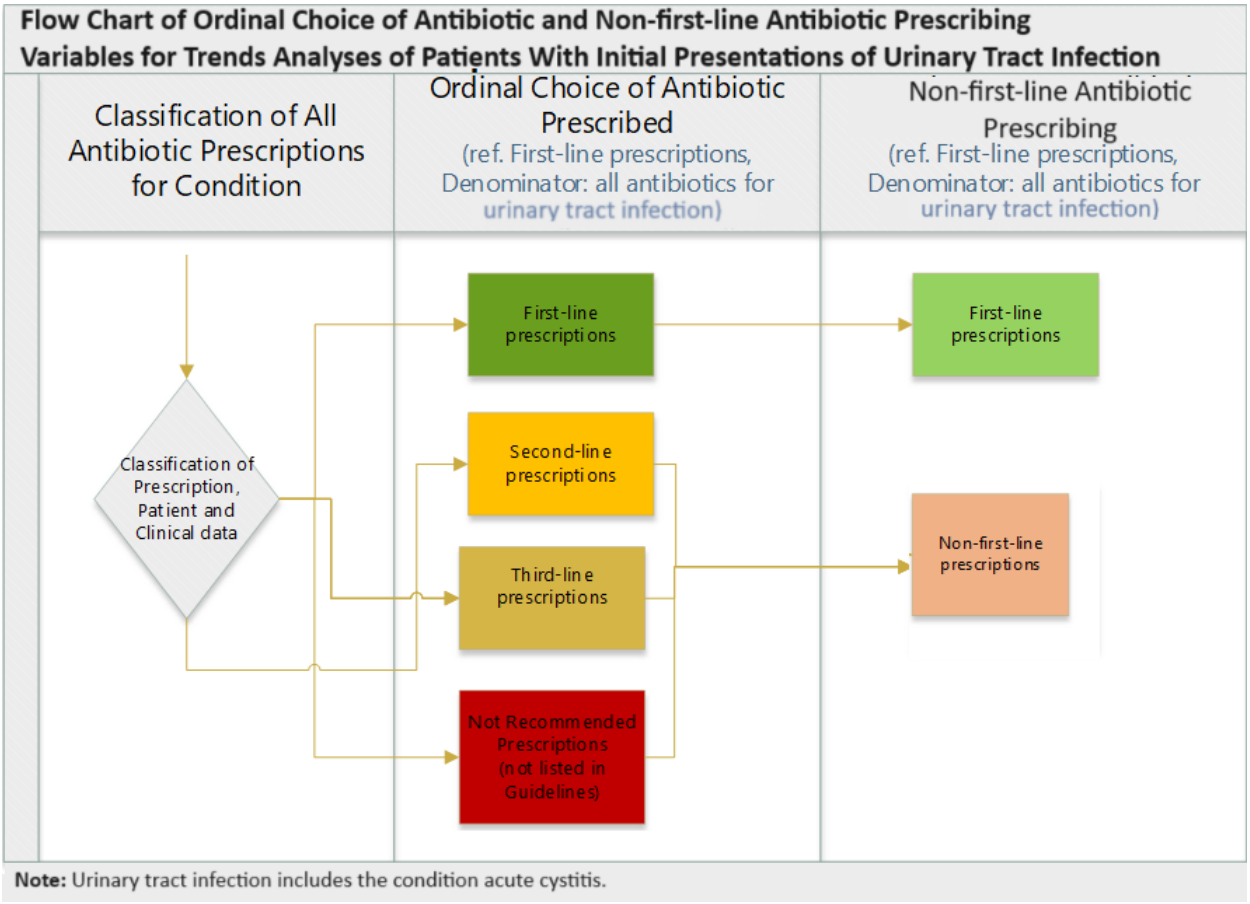


Figure 7-1: Depiction of the main outcome variables utilised in this trends analysis, and previous analyses for initial presentations of urinary tract infection

Table 7-1 serves as a reminder of the guidelines for treatment of initial presentations of UTI, which were used to categorise each specific antibiotic agent into ordinal choice based on their order of recommendation in the guidelines (29). Antibiotics which were prescribed but are not listed in **Table 7-1** were classified as not recommended. For more information, please refer to the **Methods chapter**.[12]

Improved antibiotic stewardship should result in a reduction in the proportion of prescribed antibiotics that were non-first-line antibiotics over time for all patient groups. By definition, this would also equate to an increase in the proportion of first-line antibiotics prescribed for these initial episodes of UTI, representing improved compliance by clinicians with the guidelines (29).

[12] For more information, please refer to the Methods chapter.

Table 7-1: Summary of Therapeutic Guideline: Antibiotic (29) recommendations in order of choice for acute cystitis, by patient group.

Choice	Non-pregnant Women	Men	Children >= 1 month
First-line	trimethoprim	trimethoprim	trimethoprim
Second-line	cefalexin	cefalexin	cefalexin
Third-line	amoxicillin + clavulanate	amoxicillin + clavulanate	amoxicillin + clavulanate
Third-line	nitrofurantoin	nitrofurantoin	
Last Resort	norfloxacin	Norfloxacin	norfloxacin

Note: A first-line option should be the antibiotic prescribed at initial consultations.
Third-line and Last Resort options were combined into the third ordinal level for analysis.
Where the antibiotic prescribed is not listed as an option for the condition diagnosed, the prescription was classified as 'not recommended'.

Note that the linear trend models utilise five-month moving average data, which were used to calculate mean monthly rates (414). The percentage point differences reported use the predicted values of these linear models at the start and end of the study period, January 2012 and June 2017, respectively. For more information, please refer to the Methods chapter. There were many outcomes analysed, for all patients with initial presentations of UTI, as well as for each patient group, however, only the most relevant results are presented here. For further results from this analysis, please see **Appendix F**.

7.2 Results

Each month in the study period between 72 and 83% of UTI diagnoses were women of at least sixteen years of age, while between 8 and 16% were children under sixteen years of age (**Figure 7-2**). Among all patients with initial presentations of UTI, between 81-94% of women, 58-89% of men, and 61-90% of children under sixteen, per month, received antibiotic prescriptions. Across all three patient groups receiving antibiotic prescriptions, the mean monthly percentage of each of these patient groups receiving non-first-line antibiotics remained at over 55% throughout the study period.

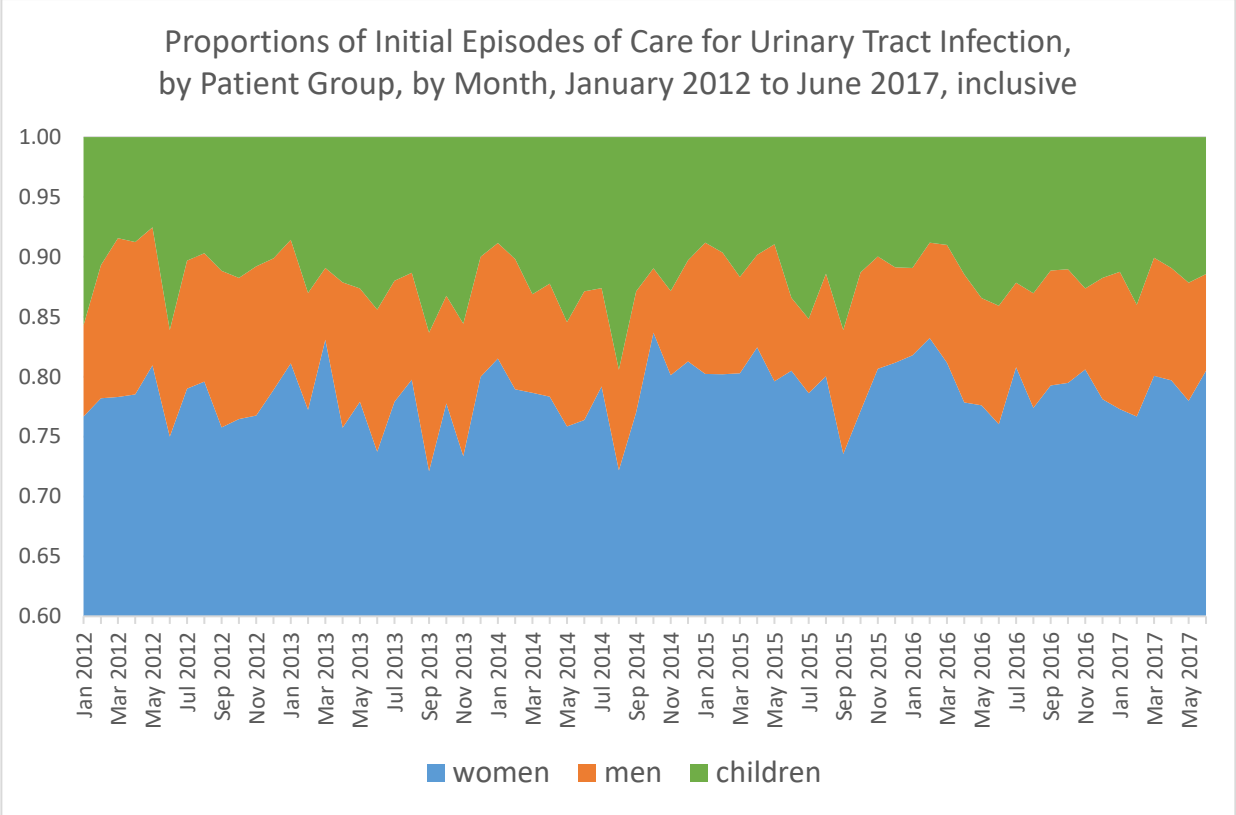


Figure 7-2: Graph of proportions of initial presentations of urinary tract infection, by patient group (women, men, and children under sixteen years) from January 2012 to June 2017, inclusive, by month

7.2.1 All patients with initial presentations of urinary tract infection

For all patients with initial presentations of UTI, there was a significant, increasing trend in the proportions of patients receiving second-line antibiotics, increasing by 0.0016 per month (p<0.001, 95%CI: 0.0014, 0.0017) (**Table 7-2)**. Although the raw coefficients from these linear regression models of the monthly aggregate data in **Table 7-2** appear 'small', it is important to realise that these represents unit changes per month. For example, when considering second-line prescribing, the linear regression coefficient of 0.0016 unit increase change per month extrapolates to an increase of two percentage points per year. When this is extrapolated to the five-and-a-half-year study period, this corresponds to a ten percentage point increase in second-line prescribing, up to 46% of all antibiotics prescribed at the end of the study.

Non-first-line prescribing increased from 56 to 64% of all antibiotic prescriptions over the study period. The linear regression model indicates an increase of 0.0009 per month (p<0.001, 95% CI: 0.0007, 0.0011), equivalent to an eight percentage point increase overall in non-first-line prescribing for UTI (**Table 7-2**). By definition, this means that there was an equal and opposite decrease in first-line antibiotic prescribing for all patients with initial presentations of UTI.

There was also a downward trend in the use of antibiotics not recommended in the guidelines for UTI of -0.0005 (p<0.001, 95%CI: -0.0006, -0.0003) (**Table 7-2**). The use of antibiotic agents not recommended in the guidelines at all decreased from 10 to 7% of all antibiotic prescriptions for all patients. See **Appendix F** for more detail.

7.2.2 Trends by patient group

After considering overall trends for all patients with initial UTI presentations altogether, the focus will now be on the individual patient groups, which is important as they have different causes, guidelines for treatment, and risks. Recall that the predicted values from linear regression models are used to report percentage point change for each outcome.

7.2.2.1 Women

Women of sixteen years and over with initial presentations of UTI comprise the majority of initial UTI diagnoses so it is expected that the prescribing for women demonstrates similar trends identified to those for all patients. Among these women prescribed any antibiotic, there were significant upward trends in second-line prescribing, increasing by 0.0016 per month (p<0.001, 95%CI: 0.0015, 0.0018) and an eleven percentage point increase over the 66 months (**Table 7-2**). As seen in **Figure 7-3**, second-line prescribing among all antibiotics prescribed to women with initial presentations of UTI increased from 34 to 44%. As with all the models presented in this chapter, the 'fit' of the linear trend model in **Figure 7-3** below varies from the smoothed series, particularly the peak in mid-2015. In this situation, the linear trend model for second-line prescribing varies with an R-squared of 87%, which is high for an error term. However, there is an undeniable upward trend overall, which the strictly linear model can reasonably estimate.

There was an increasing trend in non-first-line prescribing of 0.0010 per month (p<0.001, 95%CI: 0.0008, 0.0012), implying a seven percentage point increase over the study period, from 53 to 60% of all antibiotics prescribed to women (**Table 7-2**). The increase in second-line prescribing may be responsible for the increase in non-first-line prescribing. There was also a significant downward trend in the prescribing of antibiotics not recommended in the guidelines for women, decreasing by 0.0004 per month (p<0.001, 95%CI: -0.0005, -0.0003), implying a three percentage point decrease overall (**Table 7-2**).

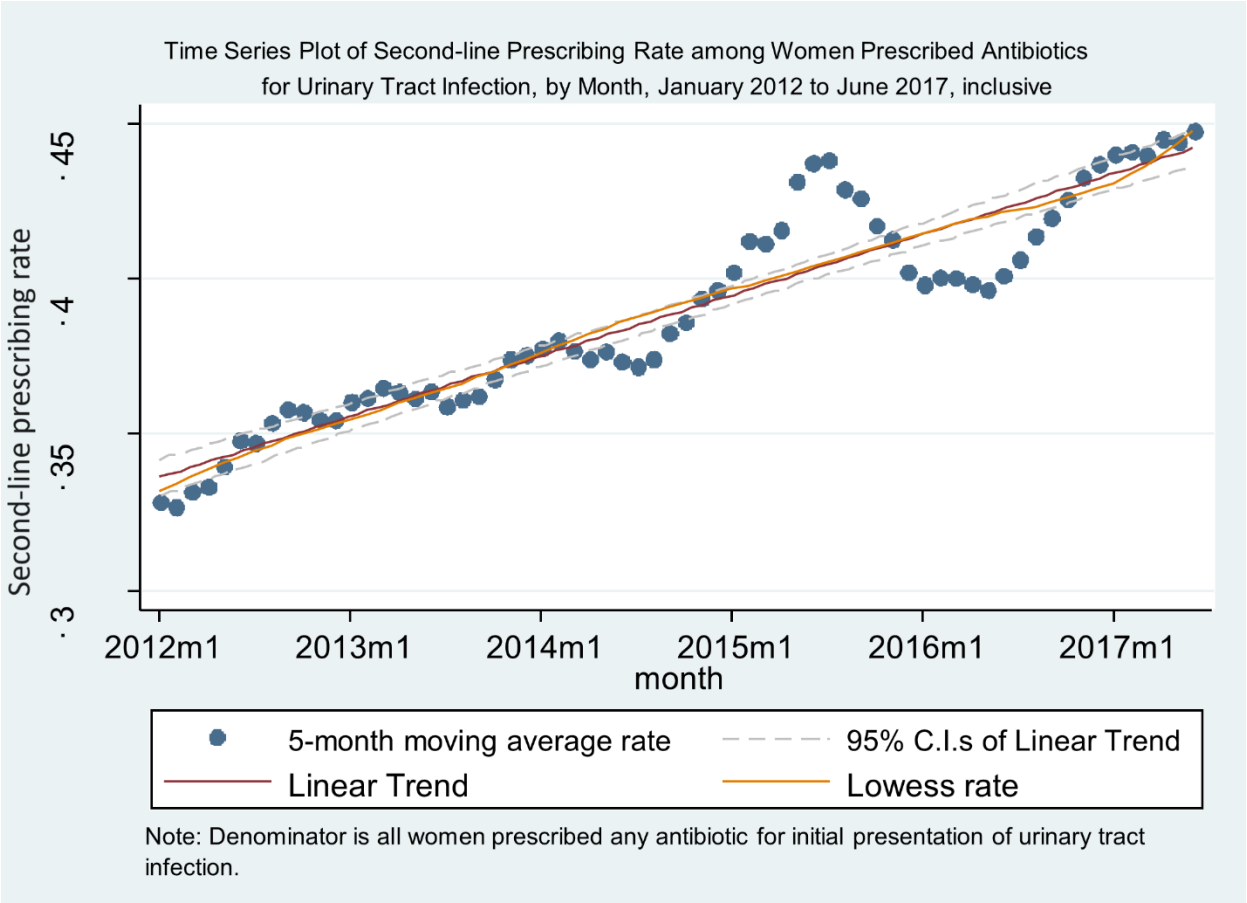


Figure 7-3: Time series plot of second-line antibiotic prescribing for all women sixteen years and over with initial presentations of urinary tract infection, from January 2012 to June 2017, inclusive, by month

By specific antibiotic, there was a significant, upward trend in the use of cefalexin among women, with an increase of 0.0016 per month (p<0.001, 95%CI: 0.0015, 0.0018). This represents an eleven percentage point increase (**Table 7-3**). There was also a seven percentage point reduction in (first-line) trimethoprim use, decreasing by 0.0010 per month (p<0.001, 95%CI: -0.0012, -0.0008). **Figure 7-4** depicts the trimethoprim prescribing rate reduction from 47 to 40%, which appears to mirror the cefalexin increase.

Table 7-2: Prescribing outcomes for each patient group with initial presentations of urinary tract infection, by patient group

Prescribing Outcomes for All Patients with initial presentation of UTI												
	Dependent Variable	a) Descriptive Statistics (Moving Average Data)			b) Linear Regression for Trend							
Patient Group	Prescribing Outcome Monthly Rate	Mean prop.	January 2012 prop.	June 2017 prop.	Coefficient (unit increase per month)	[95% Conf.	Interval]	p-value	R-squared	January 2012 predicted	June 2017 predicted value	Percentage Point Difference *
All Patients	Prescribing of Second-line	0.40	0.35	0.46	0.001555	0.0014094	0.001701	0.0000	0.8764	0.345626	0.462771	11
	Prescribing of antibiotic Not Recommended in guidelines	0.09	0.12	0.09	-0.00045	-0.000595	-0.000306	0.0000	0.378	.1031465	.0738786	-3
	Non-first-line (non-first-line) antibiotic prescribing	0.60	0.45	0.36	0.000907	0.0007352	0.0010792	0.0000	0.6344	0.561391	0.639921	8
Women at least 16	Prescribing of Second-line	0.39	0.33	0.45	0.001626	0.001471	0.001782	0.0000	0.8728	0.336198	0.441917	11
	Prescribing of antibiotic Not Recommended in guidelines	0.09	0.12	0.09	-0.00039	-0.00052	-0.00026	0.0000	0.3666	0.100878	0.075505	-3
	Non-first-line (non-first-line) antibiotic prescribing	0.56	0.51	0.60	0.001015	0.000833	0.001197	0.0000	0.6604	0.530338	0.596313	7
Men at 16 years	Prescribing of Second-line	0.36	0.35	0.43	0.001421	0.001083	0.00176	0.0000	0.5241	0.312730	0.405115	9
	Prescribing of antibiotic Not Recommended in guidelines	0.07	0.13	0.10	-9.5E-05	-0.00041	0.000218	0.5463	0.0057	0.076461	0.070279	-1
	Non-first-line (non-first-line) antibiotic prescribing	0.67	0.67	0.77	0.001969	0.00132	0.002619	0.0000	0.3642	0.606071	0.734079	13

Patient Group	Prescribing Outcome Monthly Rate	Mean prop.	January 2012 prop.	June 2017 prop.	Coefficient (unit increase per month)	[95% Conf.	Interval]	p-value	R-squared	January 2012 predicted	June 2017 predicted value	Percentage Point Difference *
Children 16 years	**Prescribing of Second-line**	0.56	0.54	0.59	0.000975	0.000737	0.001214	0.0000	0.5101	0.528409	0.591799	6
	Prescribing of antibiotic Not Recommended in guidelines	0.11	0.18	0.10	-0.00126	-0.00156	-0.00095	0.0000	0.5099	0.147108	0.065484	-8
	Non-first-line (non-first-line) antibiotic prescribing	0.83	0.87	0.84	-0.00055	-0.00083	-0.00026	0.0003	0.1871	0.843880	0.808382	-4

Note: The rate calculation for each particular prescribing outcome within each patient group was calculated with the numerator being all patients within patient group with initial presentations of UTI, who were prescribed an antibiotic classified as being part of the particular prescribing outcome. The denominator is all patients within the same patient group with initial presentations of UTI who were prescribed any antibiotic. For example, second-line antibiotic prescribing rate for men was calculated using all men at least sixteen years of age with initial presentations of UTI who were prescribed an antibiotic classified as second-line, over all men at least sixteen years of age with initial presentations of UTI who were prescribed any antibiotic.
Note *: The percentage point difference uses predicted values for first and last months of the study period, January 2012 to June 2017 inclusive.

Table 7-3: Individual antibiotic agents prescribed for urinary tract infection conditions: three antibiotics with the highest magnitude of statistically significant change

Prescribing Rates for Individual Antibiotic Agents for Women >= 16 years with initial presentations of UTI												
	Dependent Variable	**c) Descriptive Statistics (Moving Average Data)**			**d) Linear Regression Model for Trend**							
Patient Group	**Prescribing Outcome Monthly Rate**	**Mean prop.**	**January 2012 prop.**	**June 2017 prop.**	**Coefficient (unit increase per month)**	**[95% Conf.**	**Interval]**	**p-value**	**R-squared**	**January 2012 predicted**	**June 2017 predicted value**	**Percentage Point Difference***
Women at least 16 years	**amoxicillin**	0.03	0.07	0.01	-0.00072	-0.00085	-0.00059	0.0000	-0.00085	0.048543	0.001880	-5
	cefalexin	0.39	0.33	0.45	0.001626	0.001471	0.001782	0.0000	0.001471	0.336198	0.441917	11
	trimethoprim	0.44	0.49	0.40	-0.00102	-0.0012	-0.00083	0.0000	-0.0012	0.469662	0.403687	-7
Men at least 16 years	**amoxicillin**	0.03	0.08	0.02	-0.00058	-0.00078	-0.00038	0.0000	-0.00078	0.046490	0.008796	-4
	cefalexin	0.36	0.35	0.43	0.001421	0.001083	0.00176	0.0000	0.001083	0.312730	0.405115	9
	trimethoprim	0.33	0.33	0.23	-0.00197	-0.00262	-0.00132	0.0000	-0.00262	0.393929	0.265921	-13
Children under 16 years	**amoxicillin**	0.08	0.19	0.07	-0.00152	-0.00188	-0.00117	0.0000	-0.00188	0.130712	0.031651	-10
	cefalexin	0.56	0.54	0.59	0.000975	0.000737	0.001214	0.0000	0.000737	0.528409	0.591799	6
	trimethoprim	0.09	0.04	0.09	0.000629	0.000412	0.000846	0.0000	0.000412	0.073813	0.114707	4

Note: The rate calculation for each particular antibiotic agent was calculated with the numerator being all patients within specific patient group with initial presentations of UTI who were prescribed the particular antibiotic. The denominator is all patients within specific patient group with initial presentations of UTI who were prescribed any antibiotic agent.
Note *: The percentage point difference uses predicted values for first and last months of the study period, January 2012 to June 2017 inclusive.

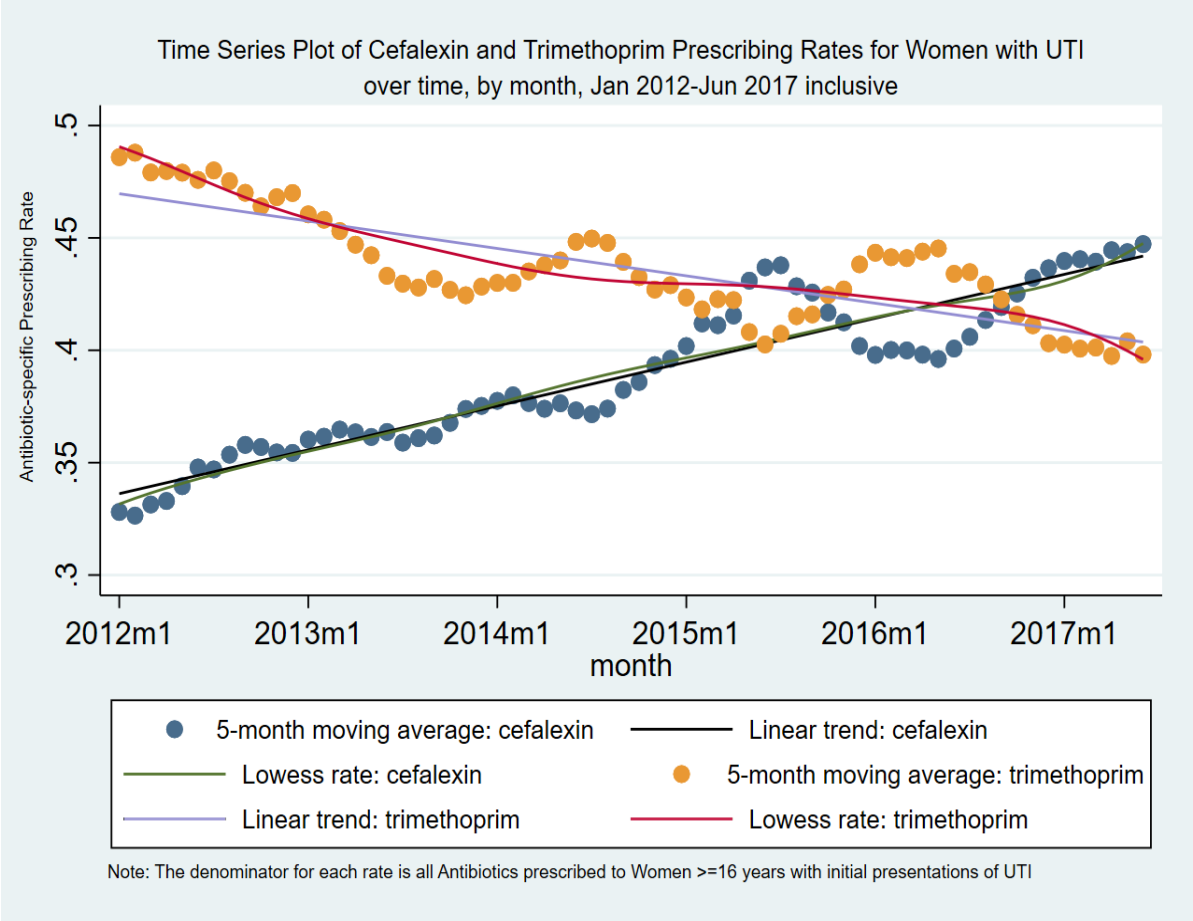


Figure 7-4: Time series plot of simple moving average prescribing rates for cefalexin and trimethoprim for women, January 2012 to June 2017, inclusive, by month

7.2.2.2 Men

For men at least sixteen years of age with initial presentations of UTI, there was a significant, upward trend in second-line antibiotic prescribing of 0.0014 per month (p<0.001, 95%CI: 0.0011, 0.0018), equating to a nine percentage point increase over the study period (**Table 7-2**). Note that in **Figure 7-5** the linear model varies from the smoothed data at multiple points. Although a strict linear trend may not appear very appropriate for this reason (and noting an R-squared of 52%), there is a clear upward trend.

There was also an overall thirteen percentage point increase in non-first-line prescribing of 0.0020 per month (p<0.001, 95%CI: 0.0013, 0.0026), among all antibiotics prescribed to men with initial presentations for UTI (**Table 7-2**). There was no statistically significant trend for the prescribing of not recommended antibiotics for men, with a coefficient of -9.5E-05 per month (p=0.546, 95%CI: -0.0004, 0.0002), which were prescribed at a mean monthly rate of 7% (**Table 7-2**).

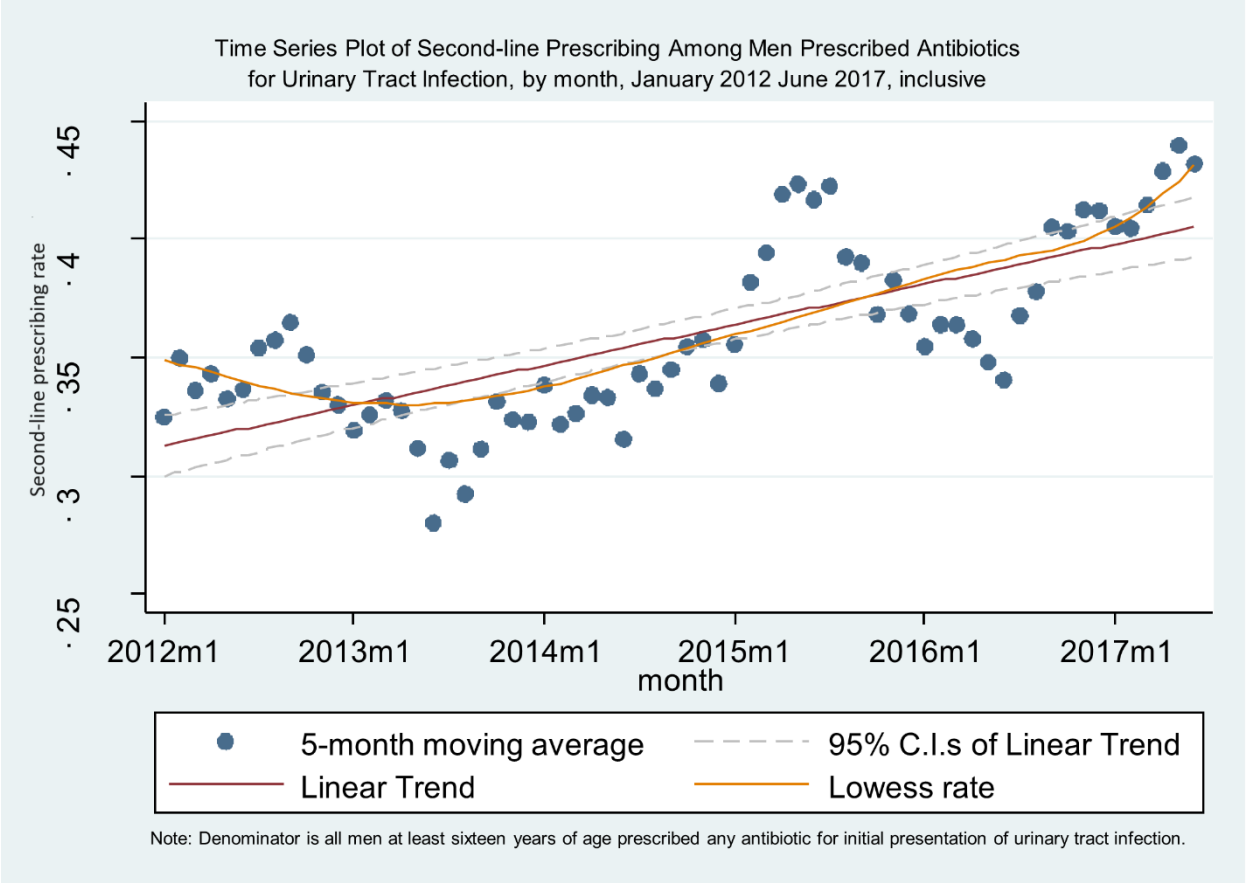


Figure 7-5: Time series plot of second-line antibiotic prescribing for all men at least sixteen years of age with initial presentations urinary tract infection, from January 2012 to June 2017, inclusive, by month

For individual antibiotics prescribed to men, there was a significant downward trend in the prescribing rate for first-line trimethoprim, reducing by 0.0020 per month (p<0.001, 95%CI: -0.0026, -0.0013), equating to a thirteen percentage point decrease overall (**Table 7-3**). There was also an upward trend in cefalexin use of 0.0014 per month (p<0.001, 95%CI: 0.0011, 0.0018), a nine percentage point increase from 31 to 41% of all antibiotics for men (**Table 7-3**). These changes in trimethoprim and cefalexin prescribing may be relevant to the ten percentage point increase in non-first-line prescribing for men.

7.2.2.3 Children

Among children under sixteen years of age with initial presentations of UTI and prescribed any antibiotic, there was a significant, upward trend in second-line prescribing, increasing by 0.0010 per month (p<0.001, 95%CI: 0.0007, 0.0012) (**Table 7-2**). This is equivalent to a six percentage point increase, from 53 to 59% of all antibiotics prescribed to children over the study period.

There was also a significant, downward trend in the use of antibiotics not recommended in the guidelines for children, decreasing by 0.0013 per month (p<0.001, 95%CI: -0.0016 -0.0010) (**Table 7-2**). This equates to an eight percentage point decrease overall from 15 to 7% of antibiotics for children. While this strictly linear model in **Figure 7-6** below may not appear especially appropriate to the data series, and noting an R-squared of 51%, the point is that there is a clear downward trend which can be estimated by the linear trend line. Non-first-line prescribing to children also decreased by 0.0006 per month (p=0.0003, 95%CI: -0.0008, -0.0003), from 84 to 81% of all antibiotics prescribed to children (**Table 7-2**). This is substantially higher than for other patient groups, and especially noting that these data were restricted to initial presentations of UTI.

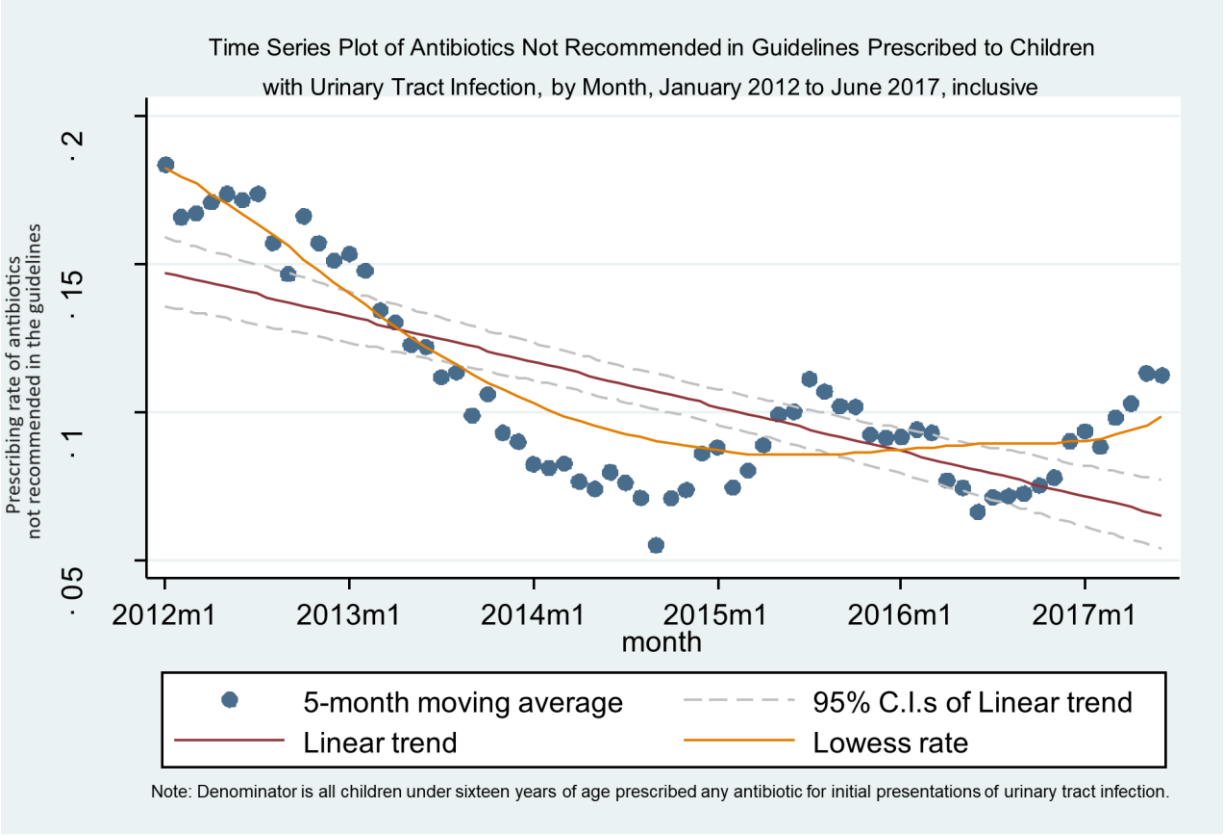


Figure 7-6: Time series plot of prescribing for not recommended antibiotic for children under sixteen years of age with initial presentations of urinary tract infection, from January 2012 to June 2017, inclusive, by month

By individual antibiotic prescribed to children, there was a significant, upward trend in cefalexin use, increasing by 0.0010 per month (p<0.001, 95%CI: 0.0007, 0.0012), representing a six percentage point increase over the study (**Table 7-3**). There was a downward trend in use of the antibiotic, amoxicillin without clavulanate, which is not

recommended, decreasing by 0.0015 per month (p<0.001, 95%CI: -0.0019, 0.0012), from thirteen to three percent (**Table 7-3**). Trimethoprim use also increased by 0.0006 per month (p<0.001, 95%CI: 0.0004, 0.0008), equivalent to a four percentage point increase, as seen in **Figure 7-7**. Both the increase in first-line trimethoprim and decrease in not recommended amoxicillin may contribute to the decrease in non-first-line prescribing. For additional results from this analysis, please see **Appendix F**.

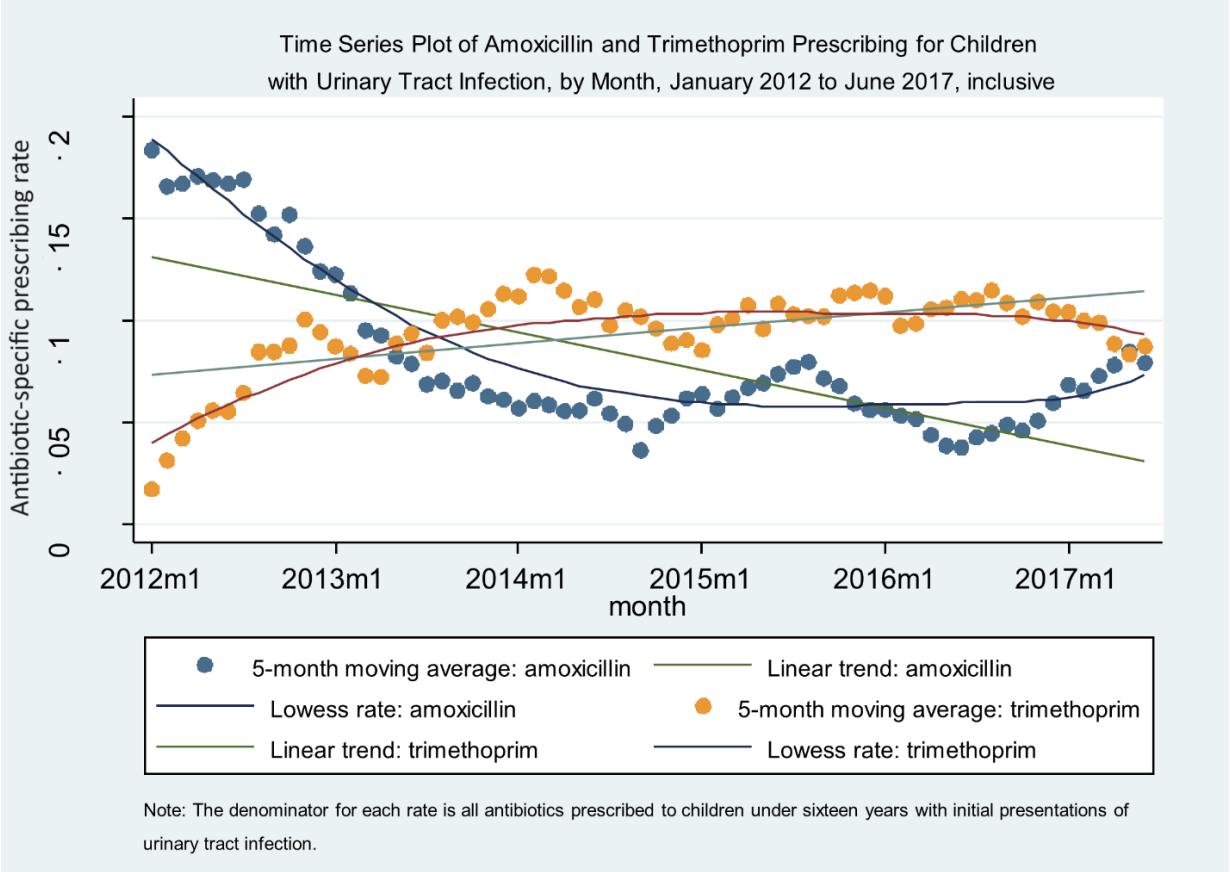


Figure 7-7: Time series plot of prescribing for antibiotic agents not recommended in the guidelines for children under sixteen years of age with initial presentations of urinary tract infection, from January 2012 to June 2017, inclusive, by month

7.3 Summary

For patients with initial presentations of UTI, there are upward trends in the prescribing of second-line antibiotics for all patient groups: women, men and children. There are upward trends in non-first-line antibiotic prescribing over time for adult patient groups, however, a downward trend for children. There were also notable downward trends in the prescribing of not recommended antibiotics for children and women.

There was a consistent increase in second-line prescribing for all patient groups during the study period, which can be attributed to the antibiotic cefalexin, as the only second-line antibiotic. The reduction in the prescribing of antibiotics not recommended in the guidelines for women and children may be in part related to decreasing use of amoxicillin without clavulanate.

Using the smoothed data, all patient groups with initial UTI had mean monthly non-first-line antibiotic prescribing rates of the over 55% of all antibiotics within each patient group, and markedly so in the case of children, with a mean of 83% prescriptions being non-first-line. Children were the patient group with the highest mean proportion of non-first-line (83%), second-line (56%), and not recommended (11%) prescribing, as a proportion of all antibiotics prescribed to each patient group.

Among the three patient groups with initial presentations of UTI, the most substantial progress over the study period appeared to be for children, however, with respect to the use of non-first-line, second-line and not recommended antibiotics. To this end, children were the only patient group with a significant reduction in non-first-line prescribing. The highest reduction in the use of not recommended antibiotics was also in children, and they also had the lowest increase in second-line antibiotics. The analysis also identified that prescribing differs by UTI patient group, which is expected and will be discussed in more detail.

It is clear that there was an increasing reliance of clinicians upon cefalexin for initial presentations of UTI during this period is clear. For adults, there may have been a gradual shift away from trimethoprim towards cefalexin. While cefalexin use also increased for children, there might be an interesting shift away from amoxicillin an increased use of trimethoprim.

These results suggest that, although there is evidence of most progress towards appropriate prescribing according to the guidelines in children, this may well be this patient group in most need of further focus in the future.

CHAPTER 8 DISCUSSION

8.1 Overall findings

This thesis demonstrates that substantial inappropriate prescribing of systemic antibiotics occurred in WA general practice, for initial episodes of care for URTI and UTI conditions, contrary to the national guidelines, called Therapeutic Guidelines: Antibiotic (the guidelines) (29). This inappropriate prescribing takes multiple forms: unnecessary prescribing for URTI conditions, non-first-line antibiotics prescribed for initial presentations of URTI and UTI without justification, and unnecessary repeats issued on many prescriptions (29).

For initial episodes of care for URTI, the strong majority (85%) of antibiotic prescriptions were found to be unnecessary. Of antibiotic prescriptions issued at these initial presentations, 60% were issued with non-first-line antibiotics. Repeats were issued on prescriptions nearly a third of the time, the majority of which were likely not required. Older patients had higher probability of receiving unnecessary antibiotic prescribing and non-first-line prescribing. Rhinosinusitis was the condition with the highest chance of unnecessary prescribing and non-first-line prescribing.

For initial presentations of UTI, 60% percent of patients with initial episodes of care for UTI received non-first-line antibiotics. Given that 82% of children under sixteen years received non-first-line antibiotics for initial consultations, children more commonly receive poor prescribing choices than other age groups. Culture testing occurred for only 2% of children, 3% of women and 3% of men. There were no children or adult males receiving prescriptions for initial UTI who received both culture and sensitivity testing, which are specified in the guidelines (29) as mandatory for children and strongly recommended for men. Repeats were issued on 28% antibiotic prescriptions for UTI.

The fact that these results are drawn from multiple levels of inappropriate prescribing further points to significant, overarching problems in general practice with respect to adherence to the guidelines (29). There is therefore substantial room (and need) for improvement in antibiotic prescribing for URTI and UTI in WA general practice. These multiple levels of inappropriate prescribing also help identify various opportunities for antibiotic stewardship and interventions in primary care. Furthermore, it was individual GP providers, rather than

practices, that were found to be source of most variance unexplained by fixed effects. This suggests that individual providers should be the focus for improving prescribing practices.

It is hopeful that this research will prove informative for general practice. The high proportions of unnecessary and non-first-line antibiotic prescribing for initial presentations of URTI and UTI conditions are concerning. While the trends analyses demonstrate some minor improvements over time, the overall situation presents a challenge for policy-makers. GPs need to do more to take responsibility and take proactive steps to improve their prescribing practices but they also need substantial government support and investment to facilitate this.

8.2 Upper respiratory tract infection

8.2.1 Main descriptive findings for upper respiratory tract infection

This thesis found that for initial presentations of URTI, 85% of antibiotic prescriptions were unnecessary, and 60% of antibiotic prescriptions were non-first-line, when first-line should be the norm. Repeats were also issued on prescriptions 32% of the time. In the Australian setting, it is known that there are high rates of antibiotic prescribing, the strong majority of which are believed to be unnecessary, in addition to low use of first-line antibiotics (12,14,17,18,26,418). For example, the second AURA report (17) for a similar time period as this thesis found that tonsillitis diagnoses received antibiotic prescriptions on 71% of occasions, however, first-line antibiotics were received by only 39% for tonsillitis. In 2022, Monaghan et al. (26) also found acute rhinosinusitis was the condition most likely to receive prescriptions when likely not required. High proportions of antibiotic prescriptions with repeats have also previously been noted (14,18,419). Similarly, in the international setting, high antibiotic prescribing rates and higher than ideal non-first-line prescribing is commonly reported from general practice (268,276,277,322,420).

8.2.2 Predictors identified for upper respiratory tract infection models

The various models for inappropriate prescribing for URTI found that patient age group was significant in all models, and young children 0-8 years were at substantially lower likelihood of the outcome in all models. The three outcomes: unnecessary prescribing; ordinal choice of antibiotic prescribing; and repeat positive prescribing predicted each other in the models,

suggesting these are all related. In addition to patient age, URTI condition was a significant predictor in these three models.

The highest-level model, inappropriate decisions, identified that patients 22-34 years, small practice size and patients with penicillin allergy labels had the highest probability of inappropriate decisions. Predictors of unnecessary prescribing included patient age group, mental health condition status, patient concession status, patient penicillin allergy label status, URTI condition, number of URTI episodes, ordinal line of antibiotic prescribed and repeat prescription status. The chance of unnecessary prescribing increased with increasing age. By URTI condition, the probability of unnecessary prescribing was highest for rhinosinusitis. Patients with penicillin allergy labels and patients with repeats issued on prescriptions were associated with lower chances of receiving unnecessary prescriptions. Note that despite having the same numerator, the difference in denominators between model 0 (inappropriate decisions among diagnoses) and (unnecessary prescribing among prescriptions) may explain some of the seemingly divergent results.

The predictors for the ordinal choice of antibiotic model included patient age group, prescribing reason recorded, URTI condition, multiple URTI episode status, patient comorbid conditions status, patient socioeconomically disadvantaged status, practice size, as well as unnecessary prescribing status and repeat prescription status. Patients aged 22-34 years were least likely to receive first-line and most likely to receive not recommended antibiotics. Unnecessary prescriptions had higher chances of being for non-first-line antibiotics than necessary prescriptions. Second-line featured minimally throughout URTI models. Instead, any decrease in first-line prescribing appeared to be met with a similar increase in not recommended antibiotics, and vice versa.

One interpretation of the increased probability of non-first-line prescribing in necessary prescribing situations compared to unnecessary prescribing situations is that the GPs might resort to prescribing the safest option (first-line) for patients despite knowing that a prescription is technically unnecessary. Whereas in situations where prescribing is genuinely necessary, GPs might tend to give non-first-line prescriptions to try to cover more bases susceptibility-wise. This finding bears resemblance to an Irish questionnaire-based study (22), in which first-line antibiotics were commonly prescribed when the GP considered a prescription not strictly necessary but were prescribed anyway.

Repeats being issued on prescriptions being linked to lower probabilities of unnecessary prescribing is equivalent to necessary prescribing being more likely to occur with repeats on the prescriptions. One feasible explanation is that GPs may tend to prescribe antibiotics with repeats on the prescription for the most seriously unwell patients in need of treatment, such as, necessary prescribing situations. Receiving repeats on prescriptions was linked to an increased probability of receiving non-first-line antibiotics for adults but to a decreased probability of non-first-line antibiotics for children. This may reflect that GPs may be more cautious with choice of antibiotic and whether to prescribe repeats when dealing with children. GPs may also be more comfortable issuing repeats for first-line agents for children.

8.2.2.1 Patient age

The likelihood of inappropriate prescribing increasing with increasing patient age, as found here, has been found in several studies in terms of both unnecessary prescribing and non-first-line prescribing (25,280,281,284,296,324). With regard to inappropriate decisions and unnecessary prescribing in this research, young children were at substantially lower likelihood than other age groups, and young adults 22-34 years were at slightly higher than older children and older adults. These results are comparable to other findings, in terms of adults being a notably higher probability of inappropriate prescribing than children. For example, a study of respiratory tract infection (RTI) in the Netherlands found that adults 18-65 years received proportionally more unnecessary prescriptions than children (281). In their study of Norwegian patients with RTI, Gjelstad et al. (329) also found that younger patient age was linked to lower probability of non-first-line antibiotics, as was the case here. Another study of children with URTI conducted in the UK found increasing prescribing rates with increasing patient age (420). As found in this thesis, an Australian study of patients presenting to the emergency department with URTI and other conditions found that increasing patient age was associated with inappropriate prescribing (48). An Italian study of paediatric URTI using patient interviews and voluntary prescriber participation also found that inappropriate prescribing increased with increasing age (421).

8.2.2.2 Interaction between patient age group and gender in inappropriate decision model

In the inappropriate decision model, there was an interaction between patient age group and gender. While for young children, males had higher probabilities than females of receiving inappropriate decisions but the opposite was true for patients aged 9-21 years and 22-34 years, while there was no difference among patients 35 years and over. One study of US

adults found that male patients were less likely to receive inappropriate prescriptions than females for RTI presentations (326), while a Belgian study found that females 30-60 years more likely to receive appropriate prescribing than males (280), both of which support these findings. Male children were also more likely subject to non-recommended management than females in a Canadian study (328). A Spanish study of female patients over fourteen years with acute bronchitis were less likely to receive appropriate management than men regarding the prescribing decision, akin to the findings of this research (341).

8.2.2.3 Upper respiratory tract infection condition

Two Norwegian studies, one of which was for children, found that patients with acute tonsillitis were less likely to receive non-first-line agents than patients with URTI (297,329), as was the case here. Steinman et al. (276) examined non-first-line antibiotic prescribing to adult US outpatients with non-pneumonic acute RTI and they found that other URTIs, namely laryngitis, pharyngitis and tracheitis, were less frequently associated with non-first-line prescribing than non-specific URTI and common cold, which was also the finding here.

8.2.2.4 Patient allergy labels for penicillin

Having an allergy label for penicillin appeared to predispose patients in this research to receiving more inappropriate decisions and yet it appeared linked to a lower probability of unnecessary prescribing. Appropriate non-prescribing is included in the denominator for inappropriate decisions but not unnecessary prescribing, and it represents the difference between the two response variables. The difference in the direction of effect between the two models may suggest that patient penicillin allergy labels are closely linked to appropriate non-prescribing. Schroek et al. (332) found that US patients with penicillin allergy presenting with RTI had increased the likelihood of inappropriate treatment, despite allergy being allowed for in antibiotic choice, as in this thesis. Patients in another study with reported beta-lactam allergies are likely to receive inappropriate antibiotic choice (422). A Singaporean oncology study found that patients with antibiotic allergy labels or comorbidities were linked to inappropriate prescribing, as was found in this research (423).

8.2.2.5 Practice size

In this research, small practice size was a predictor of non-first-line choice of antibiotics. Otters et al. (271) found that GPs working in solo practices in the Netherlands were more likely to prescribe a non-first-line antibiotic to children for cough, acute upper airway infection or acute bronchitis than group practices, which supports the findings of this research.

Multiple studies did, however, find that prescribers with higher volume patient turn-over and / or higher overall antibiotic prescribing rates were predisposed to inappropriate prescribing (270,277,284,297,321,329). Gjelstad et al. (329) found that GPs with shorter patient lists were less likely to issue non-first-line prescriptions for RTI than those with regular patient lists. Solo *versus* group physician practices has been associated with poorer patient outcomes in a US study of acute myocardial infarction (424).

8.2.2.6 Patient comorbid and mental health conditions

While this thesis found patient mental health condition status was a predictor of unnecessary prescribing, patient comorbid condition status was found to be a predictor of non-first-line antibiotics prescribed for URTI. A Spanish study of patients with acute bronchitis (39) also found that the antibiotic chosen may prove important for patients with comorbid conditions. Several studies have found that patients with comorbid conditions presenting with URTI (and in some cases additional conditions) were more frequently in receipt of inappropriate antibiotic prescriptions than patients without these conditions, particularly poor antibiotic selection (39,281,294,324,326), as was the case here. Bernado et al.'s Australian study (41) also found that patients with comorbid conditions including mental health conditions were linked to higher rates of antibiotic prescribing for ILI, although this utilised the same MedicineInsight dataset but at a national level rather than WA-based. The influence of mental health condition status on likely unnecessary prescribing suggests that clinicians may try to alleviate patient / clinician concerns regarding the health condition and avoid any potential exacerbation of mental health conditions by prescribing despite not it being indicated. It may be a similar misplaced sense of concern for patients with comorbid condition being predisposed to receiving non-first-line antibiotic prescriptions.

8.2.2.7 Other

A small Israeli study of children with AOM had similar findings to those here regarding altered prescribing on the weekends and leading up to the weekend (359). The fact that weekends are associated with lower probability of unnecessary prescribing may reflect less time pressure on weekends during which to explain to patients why they likely do not need antibiotics. High practice activity / high patient loads (and therefore time pressure) have been linked to more frequent inappropriate prescribing for patients with URTI (329,425).

It is feasible that prescribers who may diligently complete the reason for prescribing field may also prove more diligent in adhering to the guidelines. There was also infrequent culture

and sensitivity / susceptibility testing for these URTI presentations, not unlike Gunnarsson et al.'s (426) multinational study of the management of patients with sore throat. Tran et al. (427) note that the guidelines do not provide sufficient advice on diagnostic testing for bacterial sore throat.

8.2.3 Trends in prescribing for upper respiratory tract infection

In this study, there were reductions in the rate over time of likely unnecessary prescribing for rhinosinusitis and pharyngitis but not AOM. There were increases in second-line amoxicillin with clavulanate usage and decreases in first-line agent amoxicillin, and thus increasing non-first-line prescribing for rhinosinusitis and AOM. There were decreases in both unnecessary prescribing and non-first-line antibiotic prescribing for pharyngitis. All URTI conditions had downward trends for antibiotic prescribing among initial presentations, similar to findings for these conditions using national PBS dispensing data (14,18,41,428). Despite a decreasing trend for antibiotic prescribing for AOM, there was no significant change in likely unnecessary prescribing, and there was also an increase in non-first-line antibiotic use.

Increasing non-first-line prescribing for URTI has also been commonly reported in Australia and the US (12,14,295,330). For rhinosinusitis, increasing second-line amoxicillin with clavulanate use appear to mirror decreases in first-line amoxicillin over time. As was the case here, a shift in amoxicillin in favour of amoxicillin with clavulanate has been documented nationally using PBS data (12,17), with little change in overall volume over time suggesting direct replacement (12). Another study noted similarly increasing amoxicillin with clavulanate dispensing in Australian dental community care (429). For pharyngitis, first-line phenoxymethylpenicillin increases appeared to mirror decreases in not recommended amoxicillin. The only second-line antibiotic for pharyngitis / tonsillitis, benzathine penicillin, remains essentially unused in community care. For AOM, increasing first-line amoxicillin seemed to correlate with decreasing second-line amoxicillin with clavulanate.

There were favourable downward trends in antibiotic prescribing for URTI conditions including influenza / ILI. The decreasing trends for two conditions (rhinosinusitis and pharyngitis) for unnecessary prescribing and non-first-line prescribing suggests some progress overall. However, major concerns remain regarding antibiotic prescribing for URTI

conditions, including ongoing high levels of inappropriate prescribing, and increases in non-first-line prescribing.

8.3 Urinary tract infection

8.3.1 Main descriptive findings for urinary tract infection

The high rates of non-first-line prescribing for all patient groups is concerning, particularly as these are initial consultations for UTI and not secondary or chronic presentations. Non-first-line antibiotics were received in sixty percent of prescribing situations for initial episodes of care for UTI, 82% for children under sixteen, 68% men and 57% women, which is very high particularly for children. High non-first-line prescribing rates for UTI have been commonly reported elsewhere in both the Australian setting (14,17,48), and notably for children (307). Notable non-first-line prescribing rates for UTI are a frequent finding in international studies among children and women (119,290,296,323).

Culture testing was recorded for 2% children, 3% of men and 3% of women and there were no sensitivity testing results. It is concerning that culture and sensitivity testing were performed so infrequently for children and men despite being recorded in the guidelines as mandatory for children and strongly recommended for men (29). Repeats were issued on 28% of prescriptions for UTI. Of repeats on cefalexin prescriptions, 99% were likely unnecessary for adults eighteen years and over but 99% were likely necessary for children under sixteen years. There was also high variation in antibiotic duration for the cefalexin prescriptions examined, which is consistent with findings for antibiotics commonly prescribed for UTI internationally (120,285,291).

8.3.2 Predictors identified for urinary tract infection models

The predictors of increasing line of antibiotic choice included patient age group, gender, comorbid condition status, repeat prescription status and urine dipstick and culture testing. Predictors of repeat positive prescribing included patient age group, ordinal choice of antibiotic, urine dipstick testing, temperature recording status and multiple UTI episodes. Young children had the lowest probability of receiving first-line antibiotics, followed by older children, and then adult age groups. Children and men were most likely to receive second-line antibiotics. Antibiotic choice and repeat positive prescribing were also found to predict

each other. While attempting to clarify whether predominantly patient-specific factors might be driving various definitions of inappropriate prescribing of UTI, several of the predictors identified are in fact, consultation- or prescription-related.

Prescriptions issued with repeats were linked to third-line and second-line antibiotic prescribing for UTI. In the model for choice of antibiotic, male gender increased the probability of non-first-line prescribing for adult patients, and the magnitude of effect increased with increasing age. Having urine dipstick testing or culture testing performed were associated with lower chances of non-first-line prescribing for all patients, while having comorbid conditions was linked to increased chances. Adult males were more likely to receive non-first-line prescriptions as well as prescriptions issued with repeats than women. Urine dipstick testing being performed was also linked to lower probability of receiving prescriptions issued with repeats.

8.3.2.1 Patient age and gender and (un)complicated infection

Similar to the findings of this research, studies conducted in the US (323) and Italy (325) found that the youngest patients were most likely to receive inappropriate prescribing for UTI. The US study found that non-first-line prescribing for UTI was more common for children under two years, than children 13-17 years, and for female gender (323), as was found here. As UTI can be serious and potentially complicated in in children and men (123), GPs' concerns for their patients may drive the high proportions of non-first-line prescribing in these groups.

8.3.2.2 Repeats issued on prescriptions

With respect to repeats being issued on prescriptions being linked to first-line prescribing for children 5-15 years, it is possible that some school-aged children may be issued first-line prescriptions along with repeats on that prescription to limit the notable inconvenience of reattendance for parents of school-aged children presenting with UTI. It is plausible that repeats are driven by the clinician's attempts to reduce the need for re-visitation for parents, and that clinicians may be more comfortable prescribing repeats for first-line agents than non-first-line agents, particularly in children.

8.3.2.3 Urine dipstick and culture testing

It should be noted that this research did not examine pathology requests alone but results, which required both a GP request and patient completion of a pathology test. Nevertheless,

the results are so infrequent that the issue is unlikely to be predominantly due to potential patient non-compliance or difficulties acquiring urine samples from young children (307). Similar to the findings here, Peng et al. (430) also found that there was a low use of urine culture tests for groups at high risk of complicated UTI in the Australian setting, using a 25% sample of national MedicineInsight patients compared to this project's use WA data during a similar timeframe. They also found that young children were less likely to receive culture testing than young adults (430). Another Australian study of GPs found that requests for urine culture and microscopy occurred substantially less than recommended for both men and children (307), as found in this research.

The limited culture and susceptibility testing for UTI is potentially both time and cost-related, as well as potential issues with patients adhering to testing requests. It is indeed reasonable for GPs to prescribe antibiotics at the first presentation without culture or susceptibility results, due to highly uncomfortable and painful symptoms. However, referrals for such testing at initial presentations should be routine, and GPs should be insisting that patients perform testing prior to commencing antibiotics. There may also be a lag in guideline dissemination, as urine cultures were recommended in previous guidelines of 2010 (431) rather than those current at the time of prescribing (29), in which both susceptibility and culture recommended. Dipstick and culture testing may also be indicators of more diligent, more guideline-aware and antibiotic resistance-aware prescribers.

8.3.2.4 Patient comorbid conditions

The finding that comorbid conditions influence prescribing for UTI is supported by other research from Australian primary care (48). A small US qualitative study not limited to primary care found that clinicians are conflicted between adhering to guidelines and tailoring individual patient care based on comorbidities as well as sociodemographic factors (432).

8.3.3 Trends in prescribing for urinary tract infection

There was an increase in second-line prescribing for all patient groups during the study period, which can be attributed to the antibiotic cefalexin, as the only second-line antibiotic. There were upward trends in non-first-line antibiotic prescribing over time for adult patient groups, however, a downward trend for children, which may be linked to the notable decrease in use of not recommended antibiotics. There was also a downward trend in the prescribing of not recommended antibiotics for women.

While there was a modest reduction in non-first-line prescribing for children over the study period, non-first-line prescribing rates for children remain very high and may be the patient group in most need of further, focused improvement. The decreasing norfloxacin use for adults during this period is favourable, although it should be negligible for initial UTI consultations.

There was notable amoxicillin without clavulanate use for initial UTI presentations when it was not recommended in the guidelines at the time. This suggests that there may have been a potential discord between clinicians and the guidelines, however, it should be noted that it was added as an option in the subsequent guidelines for children and adult non-pregnant women and men for situations of resistance to empirical therapy recommendations (86).

8.4 Specific findings common to upper respiratory tract infection and urinary tract infection

For initial presentations of either URTI or UTI, non-first line antibiotic prescribing appears far too prominent among these Australian GPs, with limited focus on overall community AMR concerns.

Patient age was a highly influential predictor for URTI and UTI, despite differing direction of effect. Young children had the lowest probability of receiving inappropriate prescribing with URTI but were at notably high probability of receiving non-first-line prescribing for UTI. Repeats on antibiotic prescriptions were also influential for both URTI and UTI.

There have been important developments in critical antibiotic resistances in carbapenemase-producing enterobacteriaceae, fluoroquinolone non-susceptibility in *Escherichia coli, and* methicillin resistance in *Staphylococcus aureus* identified among hospitalised patients with bacteriaemia in Australia over the study period (14,18,417). These have been found to disproportionally affect patients in Northern Australia and, to some extent, Western Australia, notably Aboriginal and Torres Strait Islander patients (433-436). Clinician awareness regarding increasing antibiotic resistance, for example, may also influence decisions to prescribing non-first-line antibiotics.

The fact both mental health conditions and other comorbid conditions have emerged as predictors within differing levels of inappropriate prescribing demonstrates these do influence clinician decision making.

The modest influence of number of URTI episodes in unnecessary prescribing, choice of agent among unnecessary prescriptions, and in the model for repeat prescribing suggests that there may be increased clinician concern regarding patients with additional, albeit separate, episodes. This may potentially point to multiple clinical interpretations of what comprises a single episode of infection, and a potential blurring of definitions between separate episodes and re-consultation for the same episode. Patients having multiple episodes of UTI was also a predictor for patients receiving prescriptions with repeats present, which may also suggest this link.

Throughout all modelling processes, of variation not explained by fixed effects, the variation explained by individual provider was far greater than the variation explained by individual practice. This suggests that individual provider drives variation far more than the individual practice. The fact that other Australian data (14,17) found high variation in dispensing rates across geographical areas to suggest that individual clinician preference had a strong impact on antibiotic use also supports this. Large variability between prescribers as well as between and within practices has been reported elsewhere (257,425,437,438), although these studies focused more on differentiating between patient *versus* physician variability, rather than comparing prescriber and practice variation as in this thesis.

8.5 Implications to policy, practice and research

These results suggest that antibiotic prescribing occurs commonly despite it likely not being in the best interests of the patient, whether it be the decision to prescribe or the choice of antibiotic or the presence of a repeat. While first-line prescribing should, by definition, be the most frequent option for initial presentations of URTI where an antibiotic is prescribed, non-first-line agents represented the strong majority throughout the study. Prescribing rates also remained high throughout. Both factors suggest that there is a monumental task ahead in terms of achieving high compliance with the guidelines (29).

It is concerning that not recommended antibiotics contribute the highest proportion of any line of antibiotic prescribed for URTI. This suggests that they may be the 'go-to' for many clinicians. It appears that there has been a slight reduction in the prescribing of not recommended antibiotics over the study period, however, this remains far too high and should not be used for initial presentations.

For URTI, patients other than young children 0-8 years had notable probabilities of receiving inappropriate decisions. Unnecessary prescribing increases with increasing patient age, regardless of the URTI condition, so stewardship for URTI should focus limiting unnecessary prescribing for older patients. Pharyngitis was the condition with proportionally the most inappropriate decisions and the lowest appropriate non-prescribing rate. However, rhinosinusitis was the condition with the highest chance of receiving unnecessary prescribing. These two conditions should be prioritised for stewardship.

While several publications focus on children receiving the brunt of inappropriate antibiotic prescribing – defined by either prescribing rate for likely viral conditions, or non-first-line prescribing rate (12,17), it is unclear whether consultation / diagnosis rates have been taken into account, and it appears that they have not. When viewed in isolation, children do indeed receive the largest number of unnecessary prescriptions for URTI. However, when the high consultation rates for children with URTI are taken into account, young children are actually receiving proportionally more appropriate treatment than many other age groups. Standalone statements regarding high prescribing or dispensing rates or high non-first-line prescribing rates for children for certain conditions may not be well received by clinicians (14,18), as they are undoubtedly aware of the high consultation rates for children for common infections. Such statements, although technically correct, may be perceived as naïve and dismissed for this reason. Messages aimed at improving prescribing practices for URTI may prove to be more effective when presented in context with consultation rates.

The fact that non-first-line prescribing occurred for 68% of acute rhinosinusitis prescriptions, and this notably higher than for other conditions, is concerning. This suggests substantial room for improvement with regard to the choice of agent for acute rhinosinusitis. Given that Country WA was the only PHN in which first-line prescriptions were most common for acute pharyngitis / tonsillitis (**Appendix C.2, Table C-9**), this may suggest that Country WA practitioners may be more familiar with treating pharyngitis, and how to do so appropriately.

Aboriginal and Torres Strait Islander peoples are at high-risk for complications of pharyngitis and prescribing is therefore appropriate. GPs working in Country WA may be acutely aware of the guidelines for this condition by virtue of the high proportion of Aboriginal and Torres Strait Islander peoples. Many of these patients may also be treated within Aboriginal Health Services rather than mainstream general practice, the source of data for this research.

For UTI, the non-first-line prescribing dominates for children. Both children and men appear particularly at risk of poor prescribing choices, and the absence of important culture and sensitivity testing for these groups indicates a clear discord with the guidelines (29). There is a need for increased clinician awareness regarding the need for pathology testing for UTI diagnoses. It may also be worth giving consideration for a request to amend GP practice software to automate urine, culture and susceptibility requests for children and men with UTI (114).

It is promising that over 50% and over 80% of repeats for all patients with URTI and UTI, respectively, would likely have been prevented by the PBAC decision to limit repeats (127,128). PBAC should consider extending the repeat authority restrictions to include erythromycin and phenoxymethylpenicillin, which were used frequently for URTI and were commonly issued repeats when likely not required. Given the relationship between inappropriate prescribing and repeat prescribing, it may also be worthwhile to ask PBAC to consider shortening prescription validity (12,14,124). It is feasible that shortening prescription validity for many antibiotic prescriptions may result in limiting use of repeat prescriptions. Additionally, PBAC could consider requiring telephone PBS authority in order to prescribe end-of-the-line ‘last resort’ antibiotics, to further restrict their use and protect their efficacy.

Patient penicillin sensitivity is an important predictor of inappropriate prescribing for URTI presentations. There are limitations of current antibiotic allergy management, leading to undue use of non-first-line antibiotics (439). Ness et al. (422) note that many reactions likely do not reflect true hypersensitivity and that there is potential for safe rationalisation of patients with self-reported penicillin allergy (422,440). However, there are calls for an Australian allergy register (441), noting antimicrobials caused 48% of drug-related anaphylaxis admissions in a recent study (442).

The fact that these data show that for URTI and UTI, the individual provider has substantially more effect on inappropriate prescribing than variation in practice is suggestive an individual behavioural element, rather than practice-based culture. This offers hope in that individual prescribing behaviour at the GP level may be modifiable and that individual GPs should be the targeted in stewardship efforts for improving prescribing.

We are presented with opportunities to impact future prescribing and improve the quality of care for patients presenting to WA general practice. All of these findings should be incorporated into GP stewardship programs and interventions, such as those outlined in the Background chapter, to improve prescribing practices for GPs. These could be incorporated together with promising strategies like delayed prescribing (68,69,126,216,443), social norm feedback (126,444) and shared decision-making (126,214,443). Such stewardship programs should be coordinated at the state and primary health network level. It will be important to consult with and be guided by GPs, and organisations such as WAPHA (42), in the development of specific programs / interventions. GPs likely need more incentive for change (445), although careful consideration is required prior to implementing any new policy (446).

Additionally, the need for culture and susceptibility testing for children and men with UTI, could be incorporated into patient management software in the form of automated reminders, as well as GP stewardship activities. Antibiotic stewardship initiatives for the general public are also required to educate patients regarding the appropriate use of antibiotics and the need to preserve their effectiveness.

The accessibility and usability of the guidelines for Australian GPs has also been questioned (26,250,251). Monaghan et al. (26) highlight the need for free access to guidelines, which is not currently the case, and this should be rectified if compliance with them is to be expected.

The shortfalls in GP data access and government surveillance go beyond antibiotic prescribing. These shortfalls result in limited prescribing surveillance, as we do not have detailed population-level data from general practice by which to plan stewardship activities. The government could take action to facilitate the collection of more detailed data from general practice than it presently requires for the purposes of Medicare reimbursement of services provided. Additional data collection would simply bring GP data surveillance up to

that of a similar level as experienced by all medical practitioners working in the hospital system. This would likely be met with much discontent from many GPs not wishing to have their clinical management of patients scrutinised, however, the government could take a hard-line approach.

We must somehow reach a situation where the majority of GPs place the future of the community on par in priority with the individual patient needs. In this situation, each potential prescribing situation would be akin to weighing up the balance between prescribing for the individual patient and future impact of resistance on the community. At present it seems that a proportion of GPs do so, however, they are fighting against the tide of majority. Linder's (447) analogy of needing to 'break the cycle' of unnecessary antibiotic prescribing is fitting. There is also the possibility that the practices and respective GPs involved in MedicineInsight (168,345), which already promoted AMR stewardship and facilitated prescribing feedback, and may have been more guideline-compliant than most GPs. This raises the possibility that the prescribing by GPs in WA outside this dataset might have the potential to be even less guideline-compliant than those studied here, which is a concerning prospect.

Based on the magnitude of the inappropriate prescribing occurring at different levels, there is reason for concern. Unfortunately, no matter how one looks at it, in times of increasing resistance, the impact of poor prescribing practices is a serious matter. While it may be tempting to cite the difficult contexts GPs face, such as diagnostic uncertainty and the lack of point-of-care testing, no amount of context or explanation can alleviate the severity of the impact of poor prescribing occurring at a health system level. However, the situation is simply not good enough and more action is urgently needed. Antibiotic resistance is developing at a far greater rate than any small improvements in prescribing practices found here.

Antibiotic prescribing is a complex, multifaceted issue and many unknowns remain. Some of these factors are thought to include patient demand, perceived patient demand, time pressure, complacency, and ignorance regarding antibiotic resistance on part of the prescriber (23,180,233-239,448).

8.5.1 Future research directions

More research on drivers of inappropriate prescribing is required and more insights from GPs themselves are essential. The findings from this quantitative research should be explored with detailed qualitative inquiry, to provide complimentary, additional context to these results and gain insight into GPs' perceptions regarding inappropriate antibiotic prescribing. For example, semi-structured interviews could provide insight into GPs' perceptions regarding the circumstances in which inappropriate antibiotic prescribing occurs and perceived driving factors. Future research is also warranted to investigate factors influencing the use of antimicrobials in primary care which may not be addressed well in the guidelines, which is another opportunity to involve GPs.

Further research is needed to identify factors driving inappropriate prescribing in certain settings and for other specific conditions (294), such as community-acquired pneumonia and cellulitis in Australian general practice. Given the notable inappropriate prescribing identified to date, and the concerning variation found for duration of cefalexin prescribing for UTI, guideline compliance regarding dose and duration of antibiotic prescribing also needs further exploration. Expanding research to include the use of topical antibiotics would also be beneficial. Other options include investigating prescriptions issued without a consultation (308,318,449) and long-term antibiotic prescribing such as for acne (450). Second to GPs, other medical specialists are responsible for the most antibiotic prescriptions in the community setting (12), which would also be worthwhile to research. Time pressure and workload in relation to inappropriate prescribing are worthy of further investigation.

There is a need for further research specific to Aboriginal and Torres Strait Islander peoples and pregnant women in relation to inappropriate antibiotic prescribing. Aboriginal and Torres Strait Islander people continue to be under-identified in many Australian health-related data collections (355). They have higher levels of morbidity and mortality than non-Indigenous Australians (451,452) and are at higher risk of serious complications following infection, and therefore have a lower threshold for antimicrobial prescribing (453). Detailed study of the appropriateness of antibiotic prescribing provided to Aboriginal and Torres Strait Islander populations is important. Pregnant women are also an important part of the population which should be studied (325).

8.6 Limitations

8.6.1 Prescriptions and patient groups

Limitations of this study include the fact that delayed prescriptions could not be differentiated from those directed for immediate use, as dispensing data was unavailable. This may result in an overestimation of likely unnecessary prescribing. The uptake of delayed prescribing is uncertain due to its limited albeit promising study in Australian clinical practice (218). It is difficult to compare prescribing practices with dispensing practices, as many prescriptions are known not to be filled / dispensed by patients (60-64).

Pregnant women could not be easily identified so all women were assumed to be non-pregnant, which may have influenced the results to a small extent. Also, the variable indicating patients identifying as Aboriginal and Torres Strait Islander peoples was considered unreliable such that it was not used in analysis, in addition to the fact that dispensing via Aboriginal Health Services is not captured in these data (12).

8.6.2 Definition of inappropriate prescribing according to the guidelines

This thesis was limited to identification of 'likely' inappropriate prescribing rather than 'definitive' inappropriate prescribing according to the national therapeutic guidelines. It is inherently complex to accurately identify inappropriate prescribing from data extracted from general practice software, and free-text progress notes made by the GP are typically not available for research, due to difficulties deidentifying these data. For some conditions, the progress notes may include the indication for prescribing according to the guidelines (26), against which recorded criteria are checked to ascertain appropriateness. The possibility of obtaining progress notes was explored but could not be obtained due to confidentiality reasons. Inappropriate non-prescribing (not prescribing despite it being necessary for the patient) was also excluded as it was considered that there was insufficient information available to accurately assess this.

Misclassification would have been possible in circumstances where the recording of this important information, such as the clinical observations of fever, simply did not occur. This is a reason for using the term 'likely unnecessary' rather than a more definitive judgement. Researchers can only work on the data recorded and accessible, and this

concession was necessary to analyse large-scale patient data. A conservative approach was taken to limit potential overestimation of indications to prescribe using the data at hand (454).

8.6.3 Diagnoses

Defining an episode of infection for analysis required limiting the definition to encounters with the same diagnosis within a predefined period as a single episode. For URTI, the presence of influenza diagnoses resulting in antibiotic prescriptions may be reflective of poor coding by the GP of bacterial infection secondary to influenza. This highlights the need to be mindful that these data were not created for research purposes but for administrative purposes and this may have implications upon the coding used by GPs.

Despite the removal of UTI diagnoses coded as recurrent / chronic, some presentations for chronic / recurrent UTI may have been poorly coded as (initial presentations of) UTI. Note the guidelines used for assessment in these analyses do not define recurrent UTI in terms of a number of episodes within a specified timeframe (29). However, the guidelines for recurrent UTI published in 2019 (86), subsequent to the study period, define recurrent UTI as two or more episodes within six months, or three or more per year, and positive urine cultures (412,430,455,456).

8.6.4 Other potential covariates

Another limitation of the study was the inability to identify any patients visiting more than one practice within the dataset. There is negligible information in Australia regarding the prevalence and potential impact of this, particularly in the antibiotic prescribing context. Patient movement between practices is thought to be less likely for the young and elderly. It was also not possible to identify pathology tests requested but not subsequently performed by the patient. Practice size was unable to be obtained from MedicineInsight due to confidentiality reasons (168).

8.6.5 Statistical limitations

Although random slopes and random intercepts were the intention at each level, this proved too resource-intensive computer-wise. The absence of random slopes can result in standard

errors which may be anti-conservative (457). However, the use of mixed models (allowing for unobserved heterogeneity) is much preferred over the alternative of fixed effects, which would have put undue scrutiny on PHNs for likely unnecessary prescribing, for example.

The trends analyses involved monthly aggregate data for the five-and-a-half-year period, equating to 66 monthly data points, and as such there are limits to what one may infer from these data particularly with regard to any prediction beyond the study period. Nevertheless, this analysis provides useful insights into the overall direction and magnitude of prescribing outcomes and highlight areas of progress as well as areas of concern.

8.6.6 Complexities of the project

Access to general practice data proved politically sensitive for this research. It took some time to negotiate access to suitable data, involving the refusal for involvement by three other potential data sources. It is only through both WAPHA (42) and MedicineInsight's (168) involvement that this thesis was possible, highlighting the need for collaboration in Australian primary care research. The presence of multiple stakeholders also created minor complications with each having slightly different perspectives. Fears of upsetting member GPs, upon whom both external stakeholders rely, was an issue which arose, however, both stakeholders demonstrated ongoing commitment to this project. There were delays due to technical difficulties with managing large datasets, including obtaining sufficient processing power and data storage. Data cleaning proved more time-consuming than anticipated, particularly with regard to free-text string variables including diagnoses and pathology results.

Difficulties regarding data access relates back to Australian general practice being predominantly privately owned practices. For groups of practices in large organisations, who have invested in database management, remuneration is required to obtain access to GP data, and this is not unusual for research data, however, must be considered (182). WAPHA (42) and MedicineInsight (168) had important roles in facilitating and supporting this project, despite the possibility that the findings of this research may raise anxieties of GPs participating in their respective programs. This demonstrates their commitment to research towards limiting antibiotic resistance and improving patient care.

8.7 Significance

The project has significant potential impact both nationally and internationally. It can inform policy and practice and lead to further research. Its applications include informing the development of evidence-based interventions to reduce inappropriate antibiotic prescribing to stem the emergence of resistance.

This research goes a notable way to filling the large gap in knowledge regarding inappropriate antibiotic prescribing in Australia. The importance of this project also relates to the fact that limited research has been undertaken using large-scale data from general practice in Australia to date.

To the best of our knowledge at the time of writing, this is the first Australian research using quantitative methods and empirical data to identify predictors of inappropriate prescribing in general practice for UTI and URTI. This is also believed to particularly be the case for the state of WA. This is believed to be the first research in Australian general practice, to the best of our knowledge, limits consultations to initial presentations for the condition. This is also believed to be the first study in Australian general practice, to the best of our knowledge, which uses more information than purely the condition diagnosed to differentiate inappropriate from appropriate prescribing.

In light of the increasing international threat of antibiotic resistance, and the need for action on this front, it is vital to inform this action by measuring adherence to the guidelines and identifying any factors affecting adherence (29).

CHAPTER 9 CONCLUSION

This research identified the substantial inappropriate prescribing of systemic antibiotics occurred within WA general practice between January 2012 and June 2017, inclusive. Over 80% of antibiotic prescriptions for URTI presentations were found to be likely unnecessary. Non-first-line prescribing was found in more than half of all antibiotic prescriptions for URTI and UTI. Repeats were issued on over 25% antibiotic prescriptions occurring for URTI and UTI, the strong majority of which were unnecessary. There was concerning deviation from the guidelines for UTI for children and men (29), with infrequent culture and susceptibility testing for performed.

For URTI, the predictors of inappropriate prescribing identified were patient age, URTI condition, practice size, mental health condition status, patient concession status, patient penicillin sensitivity, number of URTI episodes, repeat prescriptions status, weekend consultation status and patients from interstate PHNs. For UTI, the predictors of inappropriate prescribing included patient age group, gender, comorbid condition status, repeat prescription status and urine dipstick and culture testing status, temperature recording status and multiple UTI episodes.

All URTI conditions had downward trends for antibiotic prescribing among initial presentations over the study period. There were also reductions in the rate of likely unnecessary prescribing for rhinosinusitis and pharyngitis but not AOM. There were upward trends in non-first-line prescribing for rhinosinusitis and AOM but a downward trend for pharyngitis. For UTI, there were increases in second-line antibiotic prescribing for all patient groups over time. There are upward trends in non-first-line antibiotic prescribing over time for adult patient groups, however, a downward trend for children.

The magnitude of inappropriate prescribing occurring at several different levels or definitions of inappropriate prescribing demonstrates that there is reason for concern. Despite some small improvements in prescribing practices found over time, more action is urgently needed.

The findings of this thesis should be incorporated into GP stewardship programs / interventions to improve prescribing practices. Antibiotic stewardship for the general public is also in need. PBAC should give consideration to various amendments to GP prescribing authorities for relevant antibiotic prescriptions. Changes regarding culture and susceptibility testing could also be incorporated into patient management software. The government could additionally consider requiring more detailed data from general practices to facilitate improved surveillance of antibiotic prescribing and enhanced planning of stewardship activities.

This thesis has covered the priority condition groups of URTI and UTI. Further areas for research should include inappropriate antibiotic prescribing for community-acquired pneumonia and cellulitis in Australian general practice, as these are prevalent conditions with large populations affected. Research should be conducted specific to Aboriginal and Torres Strait Islander peoples and pregnant women, as these groups were not clearly identifiable from the data available in this research. Both the dose and duration of antibiotic prescribing also warrant further investigation for URTI and UTI conditions. Future research should also explore the use of topical antibiotics. Time pressure and workload are important to investigate further for any association with inappropriate antibiotic prescribing in the GP setting. It may be worthwhile researching inappropriate antibiotic prescribing by medical specialists other than GPs in community setting.

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APPENDICES

TO

THESIS

Predictors of Inappropriate Antibiotic Prescribing in Australian General Practice / Primary Care Settings

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APPENDIX A – APPENDICES FOR THE BACKGROUND CHAPTER

A.1 Previous and subsequent guidelines for relevant conditions

A.1.1 Upper respiratory tract infection

A.1.1.1 Acute rhinosinusitis / non-specific upper respiratory tract infection

A.1.1.1.1 Previous guidelines version 4 (2009) Therapeutic Guidelines Respiratory (1) - relative to the guidelines used in analysis – Therapeutic Guidelines Antibiotic version 15 (2014) (2)

Prior to 2014, acute rhinosinusitis was listed within the respiratory guidelines published in 2009 (1). Within these, rhinosinusitis and rhinitis were listed together (1). For Acute rhinosinusitis, symptomatic treatment is listed as the target of treatment (1). It notes that viral infection constitutes the strong majority, and that bacterial complications eventuate in an estimated 0.5% to 2.0% of acute viral rhinosinusitis presentations (1). In cases of severe symptoms lasting in excess of five to seven days plus high fever or severe headache or worsening symptoms or unilateral maxillary tenderness of the sinus (1). Amoxicillin is listed as the first-line recommendation (1).

A.1.1.1.2 Subsequent guidelines version 16 (2019) Therapeutic Guidelines Antibiotic (3) - relative to the guidelines used in analysis - version 15 (2014) (2)

This version of the guidelines notes that acute viral and bacterial rhinosinusitis are unable to be distinguished in the first three or four days of symptoms but that bacterial presentation is rare (3). It notes that acute bacterial illness is most often self-limiting and that antibiotics have little impact (3). For patients believed to likely have acute bacterial rhinosinusitis, these patients should still receive only symptomatic therapy but with follow-up if symptoms continue or worsen (3). The first-line antibiotic of choice in situations when antibiotics are indicated is amoxicillin, followed by amoxicillin with clavulanate (3). These guidelines also mentions shared decision making as an option (3).

A.1.1.2 Acute pharyngitis / tonsillitis

A.1.1.2.1 Previous guidelines version 14 (2010) Therapeutic Guidelines Antibiotic (4) - relative to the guidelines used in analysis - version 15 (2014) (2)

Difficulties between differentiating viral and bacterial sore throat are acknowledged in this 2010 version of the guidelines (4). Justifications for prescribing antibiotics are listed as preventing non-suppurative complications of patients at high risk of complications, preventing suppurative complications or to lessen illness duration (4). These 2010 guidelines note that high-risk patients include 2-25 years in communities with high rates of acute rheumatic fever incidence, including remote Aboriginal and Torres Strait Islander communities (4). Any patient with scarlet fever or current rheumatic heart disease are also considered high-risk (4). These guidelines also note that symptomatic relief is useful for treating suppurative complications (4). Phenoxymethylpenicillin is the first-line recommendation when antibiotics are indeed indicated, followed by benzathine penicillin IM as the second-line option for non-compliant patients or for those unable to tolerate oral antibiotics (4).

A.1.1.2.1 Subsequent version 16 (2019) of Therapeutic Guidelines Antibiotic (3) - relative to the guidelines used in analysis - version 15 (2014) (2)

In this version of the guidelines, pharyngitis/tonsillitis has been amended from its own condition to within the condition of sore throat *(3)*. It notes that viral pharyngitis/tonsillitis are the most common cause and that antibiotics should not be prescribed for these *(3)*. Management is separated into patients at high risk of acute rheumatic fever and otherwise *(3)*. Furthermore, it notes that streptococcal pharyngitis/tonsillitis are most often self-limiting *(3)*. These guidelines note that the strong majority of patients not at high risk of acute rheumatic fever do not required antibiotics *(3)*. Recommendations for when antibiotics are indicated are separated into streptococcal and *Arcanobacterium haemolyticum (3)*. For streptococcal infections, phenoxymethylpenicillin and also amoxicillin are the antibiotics recommended *(3)*. For *Arcanobacterium haemlyticum*, azithromycin or erythromycin are the antibiotics of choice *(3)*.

A.1.1.3 Acute otitis media

A.1.1.3.1 Previous guidelines version 14 (2010) Therapeutic Guidelines Antibiotic (4) - relative to the guidelines used in analysis - version 15 (2014) (2)

This 2010 version of the guidelines notes that either bacterial or viral AOM most often resolves by itself (4). It notes that antibiotics provide only modest benefit, and that suppurative complications are rare (4). For Aboriginal and Torres Strait Islander peoples, however, such complications are noted as being common so antibiotics are usually recommended for these patients (4). While in this 2010 version, patients hypersensitive to penicillin are recommended cefuroxime or cefaclor (4), however, cefuroxime or trimethoprim with sulfamethoxazole are the recommendations in the 2014 version used for analysis (2).

For children of two years of age or over, the 2010 guidelines notes that symptomatic treatment is recommended initially, with follow-up and re-evaluation in case of persisting symptoms for two days (4). It also recommends that children under six months of age be treated with antibiotics (4), however, the 2014 guidelines state that symptomatic treatment may be suitable, although that it is still appropriate to prescribe (4).

A.1.1.3.2 Subsequent version 16 (2019) Therapeutic Guidelines Antibiotic (3) - relative to the guidelines used in analysis - version 15 (2014) (2)

This version of the Guidelines for AOM highlight the fact that pain is not a sufficient reason to diagnose AOM *(3)*. Ensuring pain is appropriately managed is important for symptomatic treatment for most patients *(3)*. Antibiotic treatment is appropriate for children under six months of age, systematically unwell children, bilateral infection in children under two years, immunocompromised high risk children, those with otorrhea *(3)*. There are separate recommendations for Aboriginal and Torres Strait Islander children *(3)*. Delayed prescribing and shared decision making are strategies mentioned *(3)*. Otitis media with effusion is mentioned as not requiring antibiotics *(3)*. When antibiotics are indicated, amoxicillin is the first-line option and amoxicillin with clavulanate is the second-line options recommended *(3)*.

A.1.2 Urinary tract infection

A.1.2.1 Acute cystitis

A.1.2.1.1 Previous guidelines version 14 (2010) Therapeutic Guidelines Antibiotic (4) - relative to the guidelines used in analysis - version 15 (2014) (2)

This 2010 version of the guidelines states that urine cultures should be performed before antibiotics are prescribed for pregnant women, all men and all children, and all patients who have used antibiotics recently, in the event of treatment failure or infection recurrence (4). However, it does not mention susceptibility/sensitivity testing. For men, this version includes treatment duration of fourteen days (4). These guidelines for children are divided into mild and severe infection (4). Ciprofloxacin is also listed as drug of last resort for children with mild infection as well as norfloxacin. Severe infection for children in this version includes gentamicin IV plus amoxicillin/ampicillin (or cefotaxime or ceftriaxone for hypersensitivity) (4).

A.1.2.1.2 Subsequent version 16 (2019) of the Therapeutic Guidelines Antibiotic (3) - relative to the guidelines used in analysis - version 15 (2014) (2)

This 2019 version of the guidelines clearly states that culture and susceptibility testing should be performed before prescribing antibiotics for pregnant women, men, patients in aged care, as well as any patients having received antibiotics recently, with recurrent cystitis or those at risk of multidrug-resistant bacteria (3). It notes that the broad-spectrum activity of amoxicillin with clavulanate is too wide for empirical treatment (3).

It notes that symptomatic treatment is sufficient for most women under 65 years of age (3). It warns about nitrofurantoin use in men as therapeutic concentrations not reached in the prostate (3). Several additional options are provided before last resort options for adults of fosfomycin, ciprofloxacin or norfloxacin are recommended, under the proviso of resistance to all of the prior options having been confirmed by culture and susceptibility testing before use (3). This version contains more detail on diagnostic testing for children and the differentiation between this condition and acute pyelonephritis. **Table A-1** below contains purely the first three recommendations for each patient group (3).

Table A-1: Summary of Therapeutic Guideline Antibiotic recommendations in numeric order for empirical prescribing for initial presentations of acute cystitis (3).

Line/ Choice	Non-pregnant Women	Men	Children >= 1 month
1	trimethoprim	trimethoprim	trimethoprim + sulfamethoxazole
1			trimethoprim
2	nitrofurantoin	nitrofurantoin	cefalexin
3	cefalexin	cefalexin	

A.2 Prominent antibiotic prescribing quality indicators

There are multiple, existing quality indicators designed to measure antibiotic prescribing across many settings. A summary is provided below of some prominent quality indicators focussing purely on antibiotic prescribing but is by no means exhaustive. Several of these were developed and collated by expert consensus. Note these quality indicators do not typically assess whether prescribing was in fact indicated at an individual level.

A.2.1 The European Surveillance Of Antimicrobial Consumption Network

The European Surveillance Antimicrobial Consumption Network, formerly European Surveillance of Antimicrobial Consumption (ESAC), developed a series of prescribing quality indicators (5-7). They give recommended ranges of percentages for which antibiotic prescribing should ideally remain within for presentations of specific conditions. They are good rule-of-thumb by which to assess prescribing, with the objective of trying to limit quantities of antibiotics prescribed for each condition.

A.2.1.1 Quality indicators by Coenen et al. (8)

On behalf of ESAC, in 2007 Coenen *et al.* (8) published a set of quality indicators for antibiotic prescribing in the European outpatient setting. These included quantities of antibiotic consumption for specific classes of antibiotics, percentages of these over the total of all antibiotics consumed, and a ratio of broad- to narrow-spectrum antibiotics, in addition to measures of seasonal variation in antibiotic use (8). Table 1 below provides a copy of these prescribing indicators (8).

Figure A-1: Copy of European Surveillance of Antimicrobial Consumption prescribing quality indicators presented by Coenen et al. (8)

		Resistance			Patient health benefit			Cost effectiveness			Public health policy		
Label	Description	Median	N	Consensus	Median	N	Consensus	Median	N	Consensus	Median	N	Consensus
(1) J01_DID†	Consumption of antibacterials for systemic use (J01) expressed in DID‡	8	22	+	6.5	22	+	7	21	+	8	22	+
(2) J01A_DID	Consumption of tetracyclines (J01A) expressed in DID‡	6	22	+	5	22	+	5	21	+	5	22	+
(3) J01C_DID†	Consumption of penicillins (J01C) expressed in DID‡	7	22	+	6	22	+	6	21	+	7	22	+
(4) J01D_DID†	Consumption of cephalosporins (J01D) expressed in DID‡	7	22	+	6	22	+	6	21	+	6.5	22	+
(5) J01E_DID	Consumption of sulfonamides and trimethoprim (J01E) expressed in DID‡	6.5	22	+	5	22	+	6	21	+	5.5	22	+
(6) J01F_DID†	Consumption of macrolides, lincosamides and streptogramins (J01F) expressed in DID‡	7.5	22	+	6	22	+	6	21	+	7	22	+
(7) J01M_DID†	Consumption of quinolones (J01M) expressed in DID‡	8	22	+	6	22	+	7	21	+	7.5	22	+
(8) J01A_%	Consumption of tetracycline (J01A) expressed as percentage§	5.5	22	+	5	22	+	5	21	+	6	22	+
(9) J01C_%	Consumption of penicillins (J01C) expressed as percentage§	5.5	22	+	5.5	22	+	5	21	+	6.5	22	+
(10) J01D_%	Consumption of cephalosporins (J01D) expressed as percentage§	6	22	+	5.5	22	+	6	21	+	6.5	22	+
(11) J01E_%	Consumption of sulfonamides and trimethoprim (J01E) expressed as percentage§	5	22	+	5	22	+	5	21	+	6	22	+
(12) J01F_%	Consumption of macrolides, lincosamides and streptogramins (J01F) expressed as percentage§	7	22	+	6	22	+	6	21	+	6	22	+
(13) J01M_%†	Consumption of quinolones (J01M) expressed as percentage§	7	22	+	6.5	22	+	7	21	+	7	22	+
(14) J01CE_%†	Consumption of β-lactamase sensitive penicillins (J01CE) expressed as percentage§	8	22	+	7	22	+	8	21	+	8	22	+
(15) J01CR_%†	Consumption of combination of penicillins, including β-lactamase inhibitor (J01CR) expressed as percentage§	7	22	+	7	22	+	7	21	+	7	22	+
(16) J01DD+DE_%†	Consumption of third and fourth generation of cephalosporins (J01(DD+DE)) expressed as percentage§	7	22	+	7	22	+	8	21	+	7.5	22	+
(17) J01MA_%†	Consumption of fluoroquinolones (J01MA) expressed as percentage§	7	22	+	7	22	+	7	21	+	7.5	22	+
(18) J01_B/N†	Ratio of the consumption of broad (J01(CR+DC+DD+(F-FA01))) to the consumption of narrow spectrum penicillins, cephalosporins and macrolides (J01(CE+DB+FA01))	7	22	+	7	22	+	7	21	+	7	22	+
(19) J01_SV†	Seasonal variation¶ of the total antibiotic consumption (J01)	7	22	+	7	22	+	7	21	+	7.5	22	+
(20) J01M_SV†	Seasonal variation¶ of quinolone consumption (J01M)	7	21	+	7	21	+	7	20	+	7	21	+
(21) J01M_SVDID†	Seasonal variation¶ of quinolone consumption (J01M) multiplied by their use in DID‡	6.5	22	+	6	22	+	7	21	+	7	22	+
(22) J01_TT	Index of longitudinal trends of antibiotic consumption	6	21	+	6	21	+	7	20	+	7	20	+

*A scale ranging from 1 (= completely disagree) through 5 (= uncertain) to 9 (= completely agree) was used.
†Proposed indicators were judged relevant and potentially valid if the median score for relevance was not within the 1–6 interval and if there was consensus—that is, if the number of scores within the 1–3 interval was fewer than one third of the panel. (The information provided by indicators 13 (J01M_%) and 20 (J01M_SV) overlapped with that provided by indicators 17 (J01MA_%) and 21 (J01M_SVDID), respectively.)
‡Defined daily doses (DDD) per 1000 inhabitants per day.
§Percentage of the total consumption of antibacterials for systemic use (J01) in DID‡.
¶Overuse in the winter quarters (October–December and January–March) compared with the summer quarters (July–September an April–June) of a 1-year period starting in July and ending the next calendar year in June, expressed as percentage: [DDD (winter quarters)/DDD (summer quarters) −1] ×100.

A.2.1.2 Adriaenssens et al. (6)

On behalf of ESAC, Adriaenssens *et al.* (6) published a subsequent set of quality indicators for antibiotic prescribing. This included acceptable ranges/standards for measuring prescribing against. A number of indicators are condition-specific (6). The use of 'recommended' antibiotics is also measured, in addition to the use of quinolones, for specific conditions (6). A copy of these prescribing indicators is provided below in Figure A-2 (6).

No	Title	Label	Acceptable range (%)
1a.	Percentage of patients aged between 18 and 75 years with acute bronchitis/bronchiolitis (ICPC-2-R: R78) prescribed antibacterials for systemic use (ATC: J01)	(R78_J01_%)	0–30
1b.	=1a receiving the recommended antibacterials (ATC: J01CA or J01AA)	(R78_RECOM_%)	80–100
1c.	=1a receiving quinolones (ATC: J01M)	(R78_J01M_%)	0–5
2a.	Percentage of patients older than 1 year with acute upper respiratory infection (ICPC-2-R: R74) prescribed antibacterials for systemic use (ATC: J01)	(R74_J01_%)	0–20
2b.	=2a receiving the recommended antibacterials (ATC: J01CE)	(R74_RECOM_%)	80–100
2c.	=2a receiving quinolones (ATC: J01M)	(R74_J01M_%)	0–5
3a.	Percentage of female patients older than 18 years with cystitis/ other urinary infection (ICPC-2-R: U71) prescribed antibacterials for systemic use (ATC: J01)	(U71_J01_%)	80–100
3b.	=3a. receiving the recommended antibacterials (ATC: J01XE or J01EA or J01XX)	(U71_RECOM_%)	80–100
3c.	=3a receiving quinolones (ATC: J01M)	(U71_J01M_%)	0–5
4a.	Percentage of patients older than 1 year with acute tonsillitis (ICPC-2-R: R76) prescribed antibacterials for systemic use (ATC: J01)	(R76_J01_%)	0–20
4b.	=4a receiving the recommended antibacterials (ATC: J01CE)	(R76_RECOM_%)	80–100
4c.	=4a receiving quinolones (ATC: J01M)	(R76_J01M_%)	0–5
5a.	Percentage of patients older than 18 years with acute/chronic sinusitis (ICPC-2-R: R75) prescribed antibacterials for systemic use (ATC: J01)	(R75_J01_%)	0–20
5b.	=5a receiving the recommended antibacterials (ATC: J01CA or J01CE)	(R75_RECOM_%)	80–100
5c.	=5a receiving quinolones (ATC: J01M)	(R75_J01M_%)	0–5
6a.	Percentage of patients older than 2 years with acute otitis media/myringitis (ICPC-2-R: H71) prescribed antibacterials for systemic use (ATC: J01)	(H71_J01_%)	0–20
6b.	=6a receiving the recommended antibacterials (ATC: J01CA or J01CE)	(H71_RECOM_%)	80–100
6c.	=6a receiving quinolones (ATC: J01M)	(H71_J01M_%)	0–5
7a.	Percentage of patients aged between 18 and 65 years with pneumonia (ICPC-2-R: R81) prescribed antibacterials for systemic use (ATC: J01)	(R81_J01_%)	90–100
7b.	=7a receiving the recommended antibacterials (ATC: J01CA or J01AA)	(R81_RECOM_%)	80–100
7c.	=7a receiving quinolones (ATC: J01M)	(R81_J01M_%)	0–5

*Full name of the chemical subgroup according to the Anatomical Therapeutic Chemical (ATC) classification; J01AA, tetracyclines; J01CA, penicillins with extended spectrum; J01CE, beta-lactamase sensitive penicillins; J01EA, trimethoprim and derivatives; J01M, quinolone antibacterials; J01XE, nitrofuran derivatives; J01XX, other antibacterials.

Figure A-2: Copy of European Surveillance of Antimicrobial Consumption quality indicators published by Adriaenssens *et al.* (6)

A.2.2 Quality indicators by Hansen et al. (9)

In 2010, Hansen et al. (9) published an expert consensus review on quality indicators for respiratory tract infections. They evaluated the relevance of each indicator for antibiotic resistance in addition to a separate evaluation for the relevance to patient benefit (9). They included relevant diagnostic testing being performed, such as, rapid streptococcus A antigen and CRP testing being performed for relevant conditions, by which to improve the appropriateness of prescribing (9). These do not facilitate measurement on a scale but instead detail expert opinion on which indicators are the most pressing factors to consider for each condition. The ratings for relevance for patient benefit were substantially less than that for antibiotic resistance for the strong majority of indicators (9), as seen in Figure A-3 below. Hansen et al. (9) also evaluated the importance of the type of antibiotic prescribed for each condition, per Figure A-4.

Quality indicators	Relevance for antimicrobial resistance	Relevance for patient health benefit
Patients with acute sinusitis:		
Number of patients treated with antibiotics	92* (7)	35 (4)
Number of patients treated with antibiotics without a diagnostic test	38 (4)	15 (4)
Number of patients treated with antibiotics with a CRP test < 10 mg/l	73 (6)	50 (4.5)
Patients with acute otitis media (AOM):		
Number of patients treated with antibiotics	92* (7)	50 (4.5)
Number of patients < 2 years treated with antibiotics	85* (7)	69 (5.5)
Number of patients > 2 years with less than 3 days of symptoms of AOM treated with antibiotics	96* (7)	46 (6)
Number of patients with discharging ear treated with antibiotics	73 (6)	85* (6)
Patients with acute tonsillitis/pharyngitis:		
Number of patients treated with antibiotics	88* (7)	65 (5)
Number of patients treated with antibiotics without a StrepA test	62 (6)	31 (4)
Number of patients treated with antibiotics with a positive StrepA test	77* (6.5)	50 (4.5)
Number of patients treated with antibiotics with a negative StrepA test	69 (6.5)	27 (4)
Patients with acute bronchitis:		
Number of patients treated with antibiotics	96* (7)	35 (4)
Patients with pneumonia:		
Number of patients treated with antibiotics	62 (5)	58 (6)
Patients with acute exacerbation of chronic obstructive pulmonary disease:		
Number of patients treated with antibiotics	88* (6)	50 (4.5)
Number of patients not fulfilling all the Anthonisen criteria[2] treated with antibiotics	88* (7)	62 (5)
Patients with acute lower respiratory tract infections:		
Number of patients treated with antibiotics	85* (7)	50 (4.5)
Number of patients treated with antibiotics without a preceding CRP test or X-ray of thorax	31 (4)	15 (4)
Number of patients treated with antibiotics with a CRP test < 20 mg/l	81* (6.5)	42 (4)
Patients with acute respiratory tract infections:		
Number of patients treated with antibiotics	85* (7)	50 (4.5)
Number of patients with no history of penicillin allergy treated with macrolides	92* (7)	42 (4)

Notes: The values represent agreement rates[1] in% (median on a Likert scale, range 1–7). CRP test = C-reactive protein rapid test. Strep A test = rapid Streptococcus A antigen detection test. *Consensus (agreement rate ≥75%). [1]Percentage of experts who scored the dimension ≥ 5 in the second Delphi round (n = 26) on a Likert scale, range 1–7. [2]Increased dyspnoea, increasing expectorate, and increasing purulence of expectorate.

Figure A-3: Copy of Hansen et al.'s quality indicators (9)

Quality indicators	Patients with acute sinusitis	Patients with acute otitis media	Patients with acute tonsillitis/ pharyngitis	Patients with pneumonia	Patients with acute exacerbation of COPD	Patients with acute LRTI
Number of patients treated with narrow-spectrum penicillin	85* (7)	92* (7)	96* (7)	92* (7)	62 (5)	88* (7)
Number of patients treated with broad-spectrum penicillin +/– clavulanic acid	92* (7)	92* (7)	92* (7)	100* (7)	92* (6)	92* (7)
Number of patients treated with macrolides	88* (7)	85* (7)	85* (7)	88* (6)	77* (6)	88* (6.5)
Number of patients treated with cephalosporins	81* (7)	81* (7)	88* (7)	81* (6)	73 (6)	81* (7)
Number of patients treated with quinolones	81* (7)	81* (7)	65 (6)	81* (6.5)	85* (6)	81* (7)

Notes: The values represent agreement rates[1] in% (median on a Likert scale, range 0–7). COPD = chronic obstructive pulmonary disease. LRTI = lower respiratory tract infection. *Consensus (agreement rate ≥75%). [1]Percentage of experts who scored the dimension ≥ 5 in the second Delphi round (n = 26) on a Likert scale, range 1–7.

Figure A-4: Copy of quality indicators by Hansen et al (9)

A.2.3 Quality indicators by Le Maréchal et al. (10)

Le Maréchal et al. (10) performed a systematic review of quality indicators tailored for the outpatient care setting. They included administrative aspects such as provision of access to local guidelines, documentation, provision of information to patients (10). They included multiple indicators relating to parenteral/injection antibiotics in outpatients (10). As seen in Figures A-5a and A-5b, the indicators collated by Le Maréchal et al. (10) provide sensible advice, however, do not facilitate measurement of degree of compliance/quality.

Outpatient quality indicator (OQI)	Type of indicator	References	Study design[a]
OQI-1 Antibiotics should be prescribed for (most) bacterial infections (e.g. acute pneumonia, urinary tract infections)	process	26–30	A
OQI-2 Antibiotics should not be prescribed for viral infections or (most) self-limiting bacterial infections (e.g. acute bronchitis, influenza, acute otitis media in children >2 years old)	process	26,28–42	A, B, C
OQI-3 Outpatients should receive antibiotic therapy compliant with guidelines; this includes, but is not limited to, indication, choice of the antibiotic, duration, dose and timing	process	26–31,34,36,39,40, 43,44,46–51	A, B, C
OQI-4 Some antibiotics should be rarely prescribed	process	59	B
OQI-5 Acute upper respiratory infections and bronchitis should not be treated with antibiotics within the first 3 days, unless there is documented indication for treatment	process	29,30,60,61	A, C
OQI-6 Outpatients with acute tonsillitis/pharyngitis should undergo a group A streptococcal diagnostic test to decide whether or not they should receive antibiotics	process	32	C
OQI-7 Outpatients with an acute tonsillitis/pharyngitis and positive group A streptococcal diagnostic test should be treated with antibiotics	process	29,30	A
OQI-8 Antibiotics for an acute tonsillitis/pharyngitis should be withheld, discontinued or not prescribed if an outpatient presents a diagnostic test (rapid antigen test or throat culture) negative for group A streptococci	process	40	B
OQI-9 Prescribed antibiotics should be chosen from an essential list/formulary	process	47,48,50–52,62–73	C
OQI-10 Possible contraindications should be taken into account when antibiotics are prescribed	process	79,80	A, C
OQI-11 Antibiotics from the list of essential antibiotics should be available in health facilities that dispense antibiotics	structure	47,48,50,51,62,67,70,81	A, C
OQI-12 Key antibiotics should not be out of stock in health facilities that dispense antibiotics	structure	50,51	C
OQI-13 Antibiotics in stock should not be beyond the expiry date	structure	50,81	A, C
OQI-14 Antibiotics that are dispensed to outpatients should be adequately labelled (patient name, antibiotics name, when antibiotics should be taken)	structure	47,48,50,51,65,67,70,82	C
OQI-15 Antibiotics should be adequately conserved and handled in health facilities	structure	50,51	C
OQI-16 Health facilities should keep adequate records of dispensed key antibiotics	structure	50	C
OQI-17 A copy of the essential antibiotics list should be available in health facilities	structure	47,48,50,62,67,70	C
OQI-18 Standard antibiotic treatment guidelines should be available in health facilities	structure	50	C
OQI-19 Health facilities should have access to the Summary of Product Characteristics of prescribed antibiotics, written in a local language	structure	47	C
OQI-20 Antibiotics should not be sold without prescription	structure	50	C
OQI-21 Outpatients and OPAT patients with an antibiotic prescription should be educated on how to take it, on the dosage, on expected side effects, and on the natural history of the disease	process	47,48,50,51,60,62,65,67, 70,75,76,82–86	A, B, C
OQI-22 The treatment plan should be agreed between the OPAT team and the referring clinician before start of treatment	process	84,85	B
OQI-23 All OPAT treatment plans should include dose, frequency of administration and duration of therapy	process	84	B
OQI-24 OPAT antibiotics should be correctly stored, prepared, reconstituted, dispensed and administered	structure	84,86	B
OQI-25 Administered doses of OPAT should be documented on a medication card	process	84	B
OQI-26 The first dose of a new antibiotic in an OPAT should be administered in a supervised setting	process	84	B

Figure A-5a: Prescribing quality indicators presented by Le Maréchal et al. (10)

Outpatient quality indicator (OQI)	Type of indicator	References	Study design[a]
OQI-27 OPAT antibiotics should be regularly reviewed to optimize speed of intravenous-to-oral switch	process	84	B
OQI-28 Each OPAT centre should monitor quality indicators on OPAT antibiotics	structure	84,86	B
OQI-29 An expert in OPAT (physician, nurse, pharmacist) should work in each OPAT centre	structure	86	B
OQI-30 The OPAT plan should be communicated to the general practitioner at discharge	structure	85	B
OQI-31 The OPAT programme should be accredited or certified	structure	86	B
OQI-32 In an OPAT programme, clinical and/or microbiological outcomes, including treatment failure and adverse events (including *Clostridium difficile* infections), should be recorded	outcome	84,86	B

[a]Category of the study design: A, consensus-based indicators; B, review-based indicators; C, guideline-based indicators.

Figure A-5b: Prescribing quality indicators presented by Le Maréchal et al. (10)

A.2.4 The World Health Organization's Access, Watch and Reserve program, 2019

In 2017, the World Health Organization (WHO) published a list of Selection and Use of Essential Medicines, classifying medicines into categories of Access, Watch and Reserve (AWaRe) (11,12). These classifications were proved to a useful antibiotic stewardship tool (11,13). In 2019 WHO published its AWaRe classification, containing targets for at least 60% systemic antibacterials to be from their Access list (11,12). For example, the penicillin class antibiotic, amoxicillin, is on the Access list, the macrolide azithromycin is on the Watch list, and the monobactam aztreonam is on the Reserve list within the 2019 classification (11). A second AWaRe list was subsequently published in 2021 (14).

A.2.5 Quality indicators by Thilly et al. (15)

Thilly et al. (15) published a useful collection of ten quality indicators designed for general practice. It includes indicators for patients prescribed quinolones at least twice within six months, as well as indicators on seasonal variation by assessing prescribing during the winter/flu season compared to the summer/hot season as well as one for quinolone prescribing at these times of year (15). Another indicator is presented to assess prescriptions with the course duration being over eight days for a list of specific antibiotics (15). Co-prescription of antibiotics with systemic non-steroidal anti-inflammatory drugs, as well as antibiotics with systemic corticosteroids, is also a focus (15).

1 Figure A-6: Prescribing Quality Indicators Presented by Thilly et al. (15)

Proxy indicator	Numerator description	Denominator description	Target value	Target patients
PI 1 Antibiotic prescriptions against UTI in men (ratio)	Number of prescriptions of: nitrofurantoin (J01XE01) + certain (fluoro) quinolones[a] (J01MB + J01MA06 + J01MA04 + J01MA07) + fosfomycin-trometamol (J01XX01)	100 active[b] male patients ≥ 16 years old	Optimal target: 0 Acceptable target: < 0.5	Men ≥ 16 years old
PI 2 Antibiotic prescriptions against UTI in women (ratio)	Number of prescriptions of: nitrofurantoin (J01XE01) + pivmecillinam (J01CA08) + fosfomycin-trometamol (J01XX01)	Number of prescriptions of quinolones (J01M)	Target: > 1	Women ≥ 16 years old
PI 3 Repeated prescription of quinolones (%)	Number of prescriptions of quinolones (J01M) among patients having been prescribed a quinolone (J01M) in the preceding 6 months	Total number of prescriptions of quinolones (J01M)	Optimal target: 0 Acceptable target: < 10%	Men and women ≥ 16 years old
PI 4 Seasonal variation of total antibiotic prescriptions (%)	(Number of prescriptions of antibiotics (J01) during the cold-weather season (January–March and October–December) / Number of prescriptions of antibiotics (J01) during the hot-weather season (April–September) – 1) x 100		Target: < 20%	All patients
PI 5 Seasonal variation of quinolone prescriptions (%)	(Number of prescriptions of quinolones (J01M) during the cold-weather season (January–March and October–December) / Number of prescriptions of quinolones (J01M) during the hot-weather season (April–September) – 1) x 100		Optimal target: < 5% Acceptable target: < 10%	All patients
PI 6 Amoxicillin / second-line antibiotics prescriptions (ratio)	Number of prescriptions of amoxicillin (J01CA04)	Number of prescriptions of: amoxicillin-clavulanic acid (J01CR02) + quinolones (J01M) + cephalosporins (J01D) + MLSK[c] (J01F)	Target: > 1	All patients
PI 7 Prescriptions of not indicated antibiotics (%)	Number of prescriptions of: lomefloxacin (J01MA07), moxifloxacin (J01MA14), certain (fluoro) quinolones[a] (J01MB + J01MA06 + J01MA04 + J01MA07), telithromycin (J01FA15), spiramycin-metronidazole (J01RA04) and cefaclor (J01DC04)	Total number of antibiotic prescriptions	Optimal target: 0 Acceptable target: < 0.5%	All patients
PI 8 Estimated duration of antibiotic prescriptions > 8 days (%)	Number of prescriptions > 8 days for the following antibiotics: amoxicillin (J01CA04), co-amoxiclav (J01CR02), cefuroxime, cefpodoxime, roxithromycin, clarithromycin, pristinamycin and nitrofurantoin (J01FG01)	Total number of antibiotic prescriptions for these eight antibiotics (calculation of this metric is explained in detail in supplementary Table S2)	Optimal target: < 5% Acceptable target: < 10%	All patients
PI 9 Co-prescription of antibiotic and systemic non-steroidal anti-inflammatory drugs (%)	Number of antibiotic(s) (J01) + systemic NSAID(s) (M01A) co-prescribed on the same day	Total number of antibiotic prescriptions	Optimal target: 0 Acceptable target: < 5%	All patients
PI 10 Co-prescription of antibiotic and systemic corticosteroids (%)	Number of antibiotic(s) (J01) + systemic corticosteroid(s) (H02AB) co-prescribed on the same day	Total number of antibiotic prescriptions	Optimal target: 0 Acceptable target: < 5%	All patients

UTI: urinary tract infections.

[a] J01MB (rosoxacin, nalidixic acid, piromidic acid, pipemidic acid, oxolinic acid, cinoxacin, flumequine, nemonoxacin), J01MA06 (norfloxacin) + J01MA04 (enoxacin) + J01MA07 (lomefloxacin).

[b] An active patient is a patient seen at least once by the general practitioner during the year 2017.

[c] MLSK: macrolides, lincosamides, streptogramins and ketolides.

2

A.3 Overview of the literature

A.3.1 Literature considerations

Conducting a literature review was complicated by the fact that many relevant articles utilise different keywords/subject areas and indexing, making the search significantly larger if all are included. It took some time to clarify, however, it was found that many highly relevant articles were found to use vastly different keywords and indexing. Below are two examples of relevant research with their subject search terms listed below.

For example, Cadieux et al. (21) of 2007 includes the following:

- Anti-Bacterial Agents - therapeutic use ,
- Bacterial Infections - drug therapy ,
- Bacterial Infections - epidemiology ,
- Drug Utilization Review ,
- Foreign Medical Graduates - statistics & numerical data ,
- Patients - statistics & numerical data ,
- Physicians (General practice) ,
- Practice guidelines (Medicine) ,
- Practice Patterns, Physicians' - statistics & numerical data ,
- Primary Health Care - statistics & numerical data ,
- Virus Diseases - drug therapy .

However, Barlam et al. (22) from 2015 includes the following:

- Ambulatory Care - statistics & numerical data ,
- Anti-Bacterial Agents - therapeutic use ,
- Family Practice - statistics & numerical data ,
- Inappropriate Prescribing - statistics & numerical data ,
- Internal Medicine - statistics & numerical data ,
- Lung Diseases - complications ,
- Practice Patterns, Physicians' - statistics & numerical data ,
- Respiratory Tract Infections – complications.

-
- This process was also complicated by the number of ways of referring to Guideline-compliance or non-compliance, such as broad-spectrum or quinolone antibiotic prescribing use and insufficient prescription duration to indicate inappropriate prescribing.
-
- As a result of these considerations, multiple search strategies were used (described below in the next section, **Appendix A.3.2**) as well as 'snowballing'. An overview of the literature was provided instead of a traditional literature review or systematic review, which would have required too many resources and time. For example, please see an Ovid advanced search performed below in Table A-2, demonstrating the large numbers of articles resulting with the addition of relevant search terms.

Table A-2: Summary of literature search terms performed

# ▲	Searches	Results
1	(General Practice OR Pediatrics OR Community Medicine) AND Drug Therapy AND Antibiotic Agent AND Prescriptions AND Guideline Adherence {Including Related Terms}	10003
2	limit 1 to (english language and yr="2007 -Current")	5069
3	(General Practice OR Pediatrics OR Community Medicine) AND Drug Therapy AND Antibiotic Agent AND Prescriptions AND Guideline Adherence **AND Australia** {Including Related Terms}	10033
4	limit 3 to yr="2007 -Current"	5901
5	(General Practice OR Community Medicine) AND Drug Therapy AND Antibiotic Agent AND Prescriptions AND Guideline Adherence AND Australia {No Related Terms}	327
6	limit 5 to (english language and humans)	291

A.3.2 Revised literature search strategy

A revised search strategy was implemented using multiple search terms of MESH index terms and keyword searches, in Tables A-3 to Table A-7. The combination of the results of these as mentioned in Table A-7, were intended to limit the search to a more manageable number of articles. Snowballing was also used as a strategy likely to overcome some of the issues raised above. Despite these attempts to limit the blowing out of articles to review, several thousand articles were reviewed in full.

Table A-3: Medline Mesh index terms search {including related terms}

Search #	MeSH search terms {including related terms}
1	*Anti-Bacterial Agents/tu [Therapeutic Use]
2	*Primary Health Care/ OR *Ambulatory Care/ OR *Family Practice/ OR *General Practice/ OR *Physicians, Family/
3	*Practice Patterns, Physicians'/
4	1 AND 2 AND 3

Table A-4: Medline keyword search

Search #	Medline search terms
5	(antibiotic OR antimicrobial OR anti-microbial).mp
6	(associat* OR driv* OR influenc* OR relat* OR predict*).mp
7	(general practice OR GP OR general practitioner OR community care OR primary care OR family physician OR family medicine OR general internal medicine).mp
8	(poor OR over OR inappropriate* OR adher* OR congruen* OR excess*).mp
9	(prescr* AND guideline*).mp
10	5 AND 6 AND 7 AND 8 AND 9

where [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]

Table A-5: Embase Em index terms search {including related terms}

Search #	Em search terms {including related terms}
12	*antibiotic agent/dt [Drug Therapy]
13	*prescription/
14	Ambulatory care/ OR primary medical care/ OR child health care/ OR general practice/ OR primary health care/ OR General practitioner/ OR pediatrician/
15	12 AND 13 AND 14

Table A-6: Embase keyword search

Search #	Embase search terms
16	(antibiotic OR antimicrobial OR anti-microbial).mp
17	(associat* OR driv* OR influenc* OR relat* OR predict*).mp
18	(general practice OR GP OR general practitioner OR community care OR primary care OR family physician OR family medicine OR general internal medicine).mp
19	(poor OR over OR inappropriate* OR adher* OR congruen* OR excess*).mp
20	(prescr* AND guideline*).mp
21	16 AND 17 AND 18 AND 19 AND 20

where [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]

Table A-7: Combining all four search results

Search #	search terms
22	4 OR 10
23	Automatic removing of duplicates (4 OR 10)
24	15 OR 21
25	Automatic removal of duplicates in Ovid (15 OR 21)
26	Exported to EndNote (23 OR 25)

Table A-8 below also includes examples of exclusion criteria followed thereafter.

Table A-8: Examples of removal of articles not meeting criteria

Action #	Action description
27	remove duplicate references
28	non-English full text
29	non-original research: editorials, perspectives, news, anonymous
30	non-original research: (Systematic) Reviews/Meta-analyses, Study Protocols
31	(practice)guidelines, case reports, conference abstracts/papers
32	main focus of study not on investigating inappropriate/appropriate prescribing of antibiotics
33	qualitative design only
34	research not conducted within present definition of primary care, and investigating general population not specific disease groups
35	interventions/Before&After studies/ Evaluations Guidelines or intervention effectiveness
36	no identification/differentation of inappropriate from appropriate prescribing
37	rates of prescribing only measure used to define/differentiate appropriate from inappropraite prescribing
38	hypothetical Case Vignettes, Questionnaires/Surveys where no recording of real patient consultations & prescribing
39	methods do not include investigation of relationship between patient-, prescriber-, practice-, or consultation-factors and inappropriate/appropriate prescribing
40	statistical methods do not involve multivariable investigation of relationships between patient-, prescriber-, practice-, or consultation-factors and inappropriate/appropriate prescribing
41	Addition of relevant studies identified by snowballing

APPENDIX B – APPENDICES TO THE METHODS CHAPTER

B.1 Summary of the data received

The five-and-a-half years of longitudinal data was received in SAS database datasets. MedicineInsight data was partially cleaned at the time of receipt. These were all predominantly character string files apart from the comorbid conditions file. This administrative data uses real zeros rather than censoring.

Table B-1: Summary of digital files received

File	Rows	Variables	Unique Providers	Unique Patients
Patient	791280	32	n/a	791280
Practice	52	13	n/a	n/a
Provider	11976		7893	n/a
Diagnosis	1,557,387	11	2388	658577
Prescription	12,941,223	29	26,230	614,843
Patient Comorbid Conditions	764,751	35	n/a	764751
Patient Allergy	168,931	7	1351	119614
Encounter	19,481,775	8	5586	791280
Service	9,908,909	8	954	667649
Atomic Pathology	40,121,296	13	n/a	363703
Prescription History	5668253	32	1277	617188
Observation	8538890	10	2019	492454
Non-Atomic Pathology	6837651	6	1608	445069

To improve data quality, further cleaning included checking variables for incorrect, impossible and missing entries, to standardise units of measurement, and group diagnoses. Programs were written in STATA Release 16 (16) to allow for semi-automated corrections to these data, including allocation of a missing category where appropriate (17,18). Data preparation included the creation of new variables from, and transformation of, existing variables to facilitate intended analyses.

B.2 Diagnoses

The initial diagnoses file received included 1,557,387 rows, with 275,880 different diagnoses entered. Removing impossible/erroneous dates and missing/blank diagnoses resulted in 1,489,540 rows. Diagnoses were initially explored to see what GPs were entering in the free text diagnosis field, and to collate relevant key words to use in search terms for conditions of interest. Datasets of diagnosis information for

relevant conditions were then created by searching for relevant diagnoses of interest using character string functions. This process was profoundly time-consuming.

This process varied in complexity depending upon the specific condition and the types of diagnoses commonly entered by GPs in this dataset. The number of symptoms entered as clinical diagnoses was surprising, e.g. sniffles. This was particularly the case for URTI, most notably acute rhinosinusitis. The process of refining the search terms for each condition of interest took a substantial amount of time.

While higher-line antibiotics may be appropriate to prescribe at a subsequent consultation when lower-line options have already been tried, to accurately evaluate the prescribing occurring at initial consultations, non-initial consultations need to be excluded. Similarly, it may potentially be appropriate to prescribe an antibiotic for an ongoing infection at a subsequent consultation when prescribing did not occur initially. Both points highlight the need to separate initial from non-initial consultations, to accurately examine the prescribing behaviour occurring at either. Therefore, in order to limit URTI and UTI diagnoses to initial presentations for the episode of infection (19), any diagnoses with coding suggesting non-initial or follow-up consultations, or chronic, recurrent and/or resistant infections were excluded (20), as well as removing diagnoses occurring within fourteen days of a previous consultation for the same condition group for the same patient. This time period was chosen for both URTI and UTI, as the longest typical treatment duration is up to fourteen days for UTI (2). The removal of diagnoses containing pathology and/or species-specific information followed, as these would not have been available at an initial consultation, for example, “E.coli UTI” and are therefore unlikely to represent initial consultations. Note all diagnoses used for analysis were restricted to initial presentations for the relevant condition.

Each diagnostic condition dataset were then merged with additional patient information and practice information info by matching the date, patientid, providerid and practiceid in each file.

B.2.1 Upper respiratory tract infection

Search terms for AOM focused on otitis media and diagnoses of ear infection and symptoms like serous, effusion, discharge, purulent, suppurative, and mucous. Diagnoses such as otitis externa and chronic suppurative otitis media were excluded from AOM (2). The quantity of symptoms entered as clinical diagnoses for URTI was surprisingly high, for example, “sniffles”, notably for acute rhinosinusitis.

The reason for prescribing field was string-searched to remove any diagnoses for which the reason recorded was unrelated to the above diagnoses.

B.2.1.1 Pharyngitis / tonsillitis

Search terms for pharyngitis / tonsillitis included the following diagnoses, in addition to variations on these:

- PHARYNGITIS
- PHARINGITIS
- TONSILLITIS
- TONSILITIS
- TONSILLI
- TONSILLAR
- TONASILLITIS
- TONCILITIS
- TONSILS
- SORE THROAT
- SORE THOAT DAYS

B.2.1.2 Acute otitis media

AOM is difficult to distinguish clinically from other types of otitis media, which have different guidelines. Due to this fact, it was sometimes unclear whether one should classify a diagnosis as strictly AOM or more likely relating to other types of OM and therefore excluded. Persistent Otitis Media with Effusion (OME), also known as ‘glue ear’, was most difficult to distinguish from AOM, as it is essentially a chronic version of AOM lasting three months or more, and a natural progression. Ear pain and redness of the tympanic membrane are indicative of AOM, effusion commonly occurs in both AOM

and CSOM. Based on expert GP and ENT advice, terms more likely to describe other types of OM were also removed, including ‘otitis media effusion’, ‘mucus’, ‘mucous’, and ‘purulent’ OM. However, ‘middle ear effusion’ was considered AOM if it occurred without any mention of OM in the diagnosis, and without any suggestion of it being chronic in nature.

Diagnoses including any reference to chronic, resistant, complicated, persistent infection were excluded. Chronic suppurative otitis media (CSOM) is a condition which can result in more serious physiological changes. While perforation of the tympanic membrane can also occur in AOM, diagnoses detailing ‘perforation’ were removed as they are more likely to indicate CSOM, as were instances of ‘suppurative’ and ‘adhesive’. Bullous OM were also excluded, as were any diagnoses relating to otitis externa (OE), commonly known as ‘swimmer’s ear’. Search terms included the following diagnoses, in addition to variations:

- AOM
- ACUTE OTITIS MEDIA
- OTITIS MEDIA
- MIDDLE EAR EFFUSION

The following diagnoses were excluded:

- PERSISTENT OTITIS MEDIA WITH EFFUSION
- GLUE EAR
- OTITIS MEDIA EFFUSION
- OM MUCUS
- OM MUCOUS
- PURULENT OM
- CSOM
- CHRONIC SUPPURATIVE OTITIS MEDIA
- PERFORATION
- SUPPURATIVE
- ADHESIVE
- BULLOUS OM
- OTITIS EXTERNA

- OE
- SWIMMERS' EAR

B.2.1.3 Influenza / influenza-like illness

Search terms for influenza / influenza-like illness included the following diagnoses:

- FLU
- FLU-LIKE ILLNESS
- FLU LIKE ILLNESS
- FLI
- INFLUENZA
- INFLUENZA-LIKE ILLNESS
- INFLUENZA LIKE ILLNESS
- ILI

B.2.1.4 Acute rhinosinusitis

Search terms included the following diagnoses, in addition to variations:

- URTI
- UPPER RESP TRACT INFECTION
- URT
- INFECTION;UPPER RESP TRACT
- VIRAL UPPER RESPIRATORY TRACT INFECTION
- VIRAL URTI
- INFECTIONUPPER RESP TRACT
- VIRAL UPPER RESP TRACT INFECTION
- V URTI
- UPPER RESPIRATORY TRACT INFECTION VIRUS
- PRODROMAL OF COMMON COLD
- PRODROMAL OF VIRAL RESP INFECTION
- PRODROMAL OF VIRAL URTI
- PRODROMAL VIRAL INFECTION
- PRODROMAL VIRAL URTI
- LIKELY VIRAL URTI
- COLD

- COMMON COLD
- RHINOSINUSITIS
- RHINO SINUSITIS
- RHINOISINUSITIS
- RHINORSINUSITIS
- RHINOSINISUTUS
- RHINOSINOSITIS
- RHINOSINUSIITIS
- RHINOSINUSITISVIRAL
- RHINOSINUSITS
- RHINOSINUTISITS
- RHINSOSINUSITIS

B.2.1.5 Exclusions

A large number of diagnoses picked up by the search terms but irrelevant, such as “URTICARIA”, required removal. Conditions with separate prescribing guidelines, or indicative of surgery were also excluded. Examples of diagnoses excluded are listed below:

- LOWER RESPIRATORY TRACT INFECTION
- LRTI
- RESPIRATORY TRACT INFECTION..LOWER
- PNEUMONIA
- BRONCHITIS
- BRONCIOLITIS
- CHEST INFECTION
- CHEST INF
- ASTHMA
- ALLERGIC RHINITIS
- PERENNIAL RHINITIS
- CROUP
- URTICARIA
- STOMACH FLU
- COLD SORE

- COLD AGGLUTINATION
- COLD AGGLUNTININS
- HOT & COLD
- COLD POLYP
- FLU AT <AGE>
- ILIAC
- POST SURGICAL
- TONSILS AGE <AGE>
- TONSILS AND ADENOIDS
- TONSILS GROMETS
- TONSILS REMOVED
- TONSILS, ADENOIDS
- TONSILS,GROMETS
- TONSILLAR ABSCESS

Any uncertain URTI diagnoses were removed by following strings relating to a relevant search term above were removed. (Where there was no uncertainty regarding URTI diagnosis but another concurrent diagnosis within the diagnosis string, these were included. For example, “UPPER RESPIRATORY TRACT INFECTION, DEPRESSION, ?UTI” was kept. Diagnoses including the following terms were excluded:

- QUERY
- ?
- PROBABLE
- POSSIBLE
- POSS
- PROB

Diagnoses of situations which requiring immediate action, i.e. hospital admission, were removed, as these are not suitable for treatment in the community and therefore outside the scope of the research question. For example, “URTI/FEBRILE CONVULSIONS” was removed. Diagnoses including the following terms were excluded:

- SEPTICAEMIA
- SEPTIC

- SEPSIS
- CONVULSIONS
- TO ED
- ADMIT
- ADMITTED
- ADMISSION
- ICU
- HOSPITAL

Diagnoses of certain viruses or bacteria which can only be confirmed by the lab were also removed, as these do not represent the initial consultation but either subsequent consults when laboratory results were available or the doctor upon receipt of laboratory results. Diagnoses with the following terms were excluded:

- INFLUENZA A
- INFLUENZA B
- ADENOVIRUS
- RSV
- H1N1
- SWINE FLU
- PSEUDOMONAS
- <PATHOGEN> CARRIER

Diagnoses detailing immunisations and / or vaccinations, especially influenza, were common, and were excluded using the following search terms:

- IMMUNISATION
- IMMUNIZATION
- VACCINATION
- VACCINE
- VACC
- VAX
- SHOT
- JAB
- NEEDLE

- BOOSTER
- BOOSTRIX
- INJECTION
- INJ

For URTI diagnoses, any diagnoses indicative of non-initial consultations, such as review consultations or chronic, resistant infections were removed, as follows:

- RECURRENT
- COMPLICATED
- PROLONGED
- RECENT
- FOLLOW-UP
- FOLLOW UP
- FOLLOWUP
- FUP
- F/U
- F/UP
- F UP
- FF UP
- CHRONIC
- RESISTENT
- RESISTANT
- REVIEW
- RV
- R/V
- R/O
- RX
- RECURRING
- ONGOING
- RECHECK
- CHECK UP
- PERSIST
- IMPROVED

- IMPROVING
- RESOLVING
- RESOLVED
- BETTER NOW

B.2.2 Urinary tract infection

B.2.2.1 Acute cystitis

In order to explore prescribing practices for patients presenting with initial episodes of care for uncomplicated UTI, patients were filtered by consultations considered relevant to acute cystitis in the Guidelines. This involved developing algorithms to search through character strings of consultations relating to acute cystitis.

Initial search terms were collated from the description of the condition within the Guidelines. Final search terms included the following diagnoses plus variations on these:

- UTI
- URINARY TRACT INFECTION
- ACUTE CYSTITIS
- CYSTITIS

B.2.2.2 Exclusions

Removal of any diagnoses of prostatitis or pyelonephritis, relevant to different but related conditions for which there are separate guidelines, then followed.

Diagnoses suggestive of chronic or complicated UTI or non-initial consultation were then removed. This included removal of diagnoses with any mention of UTI which was chronic, complicated, resistant, catheter-related, post-surgical, resolved infections, or review consults. This also applied to issuing scripts as prophylaxis in chronic cases. Diagnoses meeting the criteria for UTI diagnosis in addition with the strings including but not limited to the following were excluded:

- COMPLICATED
- COMPLICARTED
- CHRONIC

- MULTIPLE
- BACK UP SCRIPT
- BREAKTHROUGH
- FREQUENT UTI
- RECURANTLY
- CHANGE ABS
- CHECK
- FOLLOW
- RESULT
- RESOLVED
- PESISTANT
- SEVERAL
- RETURNING
- RECURRENCE
- RESIDUAL
- RESISTANCE
- RESISTENCE
- RESISTENT
- RESISTENT TO TRIMETHOPRIM
- REVIEW
- R/O
- RV
- R/V
- RX
- PREV
- PRIOR
- RECENT
- REC
- REPEAT
- PRONE
- PAST
- PERSISTANT
- PERSISTENT

- PERSISTING
- PHONE
- PHX
- PROPHYLAXIS
- PROPYLAXIS
- 2nd EPISODE
- UTI x 3

For UTI diagnoses, diagnoses entered regarding specific pathogenic species, such as “E. coli UTI” were also excluded from the analysis, as these diagnoses can only be made in light of pathology results and are therefore likely to represent subsequent consultations or the input of test results. Diagnoses including the following strings were excluded:

- E.COLI
- E COLI
- E. COLI
- ECOLI
- PROTEUS
- KLEBSIELLA
- KLEB
- PSEUDOMONAS
- ENTEROCOCCUS
- CITEROBACTER
- ACINETOBACTER
- CONFIRMED ON URINE MC
- STAPHYLOCOCCAL
- RESULTS

Diagnoses including a high degree of uncertainty about the diagnosis were also removed, e.g. POSS, QUERY, ?UTI. Diagnoses including mention of immediate hospital admission were also excluded, as these are not representative of uncomplicated UTI for which prescribing can be assessed. For example, when the GP cuts a consult short and sends a patient straight to the emergency department,

antibiotics may well be warranted however they will unlikely be prescribed by the GP. As such, these situations are not considered suitable for the research question at hand. Diagnoses containing UTI in addition to the following strings were excluded:

- TO ED
- ADMISSION
- ADMIT
- ADMITTED
- DELERIUM
- HOSPITAL
- SEPTICAEMIA
- SEPSIS
- INPATIENT

Duplicates of identical diagnosis, with matching date, patient id, provider id and practice id variables were also removed.

B.3 Antibiotic prescriptions

B.3.1 Antibiotic active ingredients

The prescription dataset was filtered/subset to contain only systemic antibiotics. This included searching for both active ingredients and brand names, as well as antibiotic class. The reason for including all three was to cover cases of coding errors in which class variable field may have been entered where ingredient is intended. The search was performed on the string variable entries for medicine name in the prescribing dataset received. A full list of search terms is follows, noting that many were searched with a 'string starting with (search term)' function. For example, any string starting with "Tobra" was a line of code implemented.

Search terms included:

- Aminoglycoside
- Amikacin
- Gentamicin
- Tobramycin
- Tobramycin PF

- Tobra-Day
- TOBI
- Carbapenem
- Ertapenem
- Invanz
- Imipenem
- Primaxin
- Meropenem
- Cephalosporin
- Cefaclor
- Ceclor CD
- Karlor CD
- Keflor CD
- Ozcef
- Aclor
- Ceclor
- Keflor
- Cefalexin
- Cephalex
- Cephalexin
- Cilex
- Ialex
- Ibilex
- Keflex
- Rancef
- Cefalotin
- Cephalothin
- Cefazolin
- Cefepime
- Cefotaxime
- Cefoxitin
- Ceftaroline
- Zinforo

- Ceftazidime
- Fortum
- Ceftolozane with tazobactam
- Zerbaxa
- Ceftriaxone
- Cefuroxime
- Zinnat
- Glycopeptide
- Teicoplanin
- Targocid
- Vancomycin
- Vancocin
- Vancocin CP
- Vycin
- Lincosamide
- Clindamycin
- Cleocin
- Clindamyk
- Dalacin C
- Dalacin C Phosphate
- Lincomycin
- Lincocin
- Macrolide
- Azithromycin
- Zithromax
- Zedd
- Azith
- Clarithromycin
- Clarac
- Clarithro
- Kalixocin
- Klacid
- Erythromycin

- EES
- Erythromycin Ethylsuccinate
- Eryc
- E-Mycin
- Erythrocin IV
- Roxithromycin
- Rulide D
- Biaxsig
- Roxar
- Roximycin
- Rulide
- Penicillin
- Amoxicillin
- Yomax
- Alphamox
- Amoxil Forte
- Cilamox
- Ranmoxy
- Maxamox
- Amoxil
- Ibiamox
- Fisamox
- Amoxicillin with clavulanic acid
- Augmentin Duo
- Moxiclav Duo
- AlphaClav Duo
- Curam Duo
- Moxiclav Duo Forte
- AlphaClav Duo Forte
- Augmentin Duo Forte
- Clavam
- Curam Duo Forte
- Augmentin

- Curam
- Amoxiclav
- Co-amoxiclav
- coamoxiclav
- Ampicillin
- Austrapen
- Ibimicyn
- Ampicyn
- Benzathine benzylpenicillin
- Bicillin
- Bicillin L-A
- Benzylpenicillin
- BenPen
- Dicloxacillin
- Distaph
- Flucloxacillin
- Flopen
- Staphylex
- Flucil
- Flubiclox
- Phenoxymethylpenicillin
- Aspecillin VK
- Cilicaine VK
- LPV
- Cilicaine V
- Abbocillin V
- Phenoxymethylpenicillin
- Piperacillin with tazobactam
- Pipercaillin
- Tazopip
- PiperTaz
- Tazocin EF
- Tazopip

- Piptaz
- Procaine benzylpenicillin
- Procaine penicillin
- Cilicaine
- Quinolone
- Ciprofloxacin
- Ciprol
- C-Flox
- Ciproxin
- Cifran
- Loxip
- Ciproxin IV
- Ciprofloxacin
- Moxifloxacin
- Avelox
- Norfloxacin
- Nufloxib
- Roxin
- Tetracycline
- Doxycycline
- Doxylin
- Frakas
- Doxsig
- Doryx
- Minocycline
- Akamin
- Minomycin
- Tetracycline
- Other antibacterial
- Aztreonam
- Monobactam
- Azactam
- Colistin

- Colistin
- Colistimethate sodium
- Tadim
- Daptomycin
- Cubicin
- Fidaxomicin
- Dificid
- Linezolid
- Oxazolidinone
- Linevox
- Zyvox
- Methenamine hippurate
- Hexamine hippurate
- Hiprex
- Nitrofurantoin
- Macrodantin
- Sodium fusidate
- Fucidin
- Sulfadiazine
- Sulfonamide
- Tigecycline
- Glycylcycline
- Tygacil
- Trimethoprim
- Alprim
- Triprim
- Trimethoprim with sulfamethoxazole
- Sulfamethoxazole and trimethoprim
- Co-trimoxazole
- Cotrimoxazole
- Bactrim
- Resprim
- Bactrim DS

- Resprim Forte
- Septrin Forte
- Septrin

By active ingredient, the resulting list was as follows:

Table B-2: List of final medicine active ingredients

Active Ingredient
AMOXICILLIN
AMOXICILLIN WITH CLAVULANIC ACID
AMPICILLIN
AZITHROMYCIN
BENZATHINE BENZYLPENICILLIN
CEFACLOR
CEFALEXIN
CEFTRIAXONE
CEFUROXIME
CIPROFLOXACIN
CLARITHROMYCIN
CLINDAMYCIN
DICLOXACILLIN
DOXYCYCLINE
ERYTHROMYCIN
FLUCLOXACILLIN
GENTAMICIN
MINOCYCLINE
NITROFURANTOIN
NORFLOXACIN
PHENOXYMETHYLPENICILLIN
PROCAINE BENZYLPENICILLIN (PROCAINE PENICILLIN)
ROXITHROMYCIN
TOBRAMYCIN
TRIMETHOPRIM
TRIMETHOPRIM WITH SULFAMETHOXAZOLE

Topical preparations of antibiotics were picked up in the search and then deleted from the file, such as drops, ointments and gel preparations of the above, as well as ingredients including but not limited to SILVER SULFADIAZINE, CHLORHEXIDINE GLUCONATE, BENZOYL PEROXIDE.

B.3.2 Antibiotic class

Another variable for antibiotic class was then created, sorting active ingredients into the following classes:

Table B-3: List of antibiotic classes

- AMINOGLYCOSIDES
- CARBAPENEMS
- CEPHALOSPORINS
- GLYCOPEPTIDES
- LINCOSAMIDES
- MACROLIDES
- PENICILLINS
- QUINOLONES
- TETRACYCLINES
- OTHER ANTIBACTERIALS

The prescription dataset was then merged with each condition file by matching on the date, patient id, provider id and practice id variables. Where more than one prescription for a different antibiotic was prescribed to the same patient by the same provider at the same practice on the same date, this patient and date was flagged and later rechecked to select the most appropriate antibiotic was selected for analysis once pathology data had been incorporated.

Essentially when relying on matching one diagnosis with one prescription for analysis, one must be assumed to be the intended prescription, although it must be noted that there were situations where there were more than one diagnosis made for the same patient at an encounter and more than one systemic antibiotic prescribed at that encounter. Assumptions had to be made regarding which was intended for what

diagnosis, however, the most appropriate choice was selected according to the guidelines to give the benefit of the doubt.

In order to decrease the introduction of bias, flags were created for consultations when multiple scripts for systemic antibiotics were written for same patient on same date by the same provider at the same practice. Flags for instances when more than one of the same active ingredient were then removed, leaving only occasions when different systemic antibiotics were prescribed at the same consultation. Pathology results were the incorporated, which in some cases indicate the most appropriate choice of antibiotic, for example, in the presence of a positive culture which is susceptible to the chosen antibiotic whereas the first-line choice in the guidelines would have been ineffective. In this manner, after taking into account the pathology results, the most appropriate antibiotic was then selected for analysis, making the assumption that the most appropriate was the intended antibiotic to treat the diagnosis of interest, thereby giving providers the benefit of the doubt.

B.3.3 Whether antibiotic was prescribed

A binary discrete variable was created to indicate whether or not the patient received a prescription for a systemic antibiotic following the consultation. This was performed following the matching of the systemic antibiotic prescription file with the relevant condition of interest file, and matching on all four variables: patient id, practice id, provider id and date.

B.3.4 Whether repeats were issued on the antibiotic prescription status

A repeat prescription is a numerical field, typically 0 to 5, on a pharmaceutical prescription, which is entered by the GP at the time of prescribing. This allows the patient to fill said additional numbers of the same prescription. While prescriptions should not be issued without an indication, repeats on prescriptions should also not be issued without good reason. Unfortunately, many patient management systems in Australia automatically generate one repeat on prescriptions which takes practitioners time to amend to zero, repeats are often believed to be issued without good reason. An

acceptable reason for issuing repeats on prescriptions is patient inability to access care for a period during which a prescription may be required.

Whether or not a GP issues any repeats on a prescription is feasibly considered to be a potential indicator of better or worse prescribing behaviour. A binary discrete variable was created for whether the antibiotic prescription issued was done so with or without any repeats.

B.4 Patient variables

B.4.1 Patient age groups

A continuous age variable was received in the patient dataset, in addition to five-year and ten-year age groups. Two, new ordinal categorical variables were created for patient age for URTI and UTI based on the distribution for each dataset. For stability, the base category was created for a relatively large proportion of patients compared to other age groups. Patients were thereby splitting by age group to create a stable base for analysis. Patient age was missing for n=632 of all individual patients in the dataset and n=10 observations for initial episodes of care for URTI but n=0 observations for UTI. A category for missing age was created for URTI for descriptive analyses but these observations were excluded from multivariable analyses.

For URTI, with children having the highest incidence, the base reference category was eventually selected as 0-8 years, as follows:

1. 0-8 years
2. 9-21 years
3. 22-34 years
4. >=35 years
5. Missing.

For UTI, however, incidence was highest as expected in adult women. Therefore, patient age groups were selected in decreasing age for the categorical patient age variable for UTI, as follows:

1. >= 45 years

2. 16-44 years
3. 6-15 years
4. 0-5 years

For UTI, ‘adults’ were defined to be sixteen years and over. It was considered relevant that, particularly in light of female anatomy, sexual activity is relevant to UTI and it was therefore considered relevant to include sixteen years and over rather than eighteen years and over, which is the usual definition.

B.4.2 Patient gender

For UTI, as the strong majority of patients were women. For stability, female gender was selected as the base/reference category in the assignment of binary patient gender. The same patient gender variable was used for URTI.

B.4.3 Patient allergy labels

Allergies to antibiotics was considered highly relevant to which antibiotic a patient receives, particularly in the context of penicillins, which are most relevant to the antibiotics recommended for URTIs. A higher-line antibiotic may be appropriate to prescribe for a patient who is allergic to the first-line option. This was taken into account during analysis. Allergy information contained in character strings was searched through for different penicillin-class antibiotics including brand names This was used to create binary discrete indicator of whether the patient ever had a history of penicillin sensitivity, and otherwise negative if missing.

B.4.4 Acute rheumatic fever

Acute rheumatic fever is a serious side effect from Group A streptococcus infection, and is a possible complication of acute pharyngitis, and the main justification for any antibiotic prescription to a patient presenting with pharyngitis, should the patient have risk factors predisposing them to Group A streptococcus. Prescribing of an antibiotic for pharyngitis is also perfectly justified for patients with acute rheumatic fever, a history of rheumatic heart disease, or current scarlet fever. As such, it was considered useful to

know which patients had these conditions. A binary discrete variable was there created as an indicator of this by string searching the relevant diagnoses.

B.4.5 Primary health network

A categorical variable was created for which PHN the patient's registered/provided address fell within. These were coded into a discrete categorical variable with five levels, as follows:

- Perth North PHN
- Perth South PHN
- Country WA PHN
- Any Interstate PHN
- Missing

B.4.6 Patient indigenous status

There were concerns regarding the binary variable for self-identification of Aboriginal and Torres Strait Islander peoples, for which a substantial proportion of patients were missing/unknown status. The variable was poorly recorded, and this is known to be a common occurrence (21,22). In this situation, positive status recorded in only 0.01% of patients and information missing in 45% of all patients. This variable was not used in the analysis.

B.4.7 Patient smoking status

There were also concerns regarding the smoking status (categorical) variables, for which a substantial proportion of patients were missing/unknown status. This variable was not used in the analysis.

B.4.8 Patient socio-economic disadvantage

Ordinal categorical data were created from SEIFA IRSAD Disadvantage deciles, recoded into quintiles with the base/reference category being most disadvantaged, which has higher numbers than least disadvantaged.

SEIFA IRSD Deciles for Disadvantage received were recoded into quintiles, to ensure that there were no problems encountered with numbers too small to use for modelling purposes in some categories. Additionally, the reference/base quintile was amended to the least disadvantaged category, with occurs more frequently, i.e. larger numbers and therefore more stable for analysis than the alternative of using most disadvantaged which is typically rare corresponding to small numbers.

- quintile 1 is the least disadvantaged (reference/base)
- quintile 5 is the most disadvantaged

Also look at your category patient rurality - again make sure that capital city (or whatever the metropolitan category is) is the baseline - not very remote.

A binary, discrete variable was then created as an indicator of disadvantage, including the top two most disadvantaged quintiles (i.e. top 40% most disadvantaged) as positive for practice disadvantage indicator.

Although provided with patient SEIFA and practice SEIFA and rurality for both, patient SEIFA and practice rurality, were utilised instead of patient residential address-based variables. The reason for this was that there are so few practice variables available.

B.4.9 Patient rurality

Ordinal categorical data were created from ARIA by postcode deciles, recoded into quintiles with the base/reference category being most remote, which has higher numbers than least remote. ARIA Deciles received were recoded into quintiles, to ensure that there were no problems encountered with numbers too small to use for modelling purposes in some categories. Additionally, the reference/base quintile was amended to the least disadvantaged category, with occurs more frequently, i.e. larger

numbers and therefore more stable for analysis than the alternative of using most disadvantaged which is typically rare corresponding to small numbers.

- quintile 1 is the least remote (reference/base)
- quintile 5 is the most remote

A binary, discrete variable was then created as an indicator of remoteness, including the top two most remote quintiles (i.e. top 40% most remote) as positive for practice disadvantage indicator.

Although provided with patient SEIFA and practice SEIFA and rurality for both, patient SEIFA and practice rurality, were utilised instead of patient residential address based variables. The reason for this was that there are so few practice variables available.

B.4.10 Cardiovascular disease

A binary, dichotomous variable was created to include patients with MedicineInsight-provided flags for patients with any history of cardiovascular disease, including coronary heart disease (see below), peripheral vascular disease, carotid stenosis, renal artery stenosis, heart failure, various cardiovascular disease procedures (see below), as well as any coronary heart disease related activity, such as a heart disease-related care plan, review, script or rehabilitation.

Coronary heart disease included:

- ACUTE MYOCARDIAL INFARCTION
- AMI
- AMI (ACUTE MYOCARDIAL INFARCTION)
- ANGINA
- ANGINA PECTORIS
- ANGINA PECTORIS – PRINZMETAL
- ANGINA PECTORIS – UNSTABLE
- ANTERIOR MYOCARDIAL INFARCT
- ANTEROLATERAL MYOCARDIAL INFARCT
- ATHEROSCLEROTIC HEART DISEASE

- BLOCKAGE CORONARY ARTERY
- CORONARY ARTERY DISEASE
- CORONARY ARTERY DISEASE
- CORONARY ARTERY SPASM
- CORONARY HEART DISEASE
- CORONARY INSUFFICIENCY
- CORONARY OCCLUSION
- HEART ATTACK
- IHD
- IHD (ISCHAEMIC HEART DISEASE)
- INFERIOR MYOCARDIAL INFARCTION
- ISCHAEMIC HEART DISEASE
- MI
- MYOCARDIAL DAMAGE
- MYOCARDIAL INFARCTION
- MYOCARDIAL INFARCTION – ANTERIOR
- MYOCARDIAL INFARCTION – ANTEROLATERAL
- MYOCARDIAL INFARCTION – INFERIOR
- MYOCARDIAL INFARCTION – POSTERIOR
- MYOCARDIAL INFARCTION – SUBENDOCARDIAL
- MYOCARDIAL INFARCTION – SUPERIOR
- MYOCARDIAL INFARCTION – SUPERIOR
- MYOCARDIAL INFARCTION - WITH ST ELEVATION
- MYOCARDIAL INFARCTION - WITHOUT ST ELEVATION
- MYOCARDIAL INFARCTION, ANTERIOR
- MYOCARDIAL INFARCTION, ANTEROLATERAL
- MYOCARDIAL INFARCTION, INFERIOR
- MYOCARDIAL INFARCTION, POSTERIOR
- MYOCARDIAL INFARCTION, SUBENDOCARDIAL
- MYOCARDIAL INFARCTION, SUPERIOR
- MYOCARDIAL INSUFFICIENCY
- OCCLUSION - CORONARY ARTERY
- OCCLUSION, CORONARY ARTERY

- POSTERIOR MYOCARDIAL INFARCT
- PREINFARCTION SYNDROME
- PRINZMETAL ANGINA
- STEMI (ST-ELEVATION MYOCARDIAL INFARCTION)
- SUBENDOCARDIAL INFARCT
- SUBENDOCARDIAL MYOCARDIAL INFARCT
- SUPERIOR MYOCARDIAL INFARCT
- UNSTABLE ANGINA
- UNSTABLE ANGINA - HIGH RISK
- UNSTABLE ANGINA - LOW RISK
- UNSTABLE ANGINA - MODERATE RISK
- VARIANT ANGINA

Specific cardiovascular disease procedure terms including:

- Angioplasty - coronary
- Coronary artery surgery
- Arterial stent - Coronary artery, not drug-eluting
- Coronary artery endarterectomy
- Arterial stent - Coronary artery, drug-eluting
- Angioplasty - coronary (with stent)
- Bypass - coronary
- CABG
- Coronary angioplasty, bare metal stent
- Coronary artery endarterectomy
- Coronary angioplasty, drug eluting stent
- Coronary angioplasty with stent
- Angioplasty, coronary

B.4.11 Mental health condition

Flags for patients with mental health conditions, as well as drug and alcohol addiction were combined into a single, if any, binary, dichotomous variable. Mental health conditions included bipolar affective disorder, anxiety, depression, schizophrenia.

B.5 Consultation-related variables

B.5.1 Patients with multiple, independent episodes of urinary tract infection

A binary discrete variable was created for whether the individual patient appeared with more than one episode of UTI in the dataset, as multiple episodes of infection in a single patient may feasibly predispose a treating GP to prescribing a non-first-line antibiotic (ref). A count variable was also created for the number of UTI episodes a patient presented with during the study period.

There were 25,334 initial episodes of care for uncomplicated UTI, corresponding to 23,173 individual patients seen by 958 different providers during the period. The number of initial episodes ranged from one and fourteen, with 84% having only one consultation, 7% two, 7% three, 1% four, and <1% in excess of four consultations.

Of the 16% of patients with multiple consultations, for the strong majority, there were similar proportions of antibiotic choices prescribed regardless of number of UTI consults patients had. Prescribing rates were also similar in this context. For all patients, the mean line of choice prescribed was between 1.88 to 1.92 for patients with 1 to 4 consults, representing 99% of consults.

As there appeared to be no remarkable differences in choice of antibiotic prescribing (and also whether an antibiotic prescribed in the first place) based on the specific number of UTI consultations, for the strong majority of episodes, the decision was made to create a binary discrete indicator of patients with more than one initial episode of care for UTI in the period of interest.

B.5.2 Temperature-related variables

Observation variables within the observation dataset appeared manually entered by GPs as free text, resulting in many different types of measurements being entered.

B.5.2.1 Whether temperature testing occurred

A binary discrete variable was also created for whether or not a temperature reading was recorded during the consultation. This therefore included any reasonable/non-erroneous temperature recording.

B.5.2.2 Fever indicator

Temperature readings to indicate fever and higher likelihood of bacterial infection wherein antibiotics are more likely to be warranted. A binary discrete variable was created for fever with temperature readings of at least 37.5 degrees Celsius. This was used in situations where the classification of likely/unlikely prescribing relied in part upon fever being recorded. Please note rhinosinusitis used high fever (see below).

B.5.2.3 High fever indicator

However, the guidelines indicate 39 degrees Celsius is suggestive of more serious acute rhinosinusitis, so a further binary discrete variable was coded to allow for this. This variable was used in classifying likely necessary from likely unnecessary antibiotic prescribing for rhinosinusitis.

B.5.3 Urine dipsticks for urinary tract infection testing

Observation variables within the observation dataset appeared manually entered by GPs as free text, resulting in many different types of measurements being entered.

B.5.3.1 Blood

28% of the total 20,012 relevant dipsticks were positive for blood.

B.5.3.2 Leucocyte esterase

24% of the 17,852 relevant dipsticks were positive for leucocyte esterase.

B.5.3.3 Nitrites

6% of the 16,473 total relevant dipsticks were positive for nitrites.

B.5.3.4 Dipstick tested status

A binary discrete variable was created for whether the patient underwent any form of urine dipstick testing during the consultation. This included blood, leucocyte esterase, or nitrite urine dipsticks.

B.5.3.5 Any positive dipstick result

A positive result for any of the three urine dipsticks (blood, leucocyte esterase and nitrites) was coded as positive result, and otherwise negative.

B.6 Predictors analyses

B.6.1 Explanatory data analysis

Following the completion of descriptive statistics, chi-squared tests were performed, and correlation between variables was calculated. The latter was used to inform choices regarding which explanatory variables might not be suitable to model together. The examination of clustering also occurred. This included clarification of the size of clusters of numbers of patients seen by single providers, and providers nested within and across practices.

The objective was to identify variables associated with likely inappropriate decisions within all URTI diagnoses, and for likely unnecessary prescribing among all prescriptions for URTI. For URTI and UTI, the objectives included identifying variables

associated with increasing choice of antibiotic prescribed, non-first-line prescribing, and repeat prescribing for initial presentations of the condition.

B.6.2 Linking records

The MedicineInsight data received were de-identified at the patient, provider / GP and practice levels but is equipped with unique IDs at each level to allow for the linking of records. These variables were referred to as practice ID, provider ID, and practice ID. The datasets for each diagnostic condition were then linked with the antibiotic prescription dataset. Following the linkage of diagnosis and prescription data, antibiotic prescriptions linked with a single diagnosis containing more than one infectious condition, such as, “OM / cellulitis leg”, or prescriptions linked to two, separate infectious diagnoses, were excluded as one could not be certain which diagnosis the antibiotic was intended for (23,24). The pre-prepared datasets of presentation, encounters, patient comorbid conditions, clinical observations, pathology, and provider and practice information data were then merged by matching the consultation date, patient ID, provider ID and practice ID in each row.

B.6.3 Standard of assessment

The standard used for assessment of prescribing was version 15 of the guidelines published in 2014 (2). During the study period 2012 to mid-2017, there were two different versions of these guidelines available to clinicians, as a new version was published during this time (2,4). It was considered difficult to ascertain when clinician use of the previous version published in 2010 ceased and the time taken for the promulgation of the 2014 guidelines (2,4). For this reason, it was not considered feasible to include multiple versions of the guidelines within the analysis.

A dummy variable was created for cefalexin prescriptions, for which repeats may be required to complete a single guideline-recommended course of medication.

Although the guidelines use an age cut-off of six months, patient age data was only available in years (2).

B.6.4 Base model inclusion

B.6.4.1 Base model inclusion for upper respiratory tract infection

Table B-4: Base model inclusion for each model for upper respiratory tract infection

Variable Included in Base Model	**Likely Inappropriate Decision**	**Likely Unnecessary Prescribing**	**Ordinal Line of Antibiotic Prescribed**	**Binary Non-first-line Prescribing**	**Binary Repeat Positive Antibiotic Prescribing**
Patient age group	Y	Y	Y	Y	Y
Patient gender	Y	Y	Y	Y	Y
Patient comorbid condition status	Y	Y	Y	Y	Y
Patient mental health condition status	Y	Y	Y	Y	Y
Patient socioeconomic disadvantage status	Y	Y	Y	Y	Y
Patient government concession status	Y	Y	Y	Y	Y
PHN for patient's address	Y	Y	Y	Y	Y
Measure of patient remoteness	Y	Y	Y	Y	Y
Patient penicillin allergy label	Y	Y	Y	Y	Y
Day of the week or weekend status	Y	Y	Y	Y	Y
Temperature testing status	Y	Y	Y	Y	Y
Whether reason for prescribing was recorded	**N**	Y	Y	Y	Y
Repeat prescription status	**N**	Y	Y	Y	Y
Dummy variable for cephalexin prescriptions	**N**	Y	**N**	**N**	Y
Dummy variable for annual influenza season [13]	Y	Y	Y	Y	Y
URTI condition [14]	N	N	Y	Y	Y
Likely unnecessary prescribing variable	N	n/a	Y	Y	Y
Choice of antibiotic prescribing variable	N	Y	n/a	n/a	Y
Practice size	Y	Y	Y	Y	Y

[13] All models included dummy variables for annual influenza seasons to allow seasonal effects (25-27).

[14] URTI condition was sometimes too closely linked to the outcome to permit inclusion.

B.6.4.2 Base model inclusion for urinary tract infection

Table B-5: Base model inclusion for each model for urinary tract infection

Variable Included in Base Model	**Ordinal Line of Antibiotic Prescribed**	**Binary Non-first-line Prescribing**	**Binary Repeat Positive Antibiotic Prescribing**
Patient age group	Y	Y	Y
Patient gender	Y	Y	Y
Patient comorbid condition status	Y	Y	Y
Patient mental health condition status	Y	Y	Y
patient socioeconomic disadvantage status	Y	Y	Y
Patient government concession status,	Y	Y	Y
PHN for patient's address	Y	Y	Y
Measure of patient remoteness	Y	Y	Y
Patient penicillin sensitivity status	Y	Y	Y
Day of the week or weekend status	Y	Y	Y
Urine dipstick testing status	Y	Y	Y
Culture testing status	Y	Y	Y
Temperature testing status	Y	Y	Y
Whether reason for prescribing was recorded	Y	Y	Y
Practice size	Y	Y	Y
Repeat prescription status	Y	Y	n/a
Dummy variable for cephalexin prescriptions	**Y**	**Y**	Y
Dummy variable for annual influenza season [15]	Y	Y	Y
Ordinal choice of antibiotic prescribed variable	n/a	n/a	Y

[15] All models included dummy variables for annual influenza seasons to allow seasonal effects (25-27).

B.6.5 Modeling considerations

For each model, the intention was to include both random intercept and random slope at each level. However, it was found that due to limitations of processing power with this large dataset, random slopes was not included in the model, only random intercepts. Random intercepts were included, where possible, for both individual practice and individual provider. When both levels could not be accounted for, a random intercept for the unique combination of practice and provider was used. While in theory, unique patient within unique provider effect would be preferable to provider to practice effect, the clusters were too small such that unique provider within unique practice models were settled upon. The process involved weighing up the size of effect of including three levels and whether there is a notable difference with only two.

Furthermore, the intention was to include random intercepts for practice-related variables within the practice level. However, resulting models were not ideal and the decision was made to not include random intercepts for variables at higher levels than the individual patient. For example, practice size is a variable relating to the practice level and should ideally be included at that level. However, the inclusion of a random intercept for practice size resulted in an effect so small that CIs were unable to be calculated.

Likelihood ratio tests were used to aid selection of a suitable structure for the random effects model. Starting from the base model, modelling involved manually removing variables one at a time to examine the effect of that variable on the dependent/outcome variable of inappropriate prescribing. Care was to be taken regarding exclusion of potential explanatory variables, not purely based on statistical significance but also upon clinical and policy significance. The magnitude and precision of effect also needed consideration, using percentage change of coefficients and standard error, and confidence intervals for precision. Reduction in Bayesian Information Criterion was also used as an indicator of improvement in model selection. whilst also checking for feasible size of effect, standard error, and statistical significance. Interactions were tested for effect modification such as patient age and gender, where subgroup analysis indicates sufficient power and there is a plausible reason for considering potential interaction. Routine heteroskedasticity tests could not be performed for these non-linear data.

Base models for each condition group and outcome included all potential explanatory variables of interest, from which models for the random effects structure was derived (28).

Due to the small numbers of URTI prescriptions identified as likely necessary, it was unfeasible to model the response variables within the denominator of likely appropriate decisions, (and likely unnecessary prescriptions within likely inappropriate decision). As a result, the denominator of all antibiotics prescribed for URTI, for both likely necessary and likely unnecessary prescriptions, was selected

To compare the results of this research with models without allowance for heterogeneity, equivalent, multivariable logistic regression models without random effects were developed for all outcomes.

B.7 Trends analyses

Additionally, there was also a focus on trends in antibiotic prescribing for, as well as trends in the individual antibiotic prescribed (29-34). For UTI only, outcomes included whether urine dipstick testing was recorded. The objective was to identify outcomes demonstrating both statistically significant and clinically meaningful change. **Table B-6** and **Table B-7** provide additional detail regarding the numerators and denominators for trends analyses for URTI and UTI, respectively.

Table B-6: Details of numerators and denominators for outcome rates for trends analysis for upper respiratory tract infection.

Prescribing Outcome Rate	Description of Numerator and Denominator
Likely Unnecessary antibiotic Prescribing rate	The sum of likely unnecessary antibiotic prescriptions for the particular condition or condition group, over sum of all antibiotic prescriptions for initial presentations of the same condition / condition group.
Overall Antibiotic Prescribing rate	The sum of all antibiotic prescriptions for patients with initial presentations of the particular condition / condition group, over the sum of all patients with initial diagnoses of the same condition/condition group.
Second-line antibiotic prescribing rate	The sum of second-line antibiotic prescriptions for patients with initial presentations of the particular condition / condition group, over the sum of all antibiotics prescribed to patients with initial presentations of the same condition / condition group.
Prescribing of antibiotic Not Recommended in Guidelines for the condition/condition group.	The sum of antibiotic prescriptions not recommended in the Guidelines for the condition given to patients with initial presentations of the particular condition / condition group, over the sum of all antibiotics prescribed to patients with initial presentations of the same condition/condition group. This is also referred to as the not recommended prescribing rate.
Non-first-line antibiotic prescribing	The sum of non-first-line antibiotic prescriptions for patients with initial presentations of the particular condition / condition group, over the sum of all antibiotics prescribed to patients with initial presentations of the same condition/condition group.
Repeat(s) issued on antibiotic prescription	The sum of antibiotic prescriptions with one or more repeats given to patients with initial presentations of the particular condition / condition group, over the sum of all antibiotics prescribed to patients with initial presentations of the same condition/condition group.

Table B-7: Details of numerators and denominators for outcome rates for trends analysis for urinary tract infection.

Prescribing Outcome Rate	Description of Numerator and Denominator
Overall antibiotic prescribing rate	The sum of all antibiotic prescriptions for patients (within patient group, where relevant) with initial presentations of UTI, over the sum of all patients (within same patient group, where relevant) with initial diagnoses of UTI. For example, the antibiotic prescribing rate for women used the sum of antibiotic prescriptions provided for women with initial presentations of UTI, over the sum of all women with initial presentations of UTI.
Prescribing of second-line antibiotic agent	The sum of second-line antibiotic prescriptions for patients (within patient group, where relevant) with initial presentations of UTI, over the sum of all antibiotics prescribed to patients (within same patient group, where relevant) with initial presentations of UTI.
Prescribing of third-line antibiotic agent	The sum of third-line antibiotic prescriptions for patients (within patient group, where relevant) with initial presentations of UTI, over the sum of all antibiotics prescribed to patients (within same patient group, where relevant) with initial presentations of UTI.
Prescribing of antibiotic not recommended in guidelines	The sum of antibiotic prescriptions not recommended in the Guidelines given to patients (within patient group, where relevant) with initial presentations of UTI, over the sum of all antibiotics prescribed to patients (within same patient group) with initial presentations of UTI. This is also referred to as the not recommended prescribing rate.
Non-first-line antibiotic prescribing	The sum of non-first-line antibiotic prescriptions for patients (within patient group) with initial presentations of UTI, over the sum of all antibiotics prescribed to patients (within same patient group) with initial presentations of UTI.
Repeat(s) issued on antibiotic prescription	The sum of antibiotic prescriptions positive for one or more repeats given to patients (within patient group) with initial presentations of UTI, over the sum of all antibiotics prescribed to patients (within same patient group) with initial presentations of UTI.
Urine dipstick testing occurring	The sum of patients (within patient group, where relevant) with initial presentations of UTI receiving urine dipstick testing during consultation, over the sum of all patients (within same patient group, where relevant) with initial presentations of UTI.

APPENDIX C - APPENDICES TO THE PREDICTORS OF INAPPROPRIATE PRESCRIBING FOR UPPER RESPIRATORY TRACT INFECTION CHAPTER (CHAPTER 4)

C.1 Clustering of patients and providers for initial presentations of upper respiratory tract infection

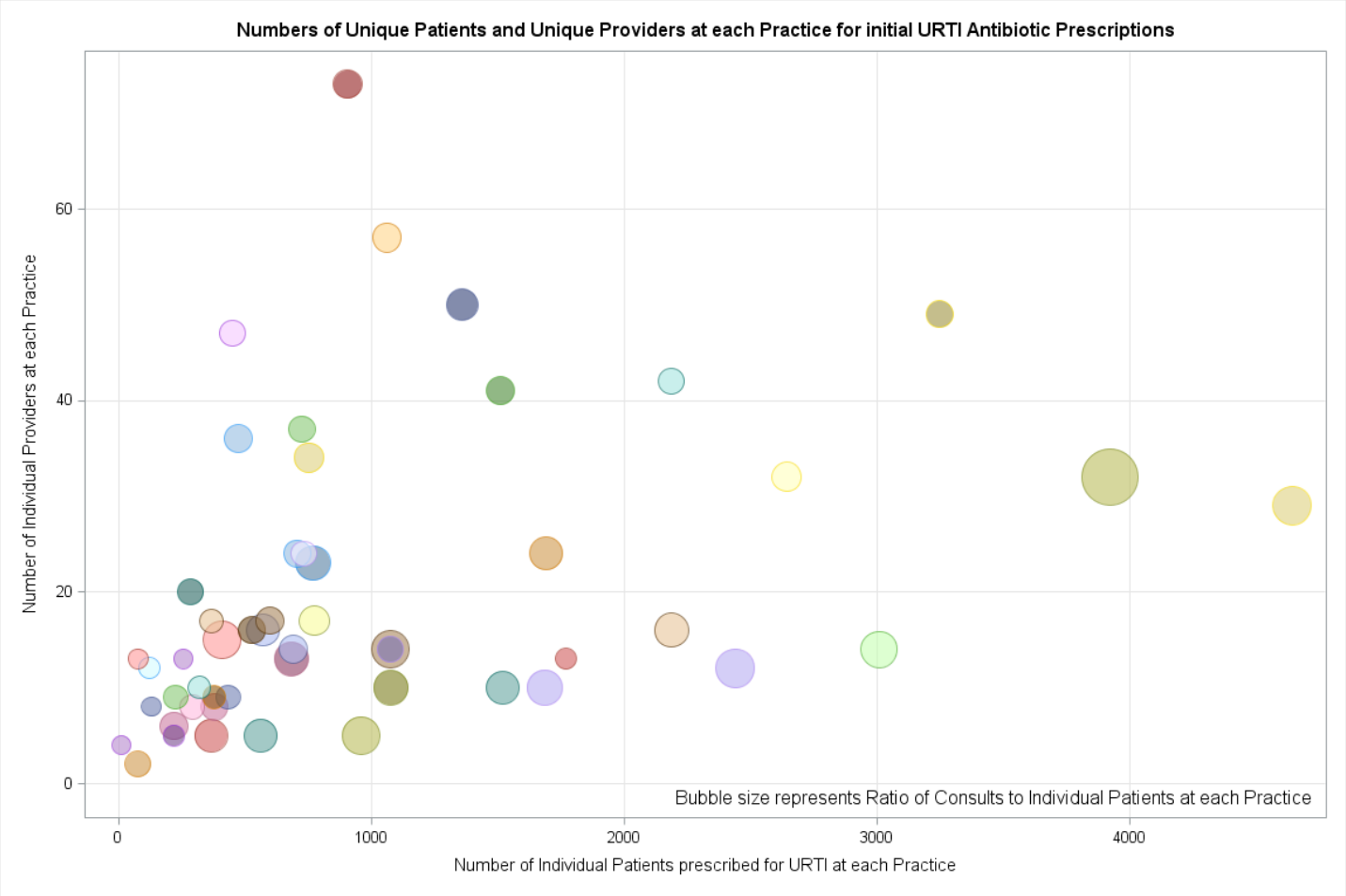


Figure C-1: Bubble plot of individual patients and providers at each practice for initial presentations of upper respiratory tract infection

C.2 Antibiotic prescriptions

Table C-1: Frequency table of antibiotic class by Anatomical Therapeutic Chemical classification (35), for systemic antibiotics prescribed for initial presentations of upper respiratory tract infection

Anatomical Therapeutic Chemical Class of Antibiotic	Frequency	Percent	Cumulative Percent
Beta-lactamase resistant penicillins	110	0.21	0.21
Beta-lactamase sensitive penicillins	10,218	19.59	19.8
Combinations of penicillins, incl. beta-lactams	11,843	22.7	42.5
Combinations of sulfonamides and trimethoprim	420	0.81	43.3
First-generation cephalosporins	5,701	10.93	54.23
Fluoroquinolones	112	0.21	54.44
Lincosamides	43	0.08	54.53
Macrolides	7,251	13.9	68.42
Nitrofuran derivatives	2	0	68.43
Other Aminoglycosides	6	0.01	68.44
Penicillins with extended spectrum	14,722	28.22	96.66
Second-generation cephalosporins	1,186	2.27	98.93
Tetracyclines	506	0.97	99.9
Third-generation cephalosporins	4	0.01	99.91
Trimethoprim and derivatives	47	0.09	100
Total	52,171	100	

Table C-2: Frequency table of patient age group by likely appropriate / likely inappropriate decision status for initial presentations of upper respiratory tract infection

	Likely Appropriate Decision	Likely Inappropriate Decision	Excluded	Total
Patient Age Group				
0-8 yrs, ref	22,252	9,266	125	31,643
	70.32	29.28	0.4	100
9-21 yrs	11,550	7,633	195	19,378
	59.6	39.39	1.01	100
22-34 yrs	17,527	14,094	210	31,831
	55.06	44.28	0.66	100
35+ yrs	16,314	13,206	118	29,638
	55.04	44.56	0.4	100
Missing	4	2	240	246
	1.63	0.81	97.56	100
Total	67,647	44,201	888	112,736
	60	39.21	0.79	100

Key
frequency
row percentage

Table C-3: Frequency table of medicine active ingredients for systemic antibiotics prescribed but not recommended in the guidelines for the condition it was prescribed for, for initial presentations of upper respiratory tract infection

Medicine active ingredient	Frequency	Percent	Cumulative Percent
AMOXICILLIN	3002	14.66	14.66
AMOXICILLIN WITH CLAVULANIC ACID	3081	15.04	29.70
AZITHROMYCIN	648	3.16	32.86
CEFACLOR	937	4.57	37.44
CEFALEXIN	3484	17.01	54.45
CEFTRIAXONE	4	0.02	54.46
CEFUROXIME	183	0.89	55.36
CIPROFLOXACIN	107	0.52	55.88
CLARITHROMYCIN	1726	8.43	64.31
CLINDAMYCIN	43	0.21	64.52
DICLOXACILLIN	4	0.02	64.54
DOXYCYCLINE	389	1.90	66.44
ERYTHROMYCIN	1488	7.26	73.70
FLUCLOXACILLIN	102	0.50	74.20
GENTAMICIN	4	0.02	74.22
MINOCYCLINE	25	0.12	74.34
NITROFURANTOIN	2	0.01	74.35
NORFLOXACIN	4	0.02	74.37
PHENOXYMETHYLPENICILLIN	605	2.95	77.32
PROCAINE BENZYLPENICILLIN (PROCAINE PENICILLIN)	1155	5.64	82.96
ROXITHROMYCIN	3068	14.98	97.94
TOBRAMYCIN	2	0.01	97.95
TRIMETHOPRIM	47	0.23	98.18
TRIMETHOPRIM WITH SULFAMETHOXAZOLE	373	1.82	100.00
Total	20,483	100	

Table C-4: Frequency table of upper respiratory tract infection condition by likely necessary / likely unnecessary prescribing status, for initial presentations of upper respiratory tract infection

	Likely Appropriate Decision	Likely Inappropriate Decision	Excluded	Total
URTI Condition				
Rhinosinusitis	1,944	17,884	236	20,064
	9.69	89.13	1.18	100
Pharyngitis/Tonsillitis	2,622	17,408	470	20,500
	12.79	84.92	2.29	100
Acute Otitis Media	2,698	8,656	0	11,354
	23.76	76.24	0	100
Influenza/ILI	0	253	0	253
	0	100	0	100
Total	7,264	44,201	706	52,171
	13.92	84.72	1.35	100

Key
frequency
row percentage

Note: 253 cases of influenza/ILI receiving antibiotic prescriptions were excluded from model of likely unnecessary prescribing as the outcome is invariable likely unnecessary prescribing.

Table C-5: Frequency table of ordinal choice of antibiotic prescribed by upper respiratory tract infection condition, for initial presentations of upper respiratory tract infection

	First-line	Second-line	Not Recommended	Excluded	Total
URTI Condition					
Rhinosinusitis	6,504	5,049	8,511	0	20,064
	32.42	25.16	42.42	0	100
Pharyngitis/Tonsillitis	8,683	0	11,817	0	20,500
	42.36	0	57.64	0	100
Acute Otitis Media	5,317	3,698	2,339	0	11,354
	46.83	32.57	20.6	0	100
Influenza/ILI	0	0	0	253	253
	0	0	0	100	100
Total	20,504	8,747	22,667	253	52,171
	39.3	16.77	43.45	0.48	100

Key
frequency
row percentage

Table C-6: Frequency table of patient primary health network by ordinal choice of antibiotic prescribed, for patients with initial presentations of acute pharyngitis / tonsillitis

Key
frequency
row percentage

Patient Primary Health Network	First-line	Not Recommended	Total
Perth North	3,427	5,619	9,046
	37.88	62.12	100
Perth South	2,332	3,770	6,102
	38.22	61.78	100
Country WA	2,702	2,149	4,851
	55.7	44.3	100
Interstate	81	114	195
	41.54	58.46	100
Missing	141	165	306
	46.08	53.92	100
Total	8,683	11,817	20,500
	42.36	57.64	100

C.3 Antibiotic prescriptions for influenza / influenza-like illness

Table C-7: Frequency table of antibiotic active ingredients prescribed for initial presentations of influenza / influenza-like illness

Medicine active ingredient	Frequency	Percent	Cumulative Percent
Amoxicillin	53	20.95	20.95
Amoxicillin with clavulanic acid	60	23.72	44.66
Azithromycin	13	5.14	49.8
Cefaclor	2	0.79	50.59
Cefalexin	24	9.49	60.08
Cefuroxime	5	1.98	62.06
Ciprofloxacin	1	0.4	62.45
Clarithromycin	47	18.58	81.03
Dicloxacillin	1	0.4	81.42
Doxycycline	9	3.56	84.98
Erythromycin	10	3.95	88.93
Flucloxacillin	2	0.79	89.72
Phenoxymethylpenicillin	9	3.56	93.28
Procaine benzylpenicillin (procaine penicillin)	1	0.4	93.68
Roxithromycin	15	5.93	99.6
Trimethoprim with sulfamethoxazole	1	0.4	100
Total	253	100	

C.4 Repeats issued on antibiotic prescription status

C.4.1 Repeats issued on all antibiotic prescriptions for upper respiratory tract infection

Table C-8: Frequency table of whether repeats were issued on prescription by likely unnecessary / necessary prescribing status, for initial presentations of upper respiratory tract infection

Repeat issued on prescription	Likely Necessary Prescribing	Likely Unnecessary Prescribing	Excluded	Total
Negative	4,539	30,142	480	35,161
	12.91	85.73	1.37	100
Positive	2,725	13,806	226	16,757
	16.26	82.39	1.35	100
Excluded	0	253	0	253
	0	100	0	100
Total	7,264	44,201	706	52,171
	13.92	84.72	1.35	100

Key
frequency
row percentage

Table C-9: Frequency table of whether repeats were issued on prescription by ordinal choice of antibiotic prescribed, for initial presentations of upper respiratory tract infection

Repeat issued on prescription	First-line	Second-line	Not Recommended	Excluded	Total
Negative	16,480	4,124	14,557	0	35,161
	46.87	11.73	41.4	0	100
Positive	4,079	4,622	8,056	0	16,757
	24.34	27.58	48.08	0	100
Excluded	0	0	0	253	253
	0	0	0	100	100
Total	20,559	8,746	22,613	253	52,171
	39.41	16.76	43.34	0.48	100

Key
frequency
row percentage

Table C-10: Frequency table of patient age group and whether repeats were issued on prescription, for initial presentations of upper respiratory tract infection

Patient Age Group	Repeat issued on Prescription: Negative	Positive	Excluded	Total
0-8 yrs,	8,912	4,422	21	13,355
	66.73	33.11	0.16	100
9-21 yrs	5,719	3,250	39	9,008
	63.49	36.08	0.43	100
22-34 yrs	11,349	4,065	70	15,484
	73.3	26.25	0.45	100
35+ yrs	9,030	4,931	123	14,084
	64.12	35.01	0.87	100
Missing	151	89	0	240
	62.92	37.08	0	100
Total	35,161	16,757	253	52,171
	67.4	32.12	0.48	100

Key
frequency
row percentage

Table C-11: Frequency table of prescriptions issued with repeats for initial presentations of influenza / influenza-like illness, by active ingredient

Medicine active ingredient	Frequency	Percent	Cumulative Percent
Amoxicillin	10	11.49	11.49
Amoxicillin with clavulanic acid	27	31.03	42.53
Azithromycin	1	1.15	43.68
Cefaclor	1	1.15	44.83
Cefalexin	10	11.49	56.32
Cefuroxime	2	2.3	58.62
Clarithromycin	19	21.84	80.46
Doxycycline	3	3.45	83.91
Erythromycin	4	4.6	88.51
Roxithromycin	10	11.49	100
Total	87	100	

C.4.2 Repeats issued on cefalexin prescriptions for treatment of acute pharyngitis / tonsillitis

Of scripts for cephalexin with repeats issued for URTI, with the denominator of antibiotics within the ordinal choice of antibiotic prescribed model, 897 were for acute pharyngitis/tonsillitis (43%). Cefalexin is an option listed in the Guidelines for acute pharyngitis/tonsillitis only (for penicillin immediate hypersensitivity patients), for which the recommended course is 1g, 12hrly for 10 days, totalling a 20g course. Children are recommended 25mg/kg up to 1g.

All 29 patients receiving 250mg strength and all 436 adults receiving 500mg did require repeats (**Table C-12**). Of liquid formulation, 10 patients required several repeats, 1 patient receiving 4 bottles did not require a repeat. Therefore, all but one adult of the 476 total did require repeats for cephalexin scripts for acute pharyngitis/tonsillitis.

Table C-12: Frequency table of medicine quantity and medicine strength, of cefalexin prescriptions with repeats present, for adults with initial presentations of pharyngitis

	Medicine quantity						
Medicine strength	1	100mL	20	4	40	6	Total
250mg	0	0	28	0	1	0	29
250mg/5mL	5	5	0	1	0	0	11
500mg	0	0	435	0	0	1	436
Total	5	5	463	1	1	1	476

There were 421 children under 18 years receiving cephalexin scripts with repeats for pharyngitis, as follows in **Table C-13**:

Table C-13: Frequency table of medicine quantity and medicine strength, of cefalexin prescriptions with repeats present, for patients under eighteen years receiving cefalexin prescriptions with repeats for initial presentations of pharyngitis / tonsillitis

	Medicine quantity				
medicine_strength	1	100mL	100mL*3	20	Total
125mg/5mL	84	11	0	0	95
250mg	0	0	0	29	29
250mg/5mL	235	38	1	0	274

500mg	0	0	0	23	23
Total	319	49	1	52	421

For children under eight years of age, the cefalexin medicine strength and quantity are displayed in **Table C-14** below. All young children under 8 are likely to have required repeats.

Table C-14: Frequency table of medicine quantity and medicine strength, of cefalexin prescriptions with repeats present, for children under eight years of age for initial presentations of pharyngitis / tonsillitis

	Medicine quantity			
Medicine strength	1	100mL	20	Total
125mg/5mL	66	11	0	77
250mg	0	0	1	1
250mg/5mL	103	19	0	122
Total	169	30	1	200

For children aged 9-16 years, as depicted in **Table C-15** below, it is also possible that all these children required repeats, particularly for liquid formulation, up to 4 100mL bottles of 25mg/5mL for maximum 20g course.

Table C-15: Frequency table of medicine quantity and medicine strength, of cefalexin prescriptions with repeats present, for children aged 9-16 years, for initial presentations of pharyngitis / tonsillitis

	Medicine quantity				
Medicine strength	1	100mL	100mL*3	20	Total
125mg/5mL	14	0	0	0	14
250mg	0	0	0	27	27
250mg/5mL	108	16	1	0	125
500mg	0	0	0	22	22
Total	122	16	1	49	188

It is possible that all but 1 patient did require repeats for cephalexin prescriptions for treatment of pharyngitis.

For adults prescribed cephalexin with repeats, the instructions for 500mg varied substantially (**Table C-16**). Although ten days is recommended (and was the most common instruction), durations appearing included five days commonly, as well as seven days and even three days.

Table C-16: Frequency table of medicine instructions, on cefalexin prescriptions of 500mg strength with repeats present, prescribed to adults with initial presentations of pharyngitis / tonsillitis

Medicine instructions	Frequency	Percent	Cumulative Percent
1 tab four times a day for 5 days	1	0.92	0.92
1 tab tds	2	1.83	2.75
10 days	3	2.75	5.5
1g BD for 10 days	3	2.75	8.26
2 cap 2 times per day for 10 days	1	0.92	9.17
2 cap 2 times per day for 10 days	2	1.83	11.01
2 cap 2 times per day for 10 days	1	0.92	11.93
2 caps bd until finished	1	0.92	12.84
2 capsules bd for 10 days	1	0.92	13.76
2 stat	3	2.75	16.51
2 tablets BD for 10 days	1	0.92	17.43
2 tabs bd for 10 days	2	1.83	19.27
5-7days	1	0.92	20.18
5d	1	0.92	21.1
For 10 days	1	0.92	22.02
For 5 days	4	3.67	25.69
For 5 days, after food	2	1.83	27.52
for 10 days	19	17.43	44.95
for 10/7	1	0.92	45.87
for 3 days	1	0.92	46.79
for 5 days	5	4.59	51.38
for 5 days for acute infections	1	0.92	52.29
for 5 days for throat infection	1	0.92	53.21
for 5 to 7 days	1	0.92	54.13
for 5-10 days	5	4.59	58.72
for 5-7 days	1	0.92	59.63
for 5-7days	1	0.92	60.55
for 7-10 days	1	0.92	61.47
for five days	1	0.92	62.39
for ten days	2	1.83	64.22
gluten and peanut free please	1	0.92	65.14
ii 12 hourly or i 6 hourly 1- days	1	0.92	66.06
ii 12 hourly or i 6 hourly 10 days	1	0.92	66.97
ii bd 10 days	2	1.83	68.81
m.d.u.	15	13.76	82.57
one BD for 7 days	1	0.92	83.49
one bd for 5 days and then one daily ..	1	0.92	84.4
one qid	8	7.34	91.74
p.c.	1	0.92	92.66
take two to start and then one 6 hourly	1	0.92	93.58

take two to start and then one capsul..	2	1.83	95.41
take two to start and then one four t..	3	2.75	98.17
twice a day for 10 days	1	0.92	99.08
until all taken.	1	0.92	100
Total	109	100	

For children receiving 500mg doses, there was notable variation from 5 to 10 days, as follows in **Table C-17**.

Table C-17: Frequency table of medicine instructions, on cefalexin prescriptions of 500mg strength with repeats present, prescribed to children for initial presentations of pharyngitis / tonsillitis

Medicine instructions	Frequency	Percent	Cumulative Percent
1 tab bd	1	14.29	14.29
10 days	1	14.29	28.57
2.5mLs TDS for 7 days	1	14.29	42.86
For 10days Start with 2 twice a day..	1	14.29	57.14
for 5 days	1	14.29	71.43
for 5-7days	2	28.57	100
Total	7	100	

Similarly for children receiving 250mg doses, there was notable variation from 5 to 10 days, as seen in **Table C-18**.

Table C-18: Frequency table of medicine instructions, on cefalexin prescriptions of 250mg strength with repeats present, prescribed to children with initial presentations of pharyngitis / tonsillitis

Medicine instructions	Frequency	Percent	Cumulative Percent
2 bd for 10 days	1	14.29	14.29
2 stat	1	14.29	28.57
for 10 days	1	14.29	42.86
For 5 days for acute infections	1	14.29	57.14
for 5-7days	1	14.29	71.43
for 6 days	1	14.29	85.71
until all taken.	1	14.29	100
Total	7	100	

The variation in instructions for liquid formulations of 250mg or 125mg / 5mL was notable with 5-7 days also being common (**Table C-19**).

Table C-19: Frequency table of medicine instructions on prescriptions for liquid formulations of cefalexin with repeats present, prescribed children with initial presentations of pharyngitis / tonsillitis

Medicine instructions	Frequency	Percent	Cumulative Percent
(27 mg/kg/day)	1	0.81	0.81
10ml stat	1	0.81	1.63
10ml to begin	1	0.81	2.44
10mls twice daily	1	0.81	3.25
11.5ml twice daily for 10 days	1	0.81	4.07
15ml twice daily for 10 days	1	0.81	4.88
16 mls bd for 10 days	1	0.81	5.69
200 mg three times per day for one week	1	0.81	6.5
250mg [5mls] six hourly for seven days	1	0.81	7.32
250mg twice daily	1	0.81	8.13
3.5mLs TDS for 7 days	1	0.81	8.94
3ml tds	1	0.81	9.76
4 mls tds	1	0.81	10.57
40 mg/kg/day 11 kilos	1	0.81	11.38
40 mg/kg/day 14 kilos	1	0.81	12.2
4ml tds	1	0.81	13.01
5 days	2	1.63	14.63
5 mL three times daily for 10 days. ..	1	0.81	15.45
5 mL three times daily for 7 days	1	0.81	16.26
5.5ml four times daily 7 days	1	0.81	17.07
5.85ml twice daily for 10 days	1	0.81	17.89
5-Jul	1	0.81	18.7
500mg twice daily for 7 days	1	0.81	19.51
6mls four times a day	1	0.81	20.33
7 days	3	2.44	22.76
7 mls tds	1	0.81	23.58
7.5 mL three times daily for 5 days	1	0.81	24.39
7mls twice a day	1	0.81	25.2
8 ml twice daily for 10 days	1	0.81	26.02
8.5 ml BD for 7 days	1	0.81	26.83
9.7ml 12-hourly for 10 days	1	0.81	27.64
9ml 12hourly for 10 days	1	0.81	28.46
For 5 days	8	6.5	34.96
For 5 days.	1	0.81	35.77
For 7 days	1	0.81	36.59
WT 69Kg	1	0.81	37.4
X 10 days	1	0.81	38.21
finish all	1	0.81	39.02
for 10 days	15	12.2	51.22
for 10 days (21kg)	1	0.81	52.03
for 10 days (OR 10 mls twice a day)	1	0.81	52.85
for 10 days - 1ml for first time …	1	0.81	53.66
for 10 days.	1	0.81	54.47
for 5 days	10	8.13	62.6
for 5 days for acute infections	1	0.81	63.41
for 5 days.	2	1.63	65.04

for 5- 7 days	1	0.81	65.85
for 5-7 days	6	4.88	70.73
for 5-7days	5	4.07	74.8
for 6 days	2	1.63	76.42
for 7 days	15	12.2	88.62
for 7 days (33 mg/kg/day)	1	0.81	89.43
for 7 days.	3	2.44	91.87
for 7-10 day	1	0.81	92.68
for 7days	1	0.81	93.5
for five days.	1	0.81	94.31
m.d.u.	5	4.07	98.37
or 10 mls twice a day for 10 days	1	0.81	99.19
until finished for throat infection	1	0.81	100
Total	123	100	

1
2

C.5 Marginal effects for the inappropriate decision model for initial presentations of upper respiratory tract infection

C.5.1 Average marginal effects

Table C-20: Average marginal effects for Model 0 – Inappropriate decisions for initial presentations of upper respiratory tract infection (unnecessary prescriptions versus reference of appropriate prescriptions together with appropriate non-prescribing situations)

Average Marginal Effects						
Inappropriate Decisions for Initial Presentations of URTI						
Independent Variable	**dy/dx**	**Std. Err.**	**Z**	**P>z**	**[95% Conf.**	**Interval]**
Patient Age Group (ref. 0-8 years)						
9-21 yrs	0.131857	0.004153	31.75	0.000	0.1237167	0.139997
22-34 yrs	0.140908	0.004149	33.97	0.000	0.132777	0.149039
35+ yrs	0.131635	0.003858	34.12	0.000	0.1240744	0.139196
Patient Gender (ref. Female)						
Male	-0.00974	0.002698	-3.61	0.000	-0.015032	-0.00446
Patient Penicillin Sensitivity Status (ref. Negative)						
Positive	0.069712	0.005978	11.66	0.000	0.0579966	0.081428
Patient Concession Status (ref. Negative)						
Positive	0.007845	0.003689	2.13	0.033	0.0006142	0.015075
Patient Mental Health Condition Status (ref. Negative)						
Positive	0.010328	0.004258	2.43	0.015	0.0019818	0.018673
Missing	0.054179	0.043696	1.24	0.215	-0.031463	0.139821
Weekend Consultation (ref. Weekday)						
Positive	0.042556	0.004889	8.71	0.000	0.0329743	0.052137
Practice Size (ref. Medium / Large)						
Small	0.103297	0.026201	3.94	0.000	0.0519446	0.154649
Patient Primary Health Network (ref. Perth North)						
Perth South	-0.0092	0.007907	-1.16	0.245	-0.024694	0.0063
Country WA	0.00659	0.009084	0.73	0.468	-0.011215	0.024395
Interstate	0.03749	0.015302	2.45	0.014	0.0074983	0.067481
Missing	0.024683	0.013058	1.89	0.059	-0.000911	0.050276
Patient Disadvantaged (ref. Negative)						
Positive	0.012041	0.006146	1.96	0.050	-5.26E-06	0.024087
Missing	-0.01588	0.006716	-2.36	0.018	-0.029045	-0.00272

C.5.2 Margins at representative values for effect on the probability of the inappropriate decision with change in patient gender, across different patient age groups

```
margins, dydx(pat_sex) at (agegrp_urti_new= (1 2 3 4))

Average marginal effects                        Number of obs     =    111,848
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 1.pat_sex

1._at        : agegrp_urti_new =           1        (0-8 yrs)

2._at        : agegrp_urti_new =           2        (9-21 yrs)

3._at        : agegrp_urti_new =           3        (22-34 yrs)

4._at        : agegrp_urti_new =           4        (35+ yrs)

------------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Male         |
         _at |
          1  |   .0090993   .0043184     2.11   0.035     .0006354    .0175633
          2  |  -.0319461   .0064397    -4.96   0.000    -.0445676   -.0193246
          3  |  -.0233131   .0060761    -3.84   0.000     -.035222   -.0114041
          4  |  -.0095587   .0053559    -1.78   0.074    -.0200562    .0009388
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

Male young children had probability 0.01 higher probability of receiving an inappropriate decision than females, whereas males 9-21 years had 0.03 less probability, and males 22-34 years had 0.02 less probability.

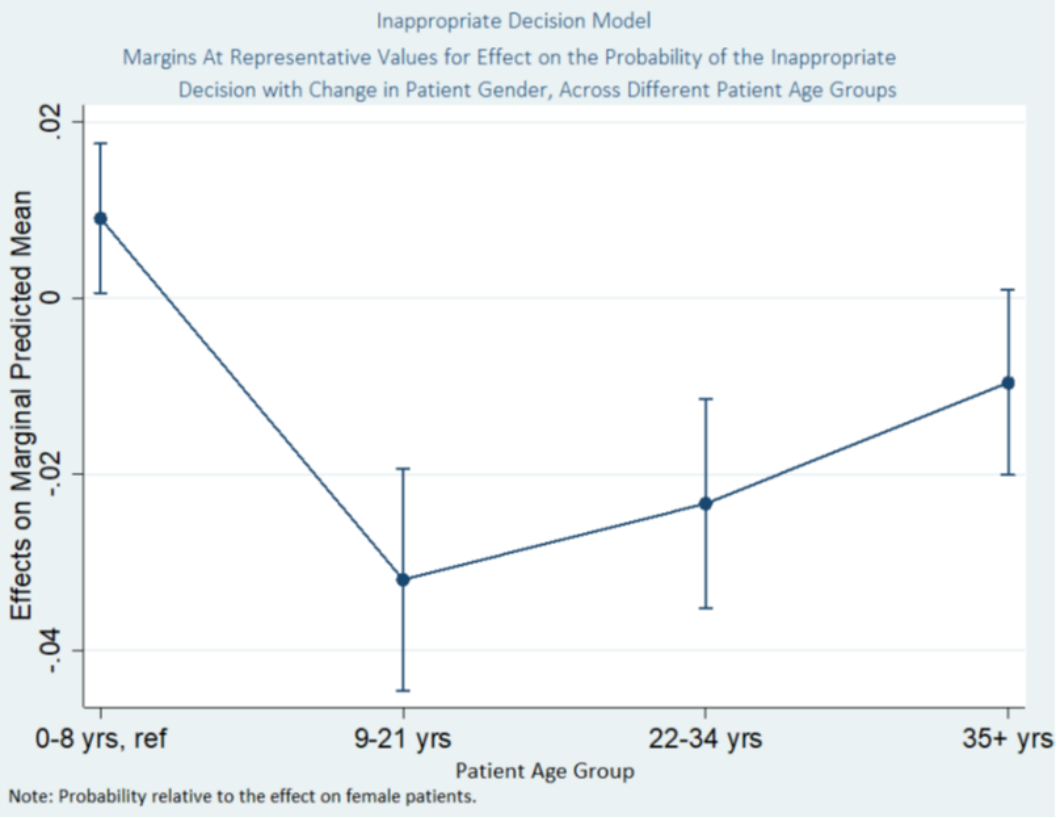


Figure C-2: Margins at representative values for effect on the probability of the inappropriate decision with change in patient gender from female to male, across different patient age groups, relative to the probability for female patients

C.5.3 Margins at representative values for the effect on inappropriate decision with change in patient age groups, across different values of patient gender

```
margins, dydx(agegrp_urti_new) at (pat_sex= (1 0))

Average marginal effects                        Number of obs     =    111,848
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 2.agegrp_urti_new 3.agegrp_urti_new 4.agegrp_urti_new

1._at        : pat_sex         =           1          (Male)

2._at        : pat_sex         =           0          (Female)
------------------------------------------------------------------------------
                   |            Delta-method
                   |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
9-21 years         |
               _at |
                1  |   .1094557   .0058061    18.85   0.000     .0980759    .1208354
                2  |   .1505011   .0055553    27.09   0.000     .1396129    .1613894
-------------------+----------------------------------------------------------------
22-34 years        |
               _at |
                1  |   .1232184   .0058257    21.15   0.000     .1118003    .1346365
                2  |   .1556308   .0053407    29.14   0.000     .1451631    .1660985
-------------------+----------------------------------------------------------------
35+ years          |
               _at |
                1  |   .1214512   .0053016    22.91   0.000     .1110602    .1318421
                2  |   .1401092   .0050342    27.83   0.000     .1302424    .1499761
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

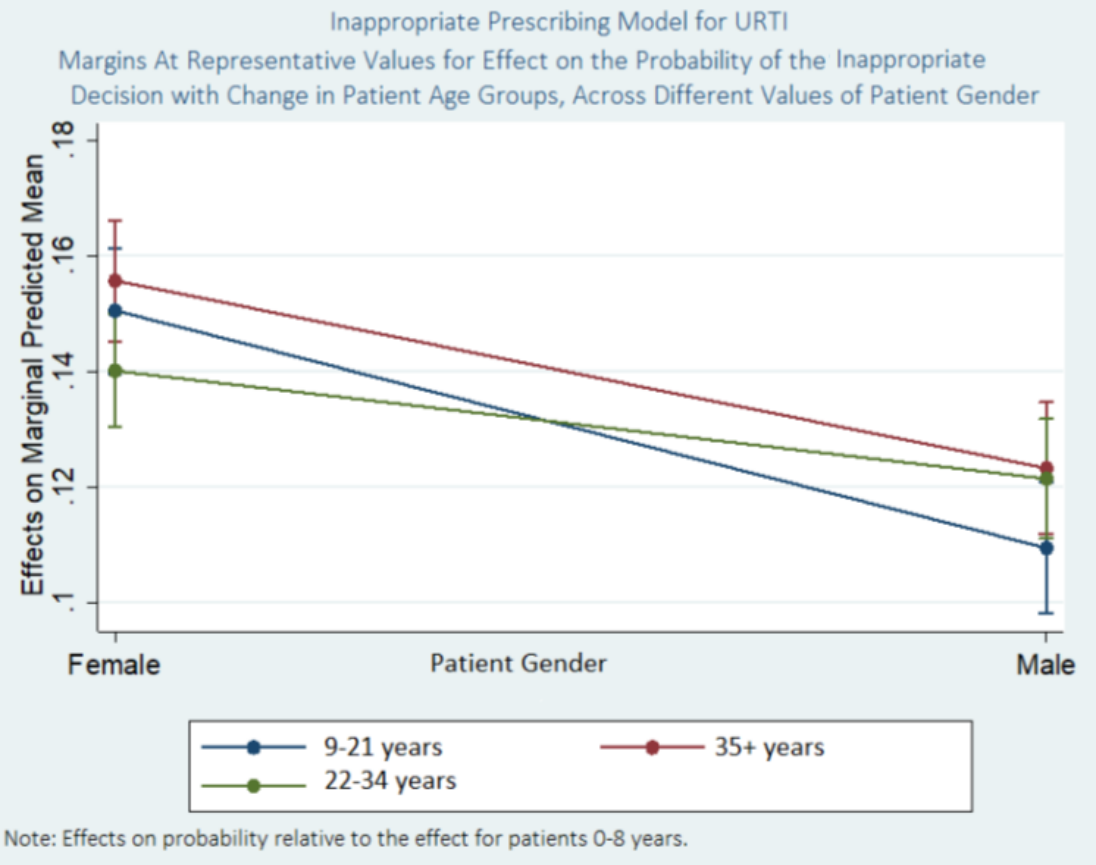


Figure C-3: Margins at representative values for the effect on the probability of inappropriate decision occurring, with change in patient age group, across different values of patient gender, relative to the probability for patients 0-8 years of age

C.5.4 Adjusted predictions for the effect on the inappropriate decision model at specific values of patient age group and patient gender

```
margins, at(pat_sex=(1 0) agegrp_urti_new=(1 2 3 4)) atmeans vsquish post

Adjusted predictions                            Number of obs     =    111,848
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
1._at        : agegrp_urti_new =           1         (0-8 years)
               pat_sex         =           1         (Male)
               0.pen_alle~y    =    .9471962 (mean)
               1.pen_alle~y    =    .0528038 (mean)
               0.pat_conc~n    =    .8303769 (mean)
               1.pat_conc~n    =    .1696231 (mean)
               1.pat_ment~A    =    .8437701 (mean)
               2.pat_ment~A    =    .1228274 (mean)
               3.pat_ment~A    =    .0334025 (mean)
               0.weekend       =    .8976557 (mean)
               1.weekend       =    .1023443 (mean)
               0.practice~w    =    .8695283 (mean)
               1.practice~w    =    .1304717 (mean)
               1.patient_~2    =    .4570489 (mean)
               2.patient_~2    =    .3342483 (mean)
               3.patient_~2    =    .1855554 (mean)
               4.patient_~2    =    .0084847 (mean)
               5.patient_~2    =    .0146628 (mean)
               1.patient_~d    =    .7830627 (mean)
               2.patient_~d    =    .0936539 (mean)
               3.patient_~d    =    .1232834 (mean)
               0.flu_s~2012    =    .9305397 (mean)
               1.flu_s~2012    =    .0694603 (mean)
               0.flu_s~2013    =    .9396592 (mean)
               1.flu_s~2013    =    .0603408 (mean)
               0.flu_s~2014    =    .9006509 (mean)
               1.flu_s~2014    =    .0993491 (mean)
               0.flu_s~2015    =    .8794256 (mean)
               1.flu_s~2015    =    .1205744 (mean)
               0.flu_s~2016    =    .8668818 (mean)
               1.flu_s~2016    =    .1331182 (mean)
               0.flu_s~2017    =    .9639868 (mean)
               1.flu_s~2017    =    .0360132 (mean)
2._at        : agegrp_urti_new =           1         (0-8 years)
               pat_sex         =           0         (Female)
               0.pen_alle~y    =    .9471962 (mean)
               1.pen_alle~y    =    .0528038 (mean)
               0.pat_conc~n    =    .8303769 (mean)
               1.pat_conc~n    =    .1696231 (mean)
               1.pat_ment~A    =    .8437701 (mean)
               2.pat_ment~A    =    .1228274 (mean)
               3.pat_ment~A    =    .0334025 (mean)
               0.weekend       =    .8976557 (mean)
               1.weekend       =    .1023443 (mean)
               0.practice~w    =    .8695283 (mean)
               1.practice~w    =    .1304717 (mean)
               1.patient_~2    =    .4570489 (mean)
               2.patient_~2    =    .3342483 (mean)
               3.patient_~2    =    .1855554 (mean)
               4.patient_~2    =    .0084847 (mean)
               5.patient_~2    =    .0146628 (mean)
               1.patient_~d    =    .7830627 (mean)
               2.patient_~d    =    .0936539 (mean)
               3.patient_~d    =    .1232834 (mean)
               0.flu_s~2012    =    .9305397 (mean)
               1.flu_s~2012    =    .0694603 (mean)
               0.flu_s~2013    =    .9396592 (mean)
               1.flu_s~2013    =    .0603408 (mean)
               0.flu_s~2014    =    .9006509 (mean)
               1.flu_s~2014    =    .0993491 (mean)
               0.flu_s~2015    =    .8794256 (mean)
               1.flu_s~2015    =    .1205744 (mean)
               0.flu_s~2016    =    .8668818 (mean)
               1.flu_s~2016    =    .1331182 (mean)
               0.flu_s~2017    =    .9639868 (mean)
               1.flu_s~2017    =    .0360132 (mean)
3._at        : agegrp_urti_new =           2         (9-21 yrs)
               pat_sex         =           1         (Male)
               0.pen_alle~y    =    .9471962 (mean)
               1.pen_alle~y    =    .0528038 (mean)
               0.pat_conc~n    =    .8303769 (mean)
               1.pat_conc~n    =    .1696231 (mean)
               1.pat_ment~A    =    .8437701 (mean)
               2.pat_ment~A    =    .1228274 (mean)
               3.pat_ment~A    =    .0334025 (mean)
               0.weekend       =    .8976557 (mean)
```

```
                  1.weekend       =    .1023443 (mean)
                  0.practice~w    =    .8695283 (mean)
                  1.practice~w    =    .1304717 (mean)
                  1.patient_~2    =    .4570489 (mean)
                  2.patient_~2    =    .3342483 (mean)
                  3.patient_~2    =    .1855554 (mean)
                  4.patient_~2    =    .0084847 (mean)
                  5.patient_~2    =    .0146628 (mean)
                  1.patient_~d    =    .7830627 (mean)
                  2.patient_~d    =    .0936539 (mean)
                  3.patient_~d    =    .1232834 (mean)
                  0.flu_s~2012    =    .9305397 (mean)
                  1.flu_s~2012    =    .0694603 (mean)
                  0.flu_s~2013    =    .9396592 (mean)
                  1.flu_s~2013    =    .0603408 (mean)
                  0.flu_s~2014    =    .9006509 (mean)
                  1.flu_s~2014    =    .0993491 (mean)
                  0.flu_s~2015    =    .8794256 (mean)
                  1.flu_s~2015    =    .1205744 (mean)
                  0.flu_s~2016    =    .8668818 (mean)
                  1.flu_s~2016    =    .1331182 (mean)
                  0.flu_s~2017    =    .9639868 (mean)
                  1.flu_s~2017    =    .0360132 (mean)
4._at           : agegrp_urti_new =           2         (9-21 yrs)
                  pat_sex         =           0         (Female)
                  0.pen_alle~y    =    .9471962 (mean)
                  1.pen_alle~y    =    .0528038 (mean)
                  0.pat_conc~n    =    .8303769 (mean)
                  1.pat_conc~n    =    .1696231 (mean)
                  1.pat_ment~A    =    .8437701 (mean)
                  2.pat_ment~A    =    .1228274 (mean)
                  3.pat_ment~A    =    .0334025 (mean)
                  0.weekend       =    .8976557 (mean)
                  1.weekend       =    .1023443 (mean)
                  0.practice~w    =    .8695283 (mean)
                  1.practice~w    =    .1304717 (mean)
                  1.patient_~2    =    .4570489 (mean)
                  2.patient_~2    =    .3342483 (mean)
                  3.patient_~2    =    .1855554 (mean)
                  4.patient_~2    =    .0084847 (mean)
                  5.patient_~2    =    .0146628 (mean)
                  1.patient_~d    =    .7830627 (mean)
                  2.patient_~d    =    .0936539 (mean)
                  3.patient_~d    =    .1232834 (mean)
                  0.flu_s~2012    =    .9305397 (mean)
                  1.flu_s~2012    =    .0694603 (mean)
                  0.flu_s~2013    =    .9396592 (mean)
                  1.flu_s~2013    =    .0603408 (mean)
                  0.flu_s~2014    =    .9006509 (mean)
                  1.flu_s~2014    =    .0993491 (mean)
                  0.flu_s~2015    =    .8794256 (mean)
                  1.flu_s~2015    =    .1205744 (mean)
                  0.flu_s~2016    =    .8668818 (mean)
                  1.flu_s~2016    =    .1331182 (mean)
                  0.flu_s~2017    =    .9639868 (mean)
                  1.flu_s~2017    =    .0360132 (mean)
5._at           : agegrp_urti_new =           3         (22-34 yrs)
                  pat_sex         =           1         (Male)
                  0.pen_alle~y    =    .9471962 (mean)
                  1.pen_alle~y    =    .0528038 (mean)
                  0.pat_conc~n    =    .8303769 (mean)
                  1.pat_conc~n    =    .1696231 (mean)
                  1.pat_ment~A    =    .8437701 (mean)
                  2.pat_ment~A    =    .1228274 (mean)
                  3.pat_ment~A    =    .0334025 (mean)
                  0.weekend       =    .8976557 (mean)
                  1.weekend       =    .1023443 (mean)
                  0.practice~w    =    .8695283 (mean)
                  1.practice~w    =    .1304717 (mean)
                  1.patient_~2    =    .4570489 (mean)
                  2.patient_~2    =    .3342483 (mean)
                  3.patient_~2    =    .1855554 (mean)
                  4.patient_~2    =    .0084847 (mean)
                  5.patient_~2    =    .0146628 (mean)
                  1.patient_~d    =    .7830627 (mean)
                  2.patient_~d    =    .0936539 (mean)
                  3.patient_~d    =    .1232834 (mean)
                  0.flu_s~2012    =    .9305397 (mean)
                  1.flu_s~2012    =    .0694603 (mean)
                  0.flu_s~2013    =    .9396592 (mean)
                  1.flu_s~2013    =    .0603408 (mean)
                  0.flu_s~2014    =    .9006509 (mean)
                  1.flu_s~2014    =    .0993491 (mean)
                  0.flu_s~2015    =    .8794256 (mean)
                  1.flu_s~2015    =    .1205744 (mean)
                  0.flu_s~2016    =    .8668818 (mean)
                  1.flu_s~2016    =    .1331182 (mean)
                  0.flu_s~2017    =    .9639868 (mean)
```

```
                  1.flu_s~2017    =    .0360132 (mean)
6._at           : agegrp_urti_new =           3          (22-34 yrs)
                  pat_sex         =           0          (Female)
                  0.pen_alle~y    =    .9471962 (mean)
                  1.pen_alle~y    =    .0528038 (mean)
                  0.pat_conc~n    =    .8303769 (mean)
                  1.pat_conc~n    =    .1696231 (mean)
                  1.pat_ment~A    =    .8437701 (mean)
                  2.pat_ment~A    =    .1228274 (mean)
                  3.pat_ment~A    =    .0334025 (mean)
                  0.weekend       =    .8976557 (mean)
                  1.weekend       =    .1023443 (mean)
                  0.practice~w    =    .8695283 (mean)
                  1.practice~w    =    .1304717 (mean)
                  1.patient_~2    =    .4570489 (mean)
                  2.patient_~2    =    .3342483 (mean)
                  3.patient_~2    =    .1855554 (mean)
                  4.patient_~2    =    .0084847 (mean)
                  5.patient_~2    =    .0146628 (mean)
                  1.patient_~d    =    .7830627 (mean)
                  2.patient_~d    =    .0936539 (mean)
                  3.patient_~d    =    .1232834 (mean)
                  0.flu_s~2012    =    .9305397 (mean)
                  1.flu_s~2012    =    .0694603 (mean)
                  0.flu_s~2013    =    .9396592 (mean)
                  1.flu_s~2013    =    .0603408 (mean)
                  0.flu_s~2014    =    .9006509 (mean)
                  1.flu_s~2014    =    .0993491 (mean)
                  0.flu_s~2015    =    .8794256 (mean)
                  1.flu_s~2015    =    .1205744 (mean)
                  0.flu_s~2016    =    .8668818 (mean)
                  1.flu_s~2016    =    .1331182 (mean)
                  0.flu_s~2017    =    .9639868 (mean)
                  1.flu_s~2017    =    .0360132 (mean)
7._at           : agegrp_urti_new =           4          (35+ yrs)
                  pat_sex         =           1          (Male)
                  0.pen_alle~y    =    .9471962 (mean)
                  1.pen_alle~y    =    .0528038 (mean)
                  0.pat_conc~n    =    .8303769 (mean)
                  1.pat_conc~n    =    .1696231 (mean)
                  1.pat_ment~A    =    .8437701 (mean)
                  2.pat_ment~A    =    .1228274 (mean)
                  3.pat_ment~A    =    .0334025 (mean)
                  0.weekend       =    .8976557 (mean)
                  1.weekend       =    .1023443 (mean)
                  0.practice~w    =    .8695283 (mean)
                  1.practice~w    =    .1304717 (mean)
                  1.patient_~2    =    .4570489 (mean)
                  2.patient_~2    =    .3342483 (mean)
                  3.patient_~2    =    .1855554 (mean)
                  4.patient_~2    =    .0084847 (mean)
                  5.patient_~2    =    .0146628 (mean)
                  1.patient_~d    =    .7830627 (mean)
                  2.patient_~d    =    .0936539 (mean)
                  3.patient_~d    =    .1232834 (mean)
                  0.flu_s~2012    =    .9305397 (mean)
                  1.flu_s~2012    =    .0694603 (mean)
                  0.flu_s~2013    =    .9396592 (mean)
                  1.flu_s~2013    =    .0603408 (mean)
                  0.flu_s~2014    =    .9006509 (mean)
                  1.flu_s~2014    =    .0993491 (mean)
                  0.flu_s~2015    =    .8794256 (mean)
                  1.flu_s~2015    =    .1205744 (mean)
                  0.flu_s~2016    =    .8668818 (mean)
                  1.flu_s~2016    =    .1331182 (mean)
                  0.flu_s~2017    =    .9639868 (mean)
                  1.flu_s~2017    =    .0360132 (mean)
8._at           : agegrp_urti_new =           4          (35+ yrs)
                  pat_sex         =           0          (Female)
                  0.pen_alle~y    =    .9471962 (mean)
                  1.pen_alle~y    =    .0528038 (mean)
                  0.pat_conc~n    =    .8303769 (mean)
                  1.pat_conc~n    =    .1696231 (mean)
                  1.pat_ment~A    =    .8437701 (mean)
                  2.pat_ment~A    =    .1228274 (mean)
                  3.pat_ment~A    =    .0334025 (mean)
                  0.weekend       =    .8976557 (mean)
                  1.weekend       =    .1023443 (mean)
                  0.practice~w    =    .8695283 (mean)
                  1.practice~w    =    .1304717 (mean)
                  1.patient_~2    =    .4570489 (mean)
                  2.patient_~2    =    .3342483 (mean)
                  3.patient_~2    =    .1855554 (mean)
                  4.patient_~2    =    .0084847 (mean)
                  5.patient_~2    =    .0146628 (mean)
                  1.patient_~d    =    .7830627 (mean)
                  2.patient_~d    =    .0936539 (mean)
                  3.patient_~d    =    .1232834 (mean)
```

```
                0.flu_s~2012    =    .9305397 (mean)
                1.flu_s~2012    =    .0694603 (mean)
                0.flu_s~2013    =    .9396592 (mean)
                1.flu_s~2013    =    .0603408 (mean)
                0.flu_s~2014    =    .9006509 (mean)
                1.flu_s~2014    =    .0993491 (mean)
                0.flu_s~2015    =    .8794256 (mean)
                1.flu_s~2015    =    .1205744 (mean)
                0.flu_s~2016    =    .8668818 (mean)
                1.flu_s~2016    =    .1331182 (mean)
                0.flu_s~2017    =    .9639868 (mean)
                1.flu_s~2017    =    .0360132 (mean)

------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         _at |
        1  M |   .3281451   .0078699    41.70   0.000     .3127205    .3435698
        1  F |    .318989   .0078286    40.75   0.000     .3036451    .3343328
        2  M |   .4383968   .0092503    47.39   0.000     .4202665     .456527
        2  F |   .4705965   .0090527    51.98   0.000     .4528536    .4883394
        3  M |   .4522684   .0092628    48.83   0.000     .4341137     .470423
        3  F |   .4757671   .0089009    53.45   0.000     .4583217    .4932125
        4  M |   .4504871   .0089128    50.54   0.000     .4330183    .4679559
        4  F |   .4601218   .0086923    52.93   0.000     .4430852    .4771584
```

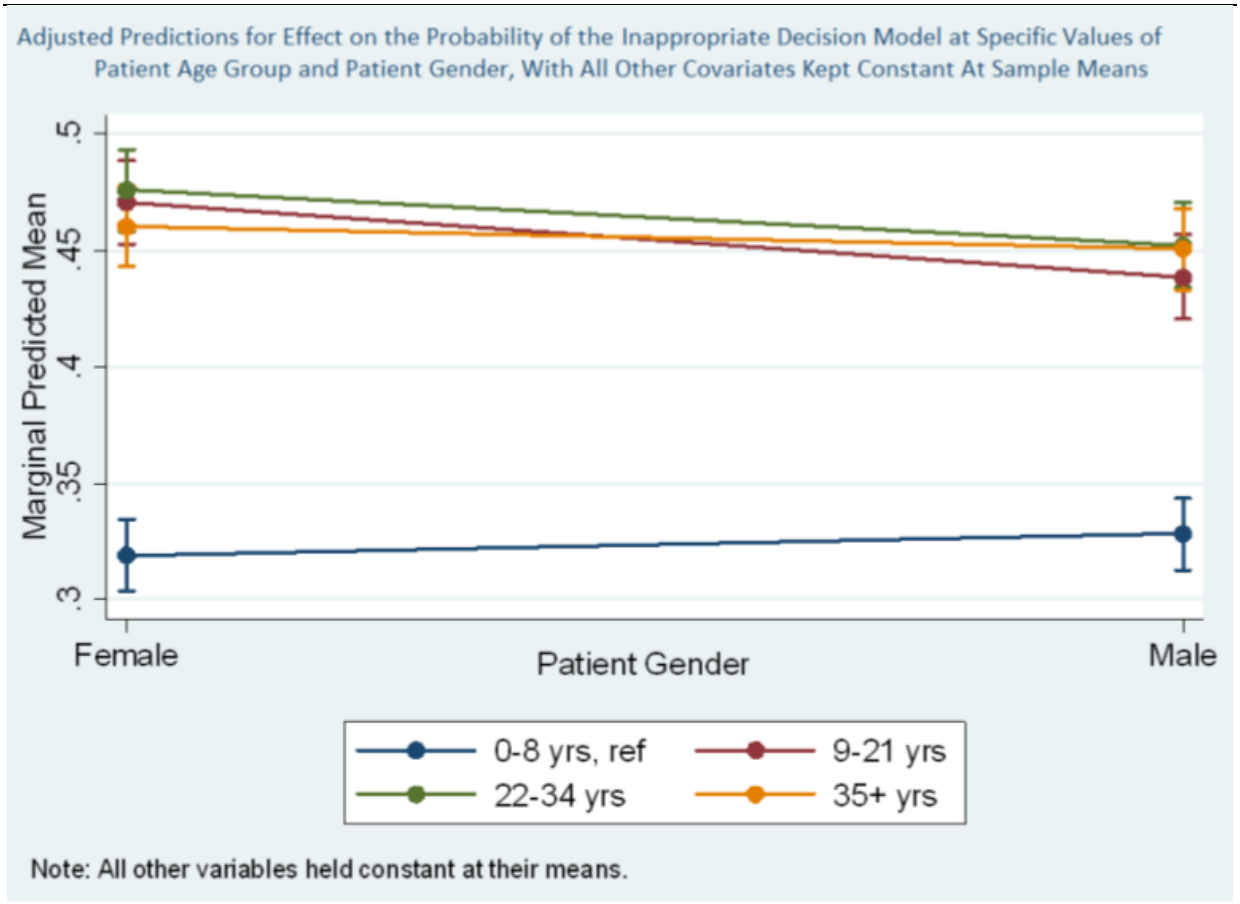


Figure C-4: Adjusted predictions for effect on the probability of the inappropriate decision model at specific values of patient age group and patient gender, with all other covariates kept constant at sample means

C.6 Marginal effects for the unnecessary antibiotic prescribing model

C.6.1 Average marginal effects

Table C-21: Average marginal effects for Model 1 – Unnecessary antibiotic prescribing for initial presentations of upper respiratory tract infection

Average Marginal Effects						
Unnecessary Antibiotic Prescribing for Initial Presentations of URTI						
Independent Variable	**dy/dx**	**Std. Err.**	**Z**	**P>z**	**[95% Conf.**	**Interval]**
Patient Age Group (ref. 0-8 years)						
9-21 yrs	0.116792	0.005048	23.14	0.000	0.106898	0.126686
22-34 yrs	0.136988	0.005517	24.83	0.000	0.126176	0.1478
35+ yrs	0.145759	0.005694	25.60	0.000	0.134599	0.156919
URTI Condition (ref. Rhinosinusitis)						
Pharyngitis / Tonsillitis	-0.04823	0.00398	-12.12	0.000	-0.05603	-0.04043
Acute Otitis Media	-0.08054	0.004419	-18.22	0.000	-0.0892	-0.07188
Ordinal Line of Antibiotic Prescribed (ref. First-line)						
Second-line	-0.01569	0.005635	-2.78	0.005	-0.02674	-0.00465
Not Recommended	0.010901	0.003105	3.51	0.000	0.004816	0.016986
Repeat Prescription Status (ref. Negative)						
Positive	-0.00818	0.003122	-2.62	0.009	-0.01429	-0.00206
Penicillin Sensitivity (ref. Negative)						
Positive	-0.01533	0.005356	-2.86	0.004	-0.02583	-0.00484
Patient Concession Status (ref. Negative)						
Positive	0.009164	0.003262	2.81	0.005	0.00277	0.015558
Patient Mental Health Condition Status (ref. Negative)						
Positive	0.01968	0.00423	4.65	0.000	0.011389	0.02797
Missing	0.01878	0.022631	0.83	0.407	-0.02558	0.063136
Patient With Multiple URTI Episodes (ref. Negative)						
Positive	-0.00852	0.002633	-3.23	0.001	-0.01368	-0.00336

C.6.2 Margins at representative values for effect on unnecessary prescribing with change in upper respiratory tract infection condition, across different levels of ordinal choice of antibiotic prescribed

```
margins, dydx(condition_urti) at (choice_urti_new = (1 2 3))

Average marginal effects                        Number of obs     =     51,210
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 2.condition_urti 3.condition_urti

1._at        : choice_urti_new =           1       (First-line)
2._at        : choice_urti_new =           2       (Second-line)
3._at        : choice_urti_new =           3       (Not Recommended)

------------------------------------------------------------------------------
                  |            Delta-method
                  |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
Rhinosinusitis    |  (base outcome)
------------------+-----------------------------------------------------------
Pharyngitis       |
             _at  |
              1   |  -.0588843   .0048901   -12.04   0.000    -.0684687   -.0492998
              2   |  -.0772112    .008473    -9.11   0.000     -.093818   -.0606045
              3   |  -.0219951   .0041466    -5.30   0.000    -.0301223   -.0138679
------------------+-----------------------------------------------------------
AOM               |
             _at  |
              1   |  -.1115931   .0062298   -17.91   0.000    -.1238032   -.0993829
              2   |  -.0322119   .0058842    -5.47   0.000    -.0437446   -.0206792
              3   |  -.0641675   .0070407    -9.11   0.000    -.0779671    -.050368
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

.
```

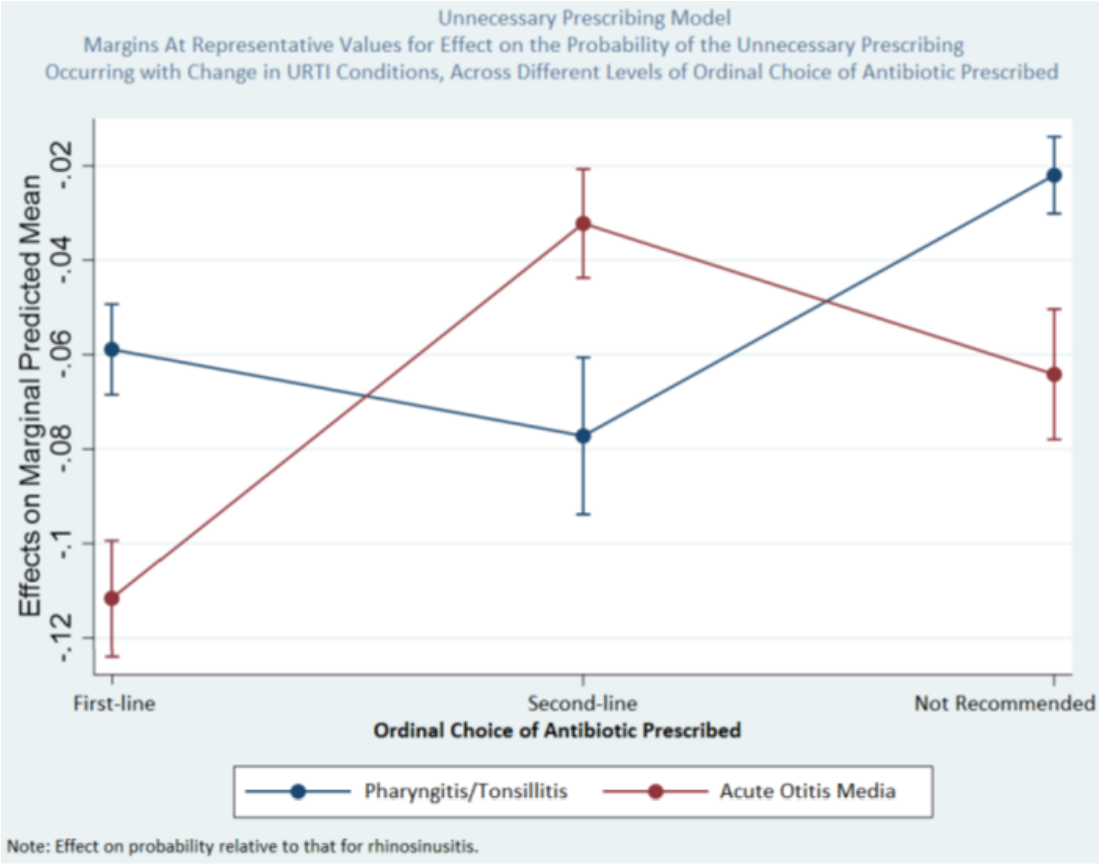


Figure C-5: Margins at representative values for effect on unnecessary prescribing occurring with change in upper respiratory tract infection condition, across different levels of ordinal choice of antibiotic prescribed, relative to the effect for unnecessary prescribing for acute rhinosinusitis

C.6.3 *Margins at representative values for the effect on unnecessary prescribing with change in ordinal choice of antibiotic prescribed, across different upper respiratory tract infection conditions*

```
. margins, dydx(choice_urti_new ) at (condition_urti = (1 2 3))

Average marginal effects                        Number of obs     =     51,210
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 2.choice_urti_new 3.choice_urti_new

1._at        : condition_urti  =           1       (Rhinosinusitis)
2._at        : condition_urti  =           2       (Pharyngitis)
3._at        : condition_urti  =           3       (AOM)

------------------------------------------------------------------------------
                    |            Delta-method
                    |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------------+---------------------------------------------------------------
First-line          |  (base outcome)
--------------------+---------------------------------------------------------------
Second-line         |
                _at |
                  1 |  -.0305784   .0051739    -5.91   0.000    -.0407191   -.0204378
                  2 |  -.0489054   .0092185    -5.31   0.000    -.0669733   -.0308376
                  3 |   .0488027    .006521     7.48   0.000     .0360217    .0615837
--------------------+---------------------------------------------------------------
Not Recommended     |
                _at |
                  1 |  -.0157176   .0044062    -3.57   0.000    -.0243537   -.0070815
                  2 |   .0211716   .0044459     4.76   0.000     .0124579    .0298854
                  3 |   .0317079   .0076216     4.16   0.000     .0167699    .0466459
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

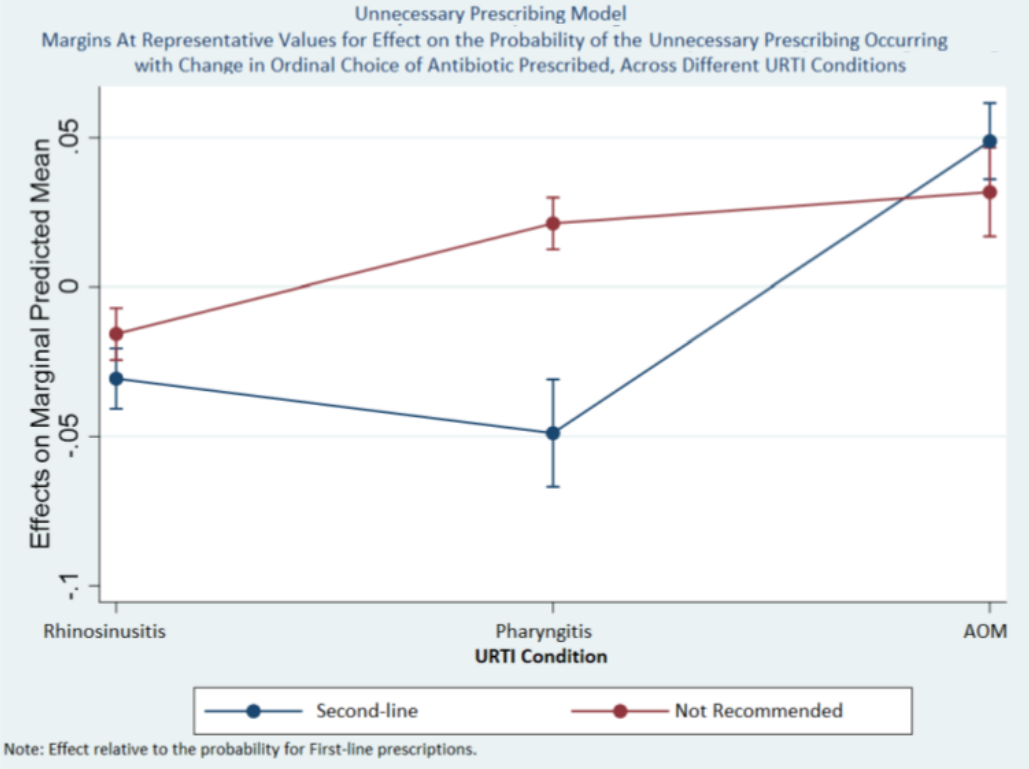


Figure C-6: Margins at representative values for the effect on the probability of unnecessary prescribing occurring, with change in ordinal choice of antibiotic prescribed, across different upper respiratory tract infection conditions, relative to the effect on the probability of unnecessary prescribing for first-line prescriptions

C.6.4 Predictive margins for the effect on unnecessary prescribing, at specific values of patient age group and upper respiratory tract infection conditions

```
. margins, at(condition_urti==(1 2 3) agegrp_urti_new==(1 2 3 4))

Predictive margins                              Number of obs     =     51,210
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()

1._at        : agegrp_urti_new =           1       (0-8 yrs)
               condition_urti  =           1       (Rhinosinusitis)

2._at        : agegrp_urti_new =           1       (0-8 yrs)
               condition_urti  =           2       (Pharyngitis)

3._at        : agegrp_urti_new =           1       (0-8 yrs)
               condition_urti  =           3       (AOM)

4._at        : agegrp_urti_new =           2       (9-21 yrs)
               condition_urti  =           1       (Rhinosinusitis)

5._at        : agegrp_urti_new =           2       (9-21 yrs)
               condition_urti  =           2       (Pharyngitis)

6._at        : agegrp_urti_new =           2       (9-21 yrs)
               condition_urti  =           3       (AOM_

7._at        : agegrp_urti_new =           3       (22-34 yrs)
               condition_urti  =           1       (Rhinosinusitis)

8._at        : agegrp_urti_new =           3       (22-34 yrs)
               condition_urti  =           2       (Pharyngitis)

9._at        : agegrp_urti_new =           3       (22-34 yrs)
               condition_urti  =           3       (AOM)

10._at       : agegrp_urti_new =           4       (35+ yrs)
               condition_urti  =           1       (Rhinosinusitis)

11._at       : agegrp_urti_new =           4       (35+ yrs)
               condition_urti  =           2       (Pharyngitis)

12._at       : agegrp_urti_new =           4       (35+ yrs)
               condition_urti  =           3       (AOM)

------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         _at |
          1  |   .8539329   .0070318   121.44   0.000      .840151    .8677149
          2  |   .7752567   .0090823    85.36   0.000     .7574558    .7930576
          3  |   .7253208   .0097771    74.19   0.000      .706158    .7444836
          4  |     .94353   .0036783   256.51   0.000     .9363206    .9507394
          5  |   .9040771   .0053585   168.72   0.000     .8935746    .9145796
          6  |   .8766895   .0066338   132.15   0.000     .8636874    .8896916
          7  |   .9578739   .0029056   329.67   0.000     .9521791    .9635688
          8  |   .9268393   .0044543   208.08   0.000     .9181091    .9355695
          9  |   .9048698   .0056731   159.50   0.000     .8937506    .9159889
         10  |    .963977   .0024899   387.15   0.000     .9590968    .9688572
         11  |   .9367782   .0039846   235.10   0.000     .9289685     .944588
         12  |   .9173445   .0050343   182.22   0.000     .9074774    .9272116
```

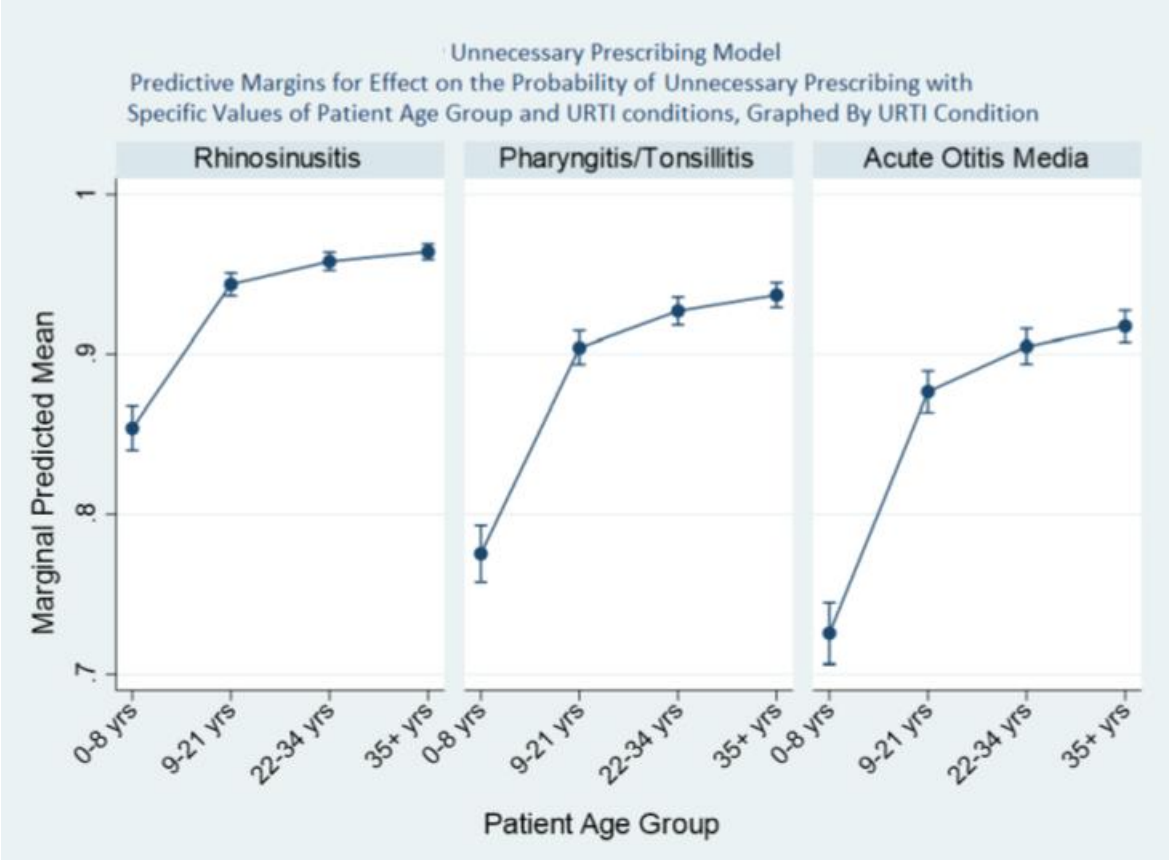


Figure C-7: Predictive margins for the effect on the probability of unnecessary prescribing with specific values of patient age group and upper respiratory tract infection condition, graphed by upper respiratory tract infection condition

C.6.5 Adjusted predictions for the effect on unnecessary prescribing, at specific values of upper respiratory trat infection condition and ordinal choice of antibiotic prescribed

The results below provide adjusted predictions for the effect on the probability of unnecessary prescribing occurring, at specific values of upper respiratory trat infection condition and ordinal choice of antibiotic prescribed, with all other covariates kept constant at sample means

```
margins, at(condition_urti=(1 2 3) choice_urti_new=(1 2 3)) atmeans vsquish post

Adjusted predictions                              Number of obs     =     51,210
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
1._at        : 1.agegrp_u~w    =    .3303456 (mean)
               2.agegrp_u~w    =     .190041 (mean)
               3.agegrp_u~w    =    .2083968 (mean)
               4.agegrp_u~w    =    .2712166 (mean)
               condition_urti  =           1                (Rhinosinusitis)
               choice_urti_new =           1                (First-line)
               0.repeat_s~t    =    .6772115 (mean)
               1.repeat_s~t    =    .3227885 (mean)
               0.pen_alle~y    =    .9357743 (mean)
               1.pen_alle~y    =    .0642257 (mean)
               0.pat_conc~n    =    .8294669 (mean)
               1.pat_conc~n    =    .1705331 (mean)
               1.pat_ment~A    =    .8341925 (mean)
               2.pat_ment~A    =    .1268893 (mean)
               3.pat_ment~A    =    .0389182 (mean)
               0.multip~RTI    =    .2286663 (mean)
               1.multip~RTI    =    .7713337 (mean)
               0.flu_s~2012    =     .923472 (mean)
               1.flu_s~2012    =     .076528 (mean)
               0.flu_s~2013    =    .9305019 (mean)
               1.flu_s~2013    =    .0694981 (mean)
```

```
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)


2._at         : 1.agegrp_u~w    =    .3303456 (mean)
                2.agegrp_u~w    =     .190041 (mean)
                3.agegrp_u~w    =    .2083968 (mean)
                4.agegrp_u~w    =    .2712166 (mean)
                condition_urti  =           1                (Rhinosinusitis)
                choice_urti_new =           2                (Second-line)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                0.pen_alle~y    =    .9357743 (mean)
                1.pen_alle~y    =    .0642257 (mean)
                0.pat_conc~n    =    .8294669 (mean)
                1.pat_conc~n    =    .1705331 (mean)
                1.pat_ment~A    =    .8341925 (mean)
                2.pat_ment~A    =    .1268893 (mean)
                3.pat_ment~A    =    .0389182 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
3._at         : 1.agegrp_u~w    =    .3303456 (mean)
                2.agegrp_u~w    =     .190041 (mean)
                3.agegrp_u~w    =    .2083968 (mean)
                4.agegrp_u~w    =    .2712166 (mean)
                condition_urti  =           1                (Rhinosinusitis)
                choice_urti_new =           3                (Not Recommended)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                0.pen_alle~y    =    .9357743 (mean)
                1.pen_alle~y    =    .0642257 (mean)
                0.pat_conc~n    =    .8294669 (mean)
                1.pat_conc~n    =    .1705331 (mean)
                1.pat_ment~A    =    .8341925 (mean)
                2.pat_ment~A    =    .1268893 (mean)
                3.pat_ment~A    =    .0389182 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
4._at         : 1.agegrp_u~w    =    .3303456 (mean)
                2.agegrp_u~w    =     .190041 (mean)
                3.agegrp_u~w    =    .2083968 (mean)
                4.agegrp_u~w    =    .2712166 (mean)
                condition_urti  =           2                (Pharyngitis)
                choice_urti_new =           1                (First-line)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                0.pen_alle~y    =    .9357743 (mean)
                1.pen_alle~y    =    .0642257 (mean)
                0.pat_conc~n    =    .8294669 (mean)
                1.pat_conc~n    =    .1705331 (mean)
                1.pat_ment~A    =    .8341925 (mean)
                2.pat_ment~A    =    .1268893 (mean)
                3.pat_ment~A    =    .0389182 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
5._at         : 1.agegrp_u~w    =    .3303456 (mean)
                2.agegrp_u~w    =     .190041 (mean)
                3.agegrp_u~w    =    .2083968 (mean)
                4.agegrp_u~w    =    .2712166 (mean)
```

```
                condition_urti  =           2               (Pharyngitis)
                choice_urti_new =           2               (Second-line)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                0.pen_alle~y    =    .9357743 (mean)
                1.pen_alle~y    =    .0642257 (mean)
                0.pat_conc~n    =    .8294669 (mean)
                1.pat_conc~n    =    .1705331 (mean)
                1.pat_ment~A    =    .8341925 (mean)
                2.pat_ment~A    =    .1268893 (mean)
                3.pat_ment~A    =    .0389182 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
6._at           : 1.agegrp_u~w  =    .3303456 (mean)
                  2.agegrp_u~w  =     .190041 (mean)
                  3.agegrp_u~w  =    .2083968 (mean)
                  4.agegrp_u~w  =    .2712166 (mean)
                condition_urti  =           2               (Pharyngitis)
                choice_urti_new =           3               (Not Raecommended)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                0.pen_alle~y    =    .9357743 (mean)
                1.pen_alle~y    =    .0642257 (mean)
                0.pat_conc~n    =    .8294669 (mean)
                1.pat_conc~n    =    .1705331 (mean)
                1.pat_ment~A    =    .8341925 (mean)
                2.pat_ment~A    =    .1268893 (mean)
                3.pat_ment~A    =    .0389182 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
7._at           : 1.agegrp_u~w  =    .3303456 (mean)
                  2.agegrp_u~w  =     .190041 (mean)
                  3.agegrp_u~w  =    .2083968 (mean)
                  4.agegrp_u~w  =    .2712166 (mean)
                condition_urti  =           3               (AOM)
                choice_urti_new =           1               (First-line)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                0.pen_alle~y    =    .9357743 (mean)
                1.pen_alle~y    =    .0642257 (mean)
                0.pat_conc~n    =    .8294669 (mean)
                1.pat_conc~n    =    .1705331 (mean)
                1.pat_ment~A    =    .8341925 (mean)
                2.pat_ment~A    =    .1268893 (mean)
                3.pat_ment~A    =    .0389182 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
8._at           : 1.agegrp_u~w  =    .3303456 (mean)
                  2.agegrp_u~w  =     .190041 (mean)
                  3.agegrp_u~w  =    .2083968 (mean)
                  4.agegrp_u~w  =    .2712166 (mean)
                condition_urti  =           3               (AOM)
                choice_urti_new =           2               (Second-line)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                0.pen_alle~y    =    .9357743 (mean)
                1.pen_alle~y    =    .0642257 (mean)
                0.pat_conc~n    =    .8294669 (mean)
                1.pat_conc~n    =    .1705331 (mean)
                1.pat_ment~A    =    .8341925 (mean)
                2.pat_ment~A    =    .1268893 (mean)
                3.pat_ment~A    =    .0389182 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
```

```
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
9._at         : 1.agegrp_u~w    =    .3303456 (mean)
                2.agegrp_u~w    =     .190041 (mean)
                3.agegrp_u~w    =    .2083968 (mean)
                4.agegrp_u~w    =    .2712166 (mean)
                condition_urti  =           3                (AOM)
                choice_urti_new =           3                (Not Recommended)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                0.pen_alle~y    =    .9357743 (mean)
                1.pen_alle~y    =    .0642257 (mean)
                0.pat_conc~n    =    .8294669 (mean)
                1.pat_conc~n    =    .1705331 (mean)
                1.pat_ment~A    =    .8341925 (mean)
                2.pat_ment~A    =    .1268893 (mean)
                3.pat_ment~A    =    .0389182 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)

------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         _at |
          1  |   .9447867   .0040706   232.10   0.000     .9368084    .9527651
          2  |   .9168631   .0053206   172.32   0.000     .9064348    .9272913
          3  |   .9305799   .0043667   213.11   0.000     .9220213    .9391385
          4  |   .8900707   .0055216   161.20   0.000     .8792485    .9008929
          5  |    .842106   .0115252    73.07   0.000     .8195171     .864695
          6  |   .9101885   .0049888   182.45   0.000     .9004105    .9199664
          7  |   .8383023   .0076615   109.42   0.000      .823286    .8533185
          8  |    .886312   .0066989   132.31   0.000     .8731824    .8994415
          9  |   .8697051   .0080933   107.46   0.000     .8538425    .8855676
------------------------------------------------------------------------------
```

C.7 Marginal effects for the ordinal choice of antibiotic prescribing model for upper respiratory tract infection

C.7.1 Average marginal effects

Table C-22: Average marginal effects for Model 2 – Ordinal choice of antibiotic prescribed for initial presentations of upper respiratory tract infection

Average Marginal Effects						
Ordinal Choice of Antibiotic Prescribed for Initial Presentations of URTI						
Independent Variable	**dy/dx**	**Std. Err.**	**z**	**P>z**	**[95% Conf.**	**Interval]**
Patient Age Group						
0-8 years	(base outcome)					
9-21 years (predict outcome:)						
First-line	-0.02193	0.0053762	-4.08	0.000	-0.03247	-0.01139
Second-line	0.002669	0.0006873	3.88	0.000	0.001321	0.004016
Not Recommended	0.01926	0.004797	4.01	0.000	0.009858	0.028662
22-34 years (predict outcome:)						
First-line	-0.05306	0.0053765	-9.87	0.000	-0.0636	-0.04253
Second-line	0.003753	0.0008168	4.60	0.000	0.002153	0.005354
Not Recommended	0.049309	0.0049305	10.00	0.000	0.039646	0.058973
35 and over years (predict outcome:)						
First-line	-0.09071	0.0052159	-17.39	0.000	-0.10093	-0.08049
Second-line	0.007518	0.0010344	7.27	0.000	0.005491	0.009546
Not Recommended	0.083193	0.0048919	17.01	0.000	0.073605	0.092781
Repeat on Prescription Status						
Negative	(base outcome)					
Positive (predict outcome:)						
First-line	-0.08096	0.0045827	-17.67	0.000	-0.08994	-0.07198
Second-line	0.003572	0.000923	3.87	0.000	0.001763	0.005381
Not Recommended	0.07739	0.0043861	17.64	0.000	0.068793	0.085987
URTI Condition						
Rhinosinusitis	(base outcome)					
Pharyngitis (predict outcome:)						
First-line	-0.02184	0.004738	-4.61	0.000	-0.03113	-0.01255
Second-line	0.002264	0.0004291	5.28	0.000	0.001423	0.003105
Not Recommended	0.019576	0.004438	4.41	0.000	0.010878	0.028274
AOM (predict outcome:)						
First-line	0.083715	0.0053492	15.65	0.000	0.073231	0.094199
Second-line	-0.00988	0.0010621	-9.30	0.000	-0.01196	-0.0078
Not Recommended	-0.07384	0.0047432	-15.57	0.000	-0.08313	-0.06454
Unnecessary / Necessary Prescription Status						
Necessary	(base outcome)					
Unnecessary (predict outcome:)						
First-line	-0.02229	0.0054337	-4.10	0.000	-0.03294	-0.01164
Second-line	0.002119	0.0006078	3.49	0.000	0.000928	0.00331
Not Recommended	0.020171	0.0048703	4.14	0.000	0.010626	0.029717

1

Average Marginal Effects continued						
Ordinal Choice of Antibiotic Prescribed for Initial Presentations of URTI						
Independent Variable	**dy/dx**	**Std. Err.**	**z**	**P>z**	**[95% Conf.**	**Interval]**
Patient with Multiple URTI Episodes						
Negative	(base outcome)					
Positive (predict outcome:)						
First-line	0.01317	0.004314	3.05	0.002	0.004715	0.021625
Second-line	-0.00109	0.0003615	-3.01	0.003	-0.0018	-0.00038
Not Recommended	-0.01208	0.0039783	-3.04	0.002	-0.01988	-0.00428
Practice Size						
Medium / Large	(base outcome)					
Small (predict outcome:)						
First-line	-0.10974	0.028583	-3.84	0.000	-0.16576	-0.05372
Second-line	0.004687	0.0011485	4.08	0.000	0.002436	0.006938
Not Recommended	0.105054	0.0287724	3.65	0.000	0.048661	0.161446
Reason for Prescribing Recorded						
Negative	(base outcome)					
Positive (predict outcome:)						
First-line	0.073287	0.0136648	5.36	0.000	0.046504	0.10007
Second-line	-0.0085	0.0019784	-4.30	0.000	-0.01238	-0.00462
Not Recommended	-0.06479	0.0118295	-5.48	0.000	-0.08797	-0.0416
Patient Disadvantage Status						
Negative	(base outcome)					
Positive (predict outcome:)						
First-line	0.019428	0.008003	2.43	0.015	0.003742	0.035113
Second-line	-0.00178	0.0008149	-2.19	0.029	-0.00338	-0.00019
Not Recommended	-0.01764	0.007213	-2.45	0.014	-0.03178	-0.00351
Missing (predict outcome:)						
First-line	0.026192	0.0077608	3.37	0.001	0.010982	0.041403
Second-line	-0.0025	0.0008479	-2.94	0.003	-0.00416	-0.00083
Not Recommended	-0.0237	0.0069567	-3.41	0.001	-0.03733	-0.01006
Patient Comorbid Condition Status						
Negative	(base outcome)					
Positive (predict outcome:)						
First-line	-0.02684	0.0049631	-5.41	0.000	-0.03657	-0.01712
Second-line	0.002104	0.0004388	4.79	0.000	0.001244	0.002964
Not Recommended	0.02474	0.0046253	5.35	0.000	0.015674	0.033805
Missing (predict outcome:)						
First-line	-0.03914	0.0494152	-0.79	0.428	-0.13599	0.05771
Second-line	0.002809	0.0026093	1.08	0.282	-0.00231	0.007923
Not Recommended	0.036333	0.046837	0.78	0.438	-0.05547	0.128132

2

C.7.2 Margins at representative values for effect on ordinal choice of antibiotic, with change in upper respiratory tract infection condition, across different values of patient age group

```
. margins, dydx(condition_urti) at (agegrp_urti_new = (1 2 3 4))

Average marginal effects                        Number of obs     =     51,210
Model VCE    : OIM

dy/dx w.r.t. : 2.condition_urti 3.condition_urti
1._predict   : Marginal predicted mean (1.choice_urti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_urti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_urti_new), predict(pr outcome(3))

1._at        : agegrp_urti_new =           1       (0-8 yrs)
2._at        : agegrp_urti_new =           2       (9-21 yrs)
3._at        : agegrp_urti_new =           3       (22-34 yrs)
4._at        : agegrp_urti_new =           4       (35+ yrs)

------------------------------------------------------------------------------
                  |            Delta-method
                  |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------------
Rhinosinusitis    |  (base outcome)
------------------+-----------------------------------------------------------------
Pharyngitis       |
     _predict#_at |
             1 1  |  -.0814757   .0078084   -10.43   0.000    -.0967798   -.0661716
             1 2  |    .017714   .0088954     1.99   0.046     .0002793    .0351487
             1 3  |   .0273729   .0083436     3.28   0.001     .0110198    .0437261
             1 4  |   -.014731   .0079023    -1.86   0.062    -.0302192    .0007572
             2 1  |    .008146   .0011457     7.11   0.000     .0059005    .0103915
             2 2  |  -.0015345    .000794    -1.93   0.053    -.0030907    .0000217
             2 3  |  -.0014387   .0005393    -2.67   0.008    -.0024957   -.0003817
             2 4  |   .0000692   .0001728     0.40   0.689    -.0002696     .000408
             3 1  |   .0733297   .0071258    10.29   0.000     .0593634     .087296
             3 2  |  -.0161795   .0081277    -1.99   0.047    -.0321095   -.0002495
             3 3  |  -.0259342   .0079004    -3.28   0.001    -.0414187   -.0104497
             3 4  |   .0146618   .0078884     1.86   0.063    -.0007992    .0301228
------------------+-----------------------------------------------------------------
AOM               |
     _predict#_at |
             1 1  |   .0830478   .0053406    15.55   0.000     .0725804    .0935152
             1 2  |   .0844255   .0053775    15.70   0.000     .0738858    .0949651
             1 3  |   .0837281   .0053308    15.71   0.000     .0732798    .0941763
             1 4  |   .0845293    .005402    15.65   0.000     .0739415     .095117
             2 1  |  -.0151681   .0012548   -12.09   0.000    -.0176276   -.0127087
             2 2  |   -.010221   .0011647    -8.78   0.000    -.0125037   -.0079382
             2 3  |   -.006916   .0010819    -6.39   0.000    -.0090365   -.0047955
             2 4  |  -.0052206   .0010477    -4.98   0.000    -.0072741   -.0031672
             3 1  |  -.0678797    .004497   -15.09   0.000    -.0766937   -.0590656
             3 2  |  -.0742045   .0047971   -15.47   0.000    -.0836066   -.0648024
             3 3  |  -.0768121   .0048766   -15.75   0.000    -.0863701   -.0672541
             3 4  |  -.0793086   .0050251   -15.78   0.000    -.0891576   -.0694597
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

  Variables that uniquely identify margins: agegrp_urti_new _deriv.
```

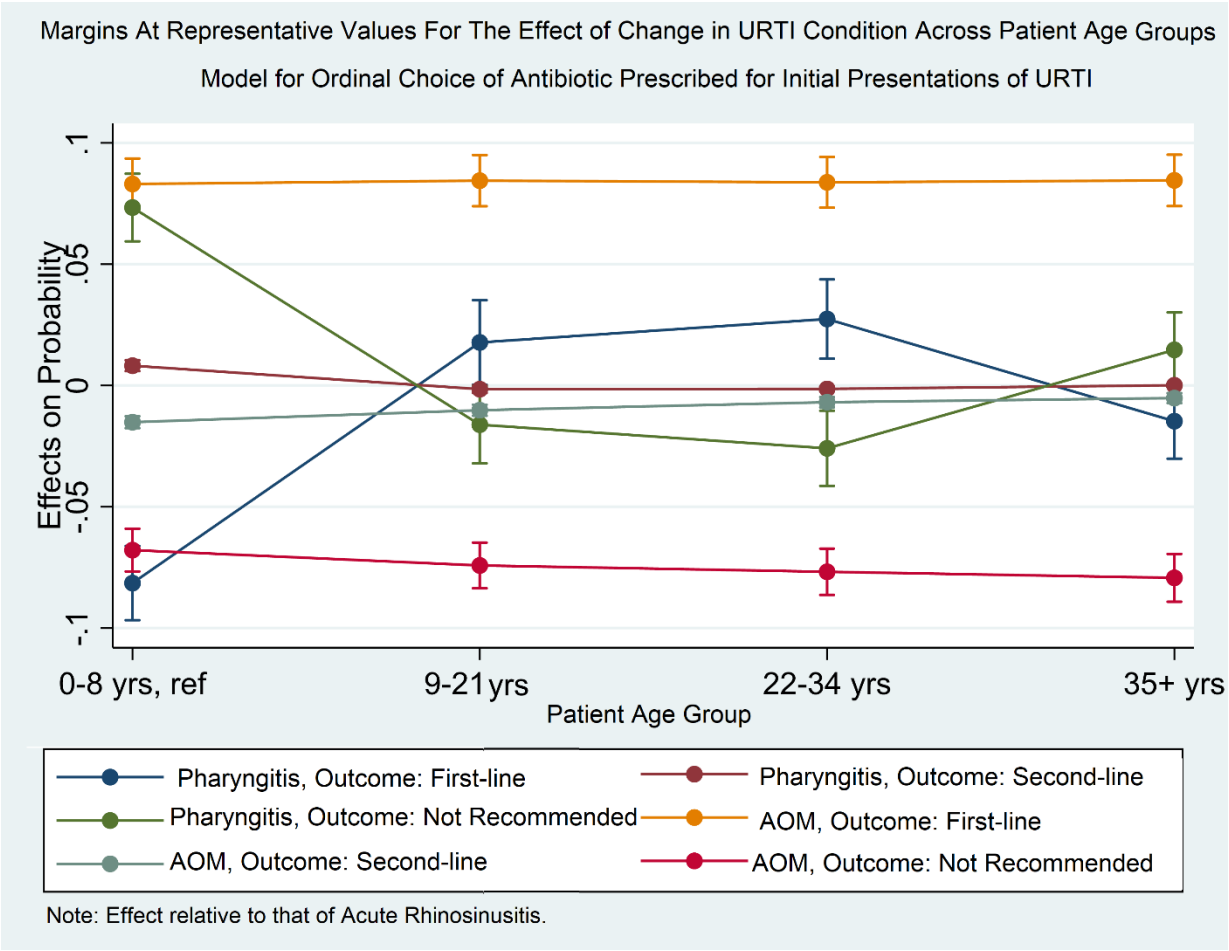


Figure C-8: Margins at representative values for the effect on the probability of each of the three outcomes of ordinal choice of antibiotic occurring, with change upper respiratory tract infection condition, across different values of patient age group, relative to the effect on the probability for acute rhinosinusitis

C.7.3 *Margins at representative values for the effect on ordinal choice of antibiotic prescribed, with change in repeat prescription status, across different values of patient age group*

```
. margins, dydx(repeat_script) at (agegrp_urti_new = (1 2 3 4))


Average marginal effects                        Number of obs     =     51,210
Model VCE    : OIM

dy/dx w.r.t. : 1.repeat_script
1._predict   : Marginal predicted mean (1.choice_urti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_urti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_urti_new), predict(pr outcome(3))

1._at        : agegrp_urti_new =           1       (0-8 yrs)
2._at        : agegrp_urti_new =           2       (9-21 yrs)
3._at        : agegrp_urti_new =           3       (22-34 yrs)
4._at        : agegrp_urti_new =           4       (35+ yrs)
------------------------------------------------------------------------------
                 |            Delta-method
                 |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------------+------------------------------------------------------------
Repeat Negative  |  (base outcome)
-----------------+------------------------------------------------------------
Repeat Positive  |
    _predict#_at |
           1 1   |  -.0251682   .0070771    -3.56   0.000    -.0390391   -.0112972
           1 2   |  -.1013548   .0091816   -11.04   0.000    -.1193504   -.0833591
           1 3   |  -.1518811   .0090275   -16.82   0.000    -.1695747   -.1341874
           1 4   |  -.0811675   .0071969   -11.28   0.000    -.0952731   -.0670618
           2 1   |   .0030207   .0008593     3.52   0.000     .0013366    .0047049
           2 2   |    .008598   .0012773     6.73   0.000     .0060945    .0111014
           2 3   |   .0059619   .0017248     3.46   0.001     .0025813    .0093425
           2 4   |    .000867   .0009336     0.93   0.353    -.0009628    .0026969
           3 1   |   .0221474   .0062626     3.54   0.000     .0098729    .0344219
           3 2   |   .0927568    .008617    10.76   0.000     .0758679    .1096457
           3 3   |   .1459192   .0090515    16.12   0.000     .1281786    .1636598
           3 4   |   .0803004   .0072428    11.09   0.000     .0661048     .094496
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

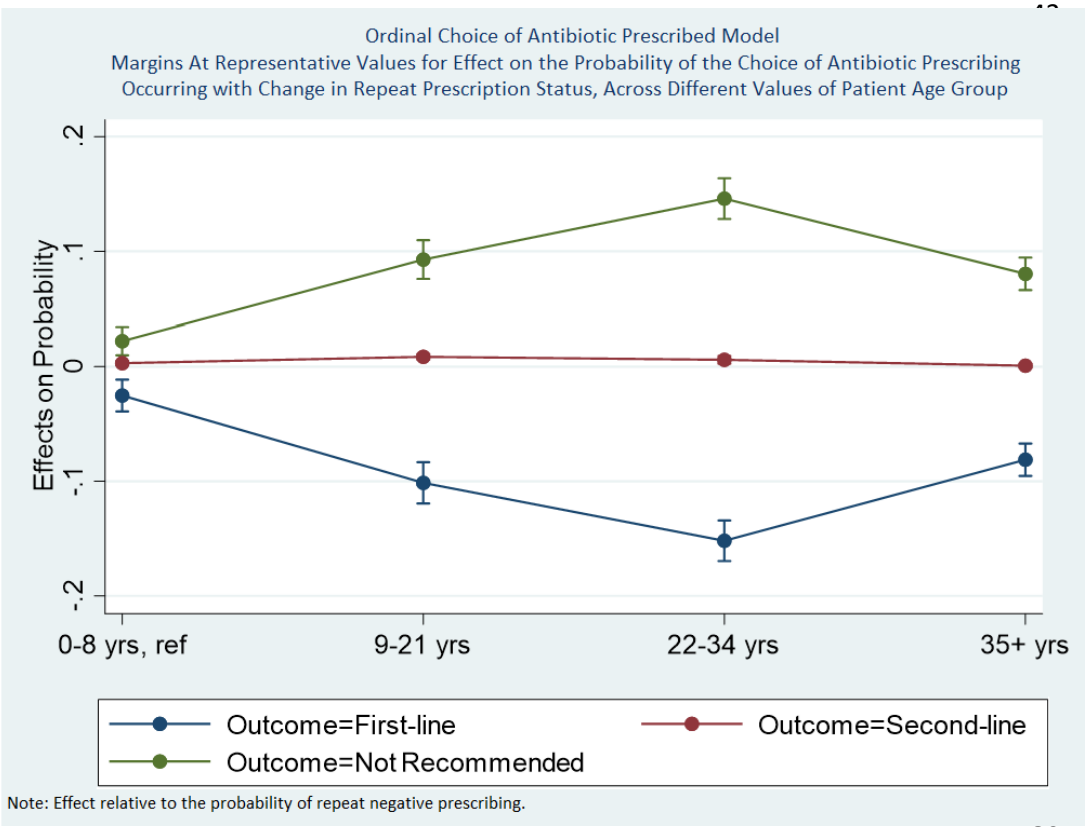


Figure C-9: Margins at representative values for the effect on the probability of each of the three outcomes of ordinal choice occurring, with change in repeat prescription status, across different values of patient age group, relative to the effect on the probability for prescriptions issued without repeats

C.7.4 Adjusted predictions for the effect on ordinal choice of antibiotic, at specific values of patient age group and upper respiratory tract infection condition

The results below provide the adjusted predictions for the effect on the probability of each of the three outcomes of ordinal choice of antibiotic occurring, at specific values of patient age group and upper respiratory tract infection condition, with all other covariates held constant at sample means.

```
margins, at(condition_urti=(1 2 3) agegrp_urti_new=(1 2 3 4)) atmeans vsquish post

Adjusted predictions                            Number of obs     =     51,210
Model VCE    : OIM

1._predict   : Marginal predicted mean (1.choice_urti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_urti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_urti_new), predict(pr outcome(3))
1._at        : agegrp_urti_new =           1                   (0-8 yrs)
               0.repeat_s~t    =    .6772115 (mean)
               1.repeat_s~t    =    .3227885 (mean)
               condition_urti  =           1                   (Rhinosinusitis)
               0.de~n_presc    =    .1418473 (mean)
               1.de~n_presc    =    .8581527 (mean)
               0.multip~RTI    =    .2286663 (mean)
               1.multip~RTI    =    .7713337 (mean)
               0.practice~w    =    .8670963 (mean)
               1.practice~w    =    .1329037 (mean)
               0.reason_r~d    =    .8835188 (mean)
               1.reason_r~d    =    .1164812 (mean)
               1.patient_~d    =    .7948252 (mean)
               2.patient_~d    =    .0884983 (mean)
               3.patient_~d    =    .1166764 (mean)
               0.pat_co~rti    =    .8081625 (mean)
               1.pat_co~rti    =    .1529194 (mean)
               2.pat_co~rti    =    .0389182 (mean)
               0.flu_s~2012    =     .923472 (mean)
               1.flu_s~2012    =     .076528 (mean)
               0.flu_s~2013    =    .9305019 (mean)
               1.flu_s~2013    =    .0694981 (mean)
               0.flu_s~2014    =           .9 (mean)
               1.flu_s~2014    =           .1 (mean)
               0.flu_s~2015    =    .8825425 (mean)
               1.flu_s~2015    =    .1174575 (mean)
               0.flu_s~2016    =    .8798477 (mean)
               1.flu_s~2016    =    .1201523 (mean)
               0.flu_s~2017    =     .973306 (mean)
               1.flu_s~2017    =     .026694 (mean)
2._at        : agegrp_urti_new =           1                   (0-8 yrs)
               0.repeat_s~t    =    .6772115 (mean)
               1.repeat_s~t    =    .3227885 (mean)
               condition_urti  =           2                   (Pharyngitis)
               0.de~n_presc    =    .1418473 (mean)
               1.de~n_presc    =    .8581527 (mean)
               0.multip~RTI    =    .2286663 (mean)
               1.multip~RTI    =    .7713337 (mean)
               0.practice~w    =    .8670963 (mean)
               1.practice~w    =    .1329037 (mean)
               0.reason_r~d    =    .8835188 (mean)
               1.reason_r~d    =    .1164812 (mean)
               1.patient_~d    =    .7948252 (mean)
               2.patient_~d    =    .0884983 (mean)
               3.patient_~d    =    .1166764 (mean)
               0.pat_co~rti    =    .8081625 (mean)
               1.pat_co~rti    =    .1529194 (mean)
               2.pat_co~rti    =    .0389182 (mean)
               0.flu_s~2012    =     .923472 (mean)
               1.flu_s~2012    =     .076528 (mean)
               0.flu_s~2013    =    .9305019 (mean)
               1.flu_s~2013    =    .0694981 (mean)
               0.flu_s~2014    =           .9 (mean)
               1.flu_s~2014    =           .1 (mean)
               0.flu_s~2015    =    .8825425 (mean)
               1.flu_s~2015    =    .1174575 (mean)
               0.flu_s~2016    =    .8798477 (mean)
               1.flu_s~2016    =    .1201523 (mean)
               0.flu_s~2017    =     .973306 (mean)
               1.flu_s~2017    =     .026694 (mean)
3._at        : agegrp_urti_new =           1                   (0-8 yrs)
               0.repeat_s~t    =    .6772115 (mean)
               1.repeat_s~t    =    .3227885 (mean)
               condition_urti  =           3                   (AOM)
               0.de~n_presc    =    .1418473 (mean)
               1.de~n_presc    =    .8581527 (mean)
               0.multip~RTI    =    .2286663 (mean)
               1.multip~RTI    =    .7713337 (mean)
               0.practice~w    =    .8670963 (mean)
               1.practice~w    =    .1329037 (mean)
               0.reason_r~d    =    .8835188 (mean)
               1.reason_r~d    =    .1164812 (mean)
               1.patient_~d    =    .7948252 (mean)
               2.patient_~d    =    .0884983 (mean)
               3.patient_~d    =    .1166764 (mean)
               0.pat_co~rti    =    .8081625 (mean)
```

```
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
4._at           : agegrp_urti_new =          2                (9-21 yrs)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                condition_urti  =          1                (Rhinosinusitis)
                0.de~n_presc    =    .1418473 (mean)
                1.de~n_presc    =    .8581527 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.practice~w    =    .8670963 (mean)
                1.practice~w    =    .1329037 (mean)
                0.reason_r~d    =    .8835188 (mean)
                1.reason_r~d    =    .1164812 (mean)
                1.patient_~d    =    .7948252 (mean)
                2.patient_~d    =    .0884983 (mean)
                3.patient_~d    =    .1166764 (mean)
                0.pat_co~rti    =    .8081625 (mean)
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
5._at           : agegrp_urti_new =          2                (9-21 yrs)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                condition_urti  =          2                (Pharyngitis)
                0.de~n_presc    =    .1418473 (mean)
                1.de~n_presc    =    .8581527 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.practice~w    =    .8670963 (mean)
                1.practice~w    =    .1329037 (mean)
                0.reason_r~d    =    .8835188 (mean)
                1.reason_r~d    =    .1164812 (mean)
                1.patient_~d    =    .7948252 (mean)
                2.patient_~d    =    .0884983 (mean)
                3.patient_~d    =    .1166764 (mean)
                0.pat_co~rti    =    .8081625 (mean)
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
6._at           : agegrp_urti_new =          2                (9-21 yrs)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                condition_urti  =          3                (AOM)
                0.de~n_presc    =    .1418473 (mean)
                1.de~n_presc    =    .8581527 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.practice~w    =    .8670963 (mean)
                1.practice~w    =    .1329037 (mean)
                0.reason_r~d    =    .8835188 (mean)
                1.reason_r~d    =    .1164812 (mean)
                1.patient_~d    =    .7948252 (mean)
                2.patient_~d    =    .0884983 (mean)
                3.patient_~d    =    .1166764 (mean)
                0.pat_co~rti    =    .8081625 (mean)
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =          .9 (mean)
                1.flu_s~2014    =          .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
```

```
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
7._at         : agegrp_urti_new =           3               (21-34 yrs)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                condition_urti  =           1               (Rhinosinusitis)
                0.de~n_presc    =    .1418473 (mean)
                1.de~n_presc    =    .8581527 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.practice~w    =    .8670963 (mean)
                1.practice~w    =    .1329037 (mean)
                0.reason_r~d    =    .8835188 (mean)
                1.reason_r~d    =    .1164812 (mean)
                1.patient_~d    =    .7948252 (mean)
                2.patient_~d    =    .0884983 (mean)
                3.patient_~d    =    .1166764 (mean)
                0.pat_co~rti    =    .8081625 (mean)
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =           .9 (mean)
                1.flu_s~2014    =           .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
8._at         : agegrp_urti_new =           3               (21-34 yrs)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                condition_urti  =           2               (Pharyngitis)
                0.de~n_presc    =    .1418473 (mean)
                1.de~n_presc    =    .8581527 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.practice~w    =    .8670963 (mean)
                1.practice~w    =    .1329037 (mean)
                0.reason_r~d    =    .8835188 (mean)
                1.reason_r~d    =    .1164812 (mean)
                1.patient_~d    =    .7948252 (mean)
                2.patient_~d    =    .0884983 (mean)
                3.patient_~d    =    .1166764 (mean)
                0.pat_co~rti    =    .8081625 (mean)
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =           .9 (mean)
                1.flu_s~2014    =           .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
9._at         : agegrp_urti_new =           3               (21-34 yrs)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                condition_urti  =           3               (AOM)
                0.de~n_presc    =    .1418473 (mean)
                1.de~n_presc    =    .8581527 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.practice~w    =    .8670963 (mean)
                1.practice~w    =    .1329037 (mean)
                0.reason_r~d    =    .8835188 (mean)
                1.reason_r~d    =    .1164812 (mean)
                1.patient_~d    =    .7948252 (mean)
                2.patient_~d    =    .0884983 (mean)
                3.patient_~d    =    .1166764 (mean)
                0.pat_co~rti    =    .8081625 (mean)
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =           .9 (mean)
                1.flu_s~2014    =           .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
10._at        : agegrp_urti_new =           4               (35+ yrs)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                condition_urti  =           1               (Rhinosinusitis)
                0.de~n_presc    =    .1418473 (mean)
                1.de~n_presc    =    .8581527 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.practice~w    =    .8670963 (mean)
                1.practice~w    =    .1329037 (mean)
```

```
                0.reason_r~d    =    .8835188 (mean)
                1.reason_r~d    =    .1164812 (mean)
                1.patient_~d    =    .7948252 (mean)
                2.patient_~d    =    .0884983 (mean)
                3.patient_~d    =    .1166764 (mean)
                0.pat_co~rti    =    .8081625 (mean)
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =           .9 (mean)
                1.flu_s~2014    =           .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
11._at       : agegrp_urti_new =           4                (35+ yrs)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                condition_urti  =           2                (Pharyngitis)
                0.de~n_presc    =    .1418473 (mean)
                1.de~n_presc    =    .8581527 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.practice~w    =    .8670963 (mean)
                1.practice~w    =    .1329037 (mean)
                0.reason_r~d    =    .8835188 (mean)
                1.reason_r~d    =    .1164812 (mean)
                1.patient_~d    =    .7948252 (mean)
                2.patient_~d    =    .0884983 (mean)
                3.patient_~d    =    .1166764 (mean)
                0.pat_co~rti    =    .8081625 (mean)
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =           .9 (mean)
                1.flu_s~2014    =           .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
12._at       : agegrp_urti_new =           4                (35+ yrs)
                0.repeat_s~t    =    .6772115 (mean)
                1.repeat_s~t    =    .3227885 (mean)
                condition_urti  =           3                (AOM)
                0.de~n_presc    =    .1418473 (mean)
                1.de~n_presc    =    .8581527 (mean)
                0.multip~RTI    =    .2286663 (mean)
                1.multip~RTI    =    .7713337 (mean)
                0.practice~w    =    .8670963 (mean)
                1.practice~w    =    .1329037 (mean)
                0.reason_r~d    =    .8835188 (mean)
                1.reason_r~d    =    .1164812 (mean)
                1.patient_~d    =    .7948252 (mean)
                2.patient_~d    =    .0884983 (mean)
                3.patient_~d    =    .1166764 (mean)
                0.pat_co~rti    =    .8081625 (mean)
                1.pat_co~rti    =    .1529194 (mean)
                2.pat_co~rti    =    .0389182 (mean)
                0.flu_s~2012    =     .923472 (mean)
                1.flu_s~2012    =     .076528 (mean)
                0.flu_s~2013    =    .9305019 (mean)
                1.flu_s~2013    =    .0694981 (mean)
                0.flu_s~2014    =           .9 (mean)
                1.flu_s~2014    =           .1 (mean)
                0.flu_s~2015    =    .8825425 (mean)
                1.flu_s~2015    =    .1174575 (mean)
                0.flu_s~2016    =    .8798477 (mean)
                1.flu_s~2016    =    .1201523 (mean)
                0.flu_s~2017    =     .973306 (mean)
                1.flu_s~2017    =     .026694 (mean)
```

```
------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_predict#_at |
       1  1  |   .5434697    .010536    51.58   0.000     .5228196    .5641199
       1  2  |   .4611133   .0110631    41.68   0.000     .4394301    .4827965
       1  3  |   .6273735    .009761    64.27   0.000     .6082424    .6465047
       1  4  |   .4814571   .0113002    42.61   0.000     .4593092     .503605
       1  5  |   .4994926   .0111713    44.71   0.000     .4775973    .5213879
       1  6  |   .5674126   .0111703    50.80   0.000     .5455193    .5893059
       1  7  |   .4452543   .0109661    40.60   0.000     .4237612    .4667475
       1  8  |   .4733862   .0111698    42.38   0.000     .4514937    .4952786
       1  9  |   .5313507   .0113707    46.73   0.000     .5090645    .5536369
       1 10  |   .4245594   .0103207    41.14   0.000     .4043312    .4447876
       1 11  |   .4096186   .0112085    36.55   0.000     .3876503    .4315869
       1 12  |   .5103737   .0108927    46.85   0.000     .4890243     .531723
       2  1  |   .1628302    .002796    58.24   0.000     .1573503    .1683102
       2  2  |   .1712407   .0026515    64.58   0.000     .1660438    .1764375
       2  3  |   .1471898   .0028729    51.23   0.000      .141559    .1528205
       2  4  |   .1698483   .0027036    62.82   0.000     .1645494    .1751473
       2  5  |   .1682292   .0027237    61.76   0.000     .1628908    .1735676
       2  6  |   .1590614   .0029151    54.56   0.000     .1533479    .1647749
       2  7  |   .1719969   .0026342    65.29   0.000      .166834    .1771597
       2  8  |   .1704566   .0026747    63.73   0.000     .1652143    .1756989
       2  9  |   .1645183   .0028288    58.16   0.000      .158974    .1700626
       2 10  |   .1725352    .002608    66.16   0.000     .1674237    .1776468
       2 11  |   .1725982   .0025967    66.47   0.000     .1675088    .1776876
       2 12  |   .1670821   .0027482    60.80   0.000     .1616958    .1724684
       3  1  |      .2937   .0091528    32.09   0.000     .2757608    .3116392
       3  2  |   .3676461   .0104371    35.22   0.000     .3471897    .3881025
       3  3  |   .2254367   .0078364    28.77   0.000     .2100777    .2407957
       3  4  |   .3486946   .0104125    33.49   0.000     .3282864    .3691027
       3  5  |   .3322782   .0101503    32.74   0.000      .312384    .3521725
       3  6  |    .273526   .0094607    28.91   0.000     .2549833    .2920687
       3  7  |   .3827488   .0104743    36.54   0.000     .3622195    .4032781
       3  8  |   .3561572    .010407    34.22   0.000     .3357599    .3765545
       3  9  |    .304131   .0099759    30.49   0.000     .2845786    .3236833
       3 10  |   .4029054   .0100546    40.07   0.000     .3831987     .422612
       3 11  |   .4177832   .0111529    37.46   0.000     .3959238    .4396425
       3 12  |   .3225443   .0097651    33.03   0.000      .303405    .3416835
------------------------------------------------------------------------------
  Where 1= First-line, 2= Second-line and 3= Not Recommended.
```

C.7.5 Predictive margins for the effect on ordinal choice, at specific values of whether repeats were issued on prescription and patient age group

```
. margins, at(repeat_script==(1 0) agegrp_urti_new==(1 2 3 4))

Predictive margins                              Number of obs     =     51,210
Model VCE    : OIM

1._predict   : Marginal predicted mean (1.choice_urti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_urti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_urti_new), predict(pr outcome(3))

1._at        : agegrp_urti_new =           1       (0-8 yrs)
               repeat_script   =           1       (Positive)

2._at        : agegrp_urti_new =           1       (0-8 yrs)
               repeat_script   =           0       (Negative)

3._at        : agegrp_urti_new =           2       (9-21 yrs)
               repeat_script   =           1       (Positive)

4._at        : agegrp_urti_new =           2       (9-21 yrs)
               repeat_script   =           0       (Negative)

5._at        : agegrp_urti_new =           3       (22-34 yrs)
               repeat_script   =           1       (Positive)

6._at        : agegrp_urti_new =           3       (22-34 yrs)
               repeat_script   =           0       (Negative)


7._at        : agegrp_urti_new =           4       (35+ yrs)
               repeat_script   =           1       (Positive)

8._at        : agegrp_urti_new =           4       (35+ yrs)
               repeat_script   =           0       (Negative)
```

	Delta-method				
	Margin	Std. Err.	z	P>|z|	[95% Conf. Interval]
_predict#_at					
1 1	.5124754	.0107828	47.53	0.000	.4913416 .5336093
1 2	.5376436	.0099114	54.24	0.000	.5182176 .5570696
1 3	.4389829	.0116898	37.55	0.000	.4160713 .4618945
1 4	.5403377	.0104434	51.74	0.000	.519869 .5608063
1 5	.3736665	.0114366	32.67	0.000	.3512511 .3960819
1 6	.5255476	.0103313	50.87	0.000	.5052985 .5457966
1 7	.3839309	.0105993	36.22	0.000	.3631567 .4047051
1 8	.4650984	.0101089	46.01	0.000	.4452853 .4849115
2 1	.1631334	.0026331	61.95	0.000	.1579725 .1682942
2 2	.1601126	.0026161	61.20	0.000	.1549852 .1652401
2 3	.169565	.0025937	65.37	0.000	.1644814 .1746486
2 4	.160967	.0027073	59.46	0.000	.1556608 .1662732
2 5	.1688535	.0025769	65.53	0.000	.163803 .1739041
2 6	.1628917	.0026809	60.76	0.000	.1576371 .1681462
2 7	.1691141	.0025603	66.05	0.000	.164096 .1741323
2 8	.1682471	.0025988	64.74	0.000	.1631535 .1733406
3 1	.3243912	.0097768	33.18	0.000	.3052289 .3435535
3 2	.3022438	.0088161	34.28	0.000	.2849646 .319523
3 3	.3914521	.0113274	34.56	0.000	.3692507 .4136535
3 4	.2986953	.0092197	32.40	0.000	.2806249 .3167657
3 5	.45748	.0118457	38.62	0.000	.4342629 .4806971
3 6	.3115608	.009246	33.70	0.000	.2934389 .3296827
3 7	.4469549	.0108476	41.20	0.000	.4256941 .4682158
3 8	.3666545	.0095796	38.27	0.000	.3478789 .3854302

Where 1= First-line, 2= Second-line and 3= Not Recommended.

.

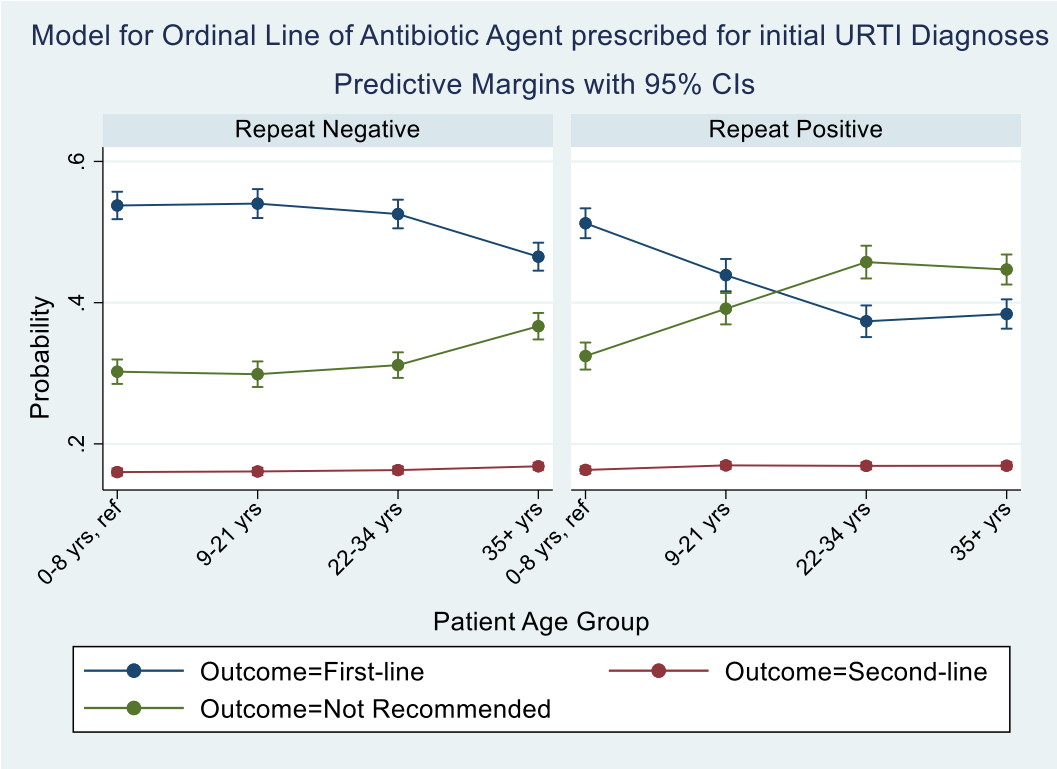


Figure C-10: Predictive margins for the effect on the probability of each of the three outcomes of ordinal choice of antibiotic occurring, at specific values of whether repeats were issued on prescription and patient age group, graphed by repeat on prescription status

C.7.6 Predictive margins for the effect on ordinal choice of antibiotic prescribed, at specific values of upper respiratory tract infection condition and patient age group, graphed by upper respiratory tract infection condition

```
margins, at(condition_urti==(1 2 3) agegrp_urti_new==(1 2 3 4))

Predictive margins                              Number of obs     =     51,210
Model VCE    : OIM

1._predict   : Marginal predicted mean (1.choice_urti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_urti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_urti_new), predict(pr outcome(3))

1._at        : agegrp_urti_new =           1       (0-8 yrs)
               condition_urti  =           1       (Rhinosinusitis)

2._at        : agegrp_urti_new =           1       (0-8 yrs)
               condition_urti  =           2       (Pharyngitis)

3._at        : agegrp_urti_new =           1       (0-8 yrs)
               condition_urti  =           3       (AOM)

4._at        : agegrp_urti_new =           2       (9-21 yrs)
               condition_urti  =           1       (Rhinosinusitis)

5._at        : agegrp_urti_new =           2       (9-21 yrs)
               condition_urti  =           2       (Pharyngitis)

6._at        : agegrp_urti_new =           2       (9-21 yrs)
               condition_urti  =           3       (AOM_

7._at        : agegrp_urti_new =           3       (22-34 yrs)
               condition_urti  =           1       (Rhinosinusitis)

8._at        : agegrp_urti_new =           3       (22-34 yrs)
               condition_urti  =           2       (Pharyngitis)

9._at        : agegrp_urti_new =           3       (22-34 yrs)
               condition_urti  =           3       (AOM)

10._at       : agegrp_urti_new =           4       (35+ yrs)
               condition_urti  =           1       (Rhinosinusitis)

11._at       : agegrp_urti_new =           4       (35+ yrs)
               condition_urti  =           2       (Pharyngitis)

12._at       : agegrp_urti_new =           4       (35+ yrs)
               condition_urti  =           3       (AOM)

------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_predict#_at |
       1  1  |   .5431247   .0104344    52.05   0.000     .5226736    .5635757
       1  2  |   .4616489   .0109319    42.23   0.000     .4402229     .483075
       1  3  |   .6261724   .0097101    64.49   0.000     .6071409     .645204
       1  4  |   .4819812   .0110951    43.44   0.000     .4602352    .5037271
       1  5  |   .4996952   .0109674    45.56   0.000     .4781995    .5211909
       1  6  |   .5664066   .0109891    51.54   0.000     .5448685    .5879448
       1  7  |   .4471569   .0106603    41.95   0.000      .426263    .4680507
       1  8  |   .4745298   .0108429    43.76   0.000      .453278    .4957816
       1  9  |   .5308849   .0110613    47.99   0.000     .5092051    .5525647
       1 10  |   .4258416   .0101544    41.94   0.000     .4059393     .445744
       1 11  |   .4111107   .0110214    37.30   0.000      .389509    .4327123
       1 12  |   .5103709   .0107265    47.58   0.000     .4893474    .5313945
       2  1  |   .1613109   .0027472    58.72   0.000     .1559266    .1666952
       2  2  |   .1694569   .0026319    64.39   0.000     .1642986    .1746153
       2  3  |   .1461428   .0028054    52.09   0.000     .1406444    .1516412
       2  4  |   .1669502   .0026383    63.28   0.000     .1617792    .1721212
       2  5  |   .1654157   .0026394    62.67   0.000     .1602427    .1705887
       2  6  |   .1567293   .0028157    55.66   0.000     .1512105     .162248
       2  7  |    .167312   .0025306    66.12   0.000     .1623522    .1722719
       2  8  |   .1658733   .0025461    65.15   0.000     .1608831    .1708636
       2  9  |   .1603961   .0026828    59.79   0.000     .1551379    .1656543
       2 10  |   .1699462    .002572    66.07   0.000     .1649051    .1749873
       2 11  |   .1700154   .0025636    66.32   0.000     .1649909    .1750399
       2 12  |   .1647256   .0026829    61.40   0.000     .1594672     .169984
       3  1  |   .2955644   .0091483    32.31   0.000     .2776341    .3134948
       3  2  |   .3688941   .0103807    35.54   0.000     .3485483    .3892399
       3  3  |   .2276848   .0078896    28.86   0.000     .2122215     .243148
       3  4  |   .3510686   .0102884    34.12   0.000     .3309038    .3712334
       3  5  |   .3348891   .0100682    33.26   0.000     .3151559    .3546224
       3  6  |   .2768641    .009402    29.45   0.000     .2584366    .2952916
       3  7  |   .3855311   .0102339    37.67   0.000     .3654731    .4055891
       3  8  |   .3595969   .0102186    35.19   0.000     .3395687     .379625
       3  9  |    .308719   .0098092    31.47   0.000     .2894933    .3279448
       3 10  |   .4042122   .0099331    40.69   0.000     .3847437    .4236807
       3 11  |    .418874   .0110148    38.03   0.000     .3972853    .4404627
       3 12  |   .3249035    .009692    33.52   0.000     .3059076    .3438994
------------------------------------------------------------------------------
  Where 1= First-line, 2= Second-line and 3= Not Recommended.
```

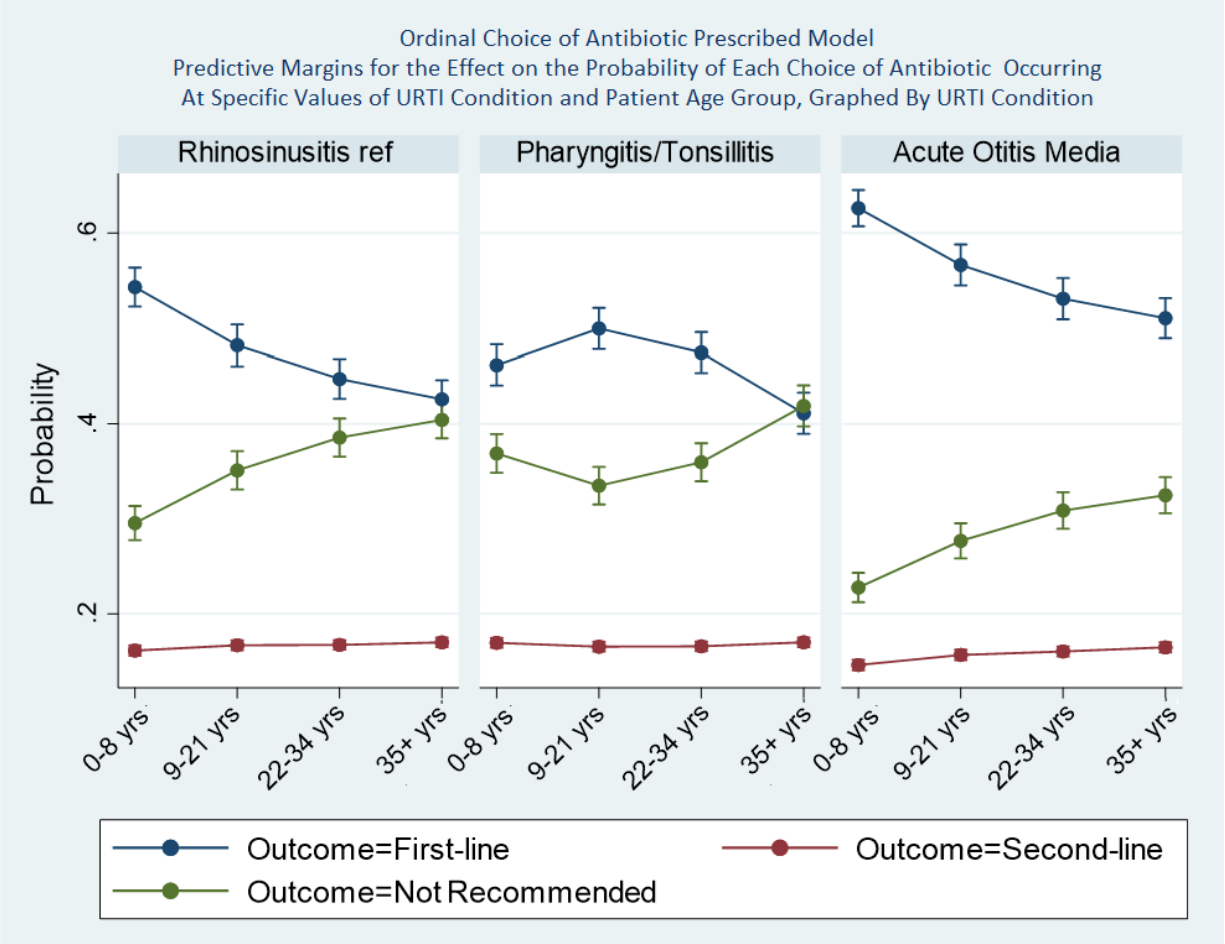


Figure C-11: Predictive margins for the effect on the probability of each of the three outcomes of ordinal choice of antibiotic occurring, at specific values of upper respiratory tract infection condition and patient age group, graphed by upper respiratory tract infection condition

C.8 Non-first-line antibiotic prescribing model for upper respiratory tract infection

C.8.1 Average marginal effects

Table C-23: Average marginal effects for the binary model for non-first-line antibiotic prescribing for upper respiratory tract infection

	dy/dx	Std. Err.	z	P>z	[95% Conf.	Interval]
Patient Age Group (ref. 0-8 years)						
9-21 yrs	0.059784	0.00619	9.66	0.000	0.047652	0.071916
22-34 yrs	0.125014	0.006257	19.98	0.000	0.112752	0.137277
35+ yrs	0.169652	0.006081	27.90	0.000	0.157734	0.181571
Repeat Prescription Status (ref. Negative)						
Positive	0.163342	0.005593	29.21	0.000	0.152381	0.174304
URTI Condition (ref. Rhinosinusitis)						
Pharyngitis/Tonsillitis	-0.12464	0.005462	-22.82	0.000	-0.13534	-0.11393
Acute Otitis Media	-0.04221	0.006147	-6.87	0.000	-0.05426	-0.03016
Unnecessary/Necessary Prescription Status (ref. Necessary)						
Unnecessary	0.005801	0.006556	0.88	0.376	-0.00705	0.018649
Patient Gender (ref. Female)						
Male	0.01559	0.003963	3.93	0.000	0.007822	0.023357
Patient with Multiple URTI Episodes (ref. Negative)						
Positive	-0.01761	0.004851	-3.63	0.000	-0.02712	-0.00811
Practice Size (ref. Medium/Large)						
Small	0.103144	0.028858	3.57	0.000	0.046584	0.159703
Reason for Prescribing Recorded (ref. Negative)						
Positive	-0.06702	0.014037	-4.77	0.000	-0.09453	-0.03951
Patient Disadvantage Status (ref. Negative)						
Positive	-0.016	0.008947	-1.79	0.074	-0.03353	0.001541
Missing	-0.02988	0.008463	-3.53	0.000	-0.04647	-0.0133
Patient Comorbid Condition Status (ref. Negative)						
Positive	0.022818	0.005685	4.01	0.000	0.011677	0.033959
Missing	0.005486	0.049646	0.11	0.912	-0.09182	0.10279

C.9 Repeats being issued on prescriptions model for upper respiratory tract infection

C.9.1 Model

Table C-24: Mixed effects logit model for repeats being issued on antibiotic prescriptions for initial presentations of upper respiratory tract infection (Model 4)

Model	**Repeat Positive Antibiotic Prescribing (ref. Repeat Negative)**	
Independent Variable	**Odds Ratio**	**95% C.I.**
Patient Age group, (ref 0-8 yrs)		
9-21 years	0.676***	[0.571, 0.801]
22-34 years	0.425***	[0.358, 0.505]
35+ years	0.790**	[0.680, 0.917]
Patient penicillin sensitivity recorded, (ref Negative)		
Positive	1.228***	[1.116, 1.351]
Unnecessary Prescribing status (ref Necessary)		
Unnecessary	0.827***	[0.765, 0.895]
Patient Comorbid Condition (ref Negative)		
Positive	1.164***	[1.089, 1.245]
Missing	0.964	[0.473, 1.965]
URTI Condition, (ref rhinosinusitis)		
Pharyngitis/Tonsillitits	1.654***	[1.476, 1.853]
AOM	1.265***	[1.133, 1.411]
Ordinal Line Agent Prescribed, (ref First-line)		
Second-line	2.627***	[2.323, 2.972]
Not Recommended	1.035	[0.938, 1.141]
Patient Age Group # Ordinal Line Prescribed		
9-21 yrs#Second-line	2.043***	[1.648, 2.533]
9-21 yrs#Not Recommended	2.272***	[1.942, 2.658]
22-34 yrs#Second-line	3.015***	[2.428, 3.744]
22-34 yrs#Not Recommended	4.315***	[3.657, 5.093]
35+ yrs#Second-line	2.222***	[1.852, 2.666]
35+ yrs#Not Recommended	2.934***	[2.524, 3.411]
Patient Age Group # URTI Condition		
9-21 yrs#Pharyngitis/Tonsillitis	0.630***	[0.528, 0.752]
9-21 yrs#Acute Otitis Media	1.628***	[1.340, 1.979]
22-34 yrs#Pharyngitis/Tonsillitis	0.528***	[0.445, 0.627]
22-34 yrs#Acute Otitis Media	1.685***	[1.365, 2.080]
35+ yrs#Pharyngitis/Tonsillitis	0.429***	[0.367, 0.502]
35+ yrs#Acute Otitis Media	1.242*	[1.046, 1.476]
Patient's Primary Health Network, (ref Perth North)		
Perth South	1.188*	[1.026, 1.376]
Country WA	1.071	[0.915, 1.253]
Interstate PHN	1.132	[0.865, 1.480]
Patient's PHN Missing	1.045	[0.847, 1.288]
Seasonality allowed for in form of dummy variables for annual influenza seasons		
var(_cons)	2.574 (0.18501)	[2.236, 2.963]
N	51210	
AIC	44371.6	
BIC	44690	
ICC Level: Unique combination of provider ID & practice ID	0.439 (0.01770)	[0.405, 0.474]
Note: SE in parentheses, *** p<0.01, ** p<0.05, * p<0.1		

Patients with a history of comorbid conditions were two percentage points more likely to receive a repeat than patients without comorbid conditions *(0.021, p<0.001, 95%CI: 0.012, 0.030).* Meanwhile patients with missing comorbid condition status were not significantly different from patients without comorbid conditions *(-0.00488, p=0.920, 95%CI: -0.100, 0.091).* Patients with a recorded sensitivity to penicillin were three percentage points more likely to receive a repeat on prescription than patients with no such history *(0.029, p<0.001, 95%CI: 0.015, 0.042)*. Having temperature recording during the consultation was associated with a one percentage point increase in likelihood of receiving a repeat on the prescription *(0.0136, p=0.011, 95%CI: 0.003, 0.024),* compared with patients who did not receive temperature testing. Compared to patients residing within the Perth North PHN, patients residing in Perth South PHN were two percentage points more likely to receive a repeat *(0.024, p=0.022, 0.003, 0.044).* There were no significant differences for patients residing within the Country WA PHN *(0.00925, p=0.392, 95%CI: -0.012, 0.030),* an interstate PHN *(0.0168, p=0.372, 95%CI: -0.020, 0.054*), or with missing PHN information *(0.00586, p=0.684, 95%CI: -0.022, 0.034).*

C.9.2 Model explanation

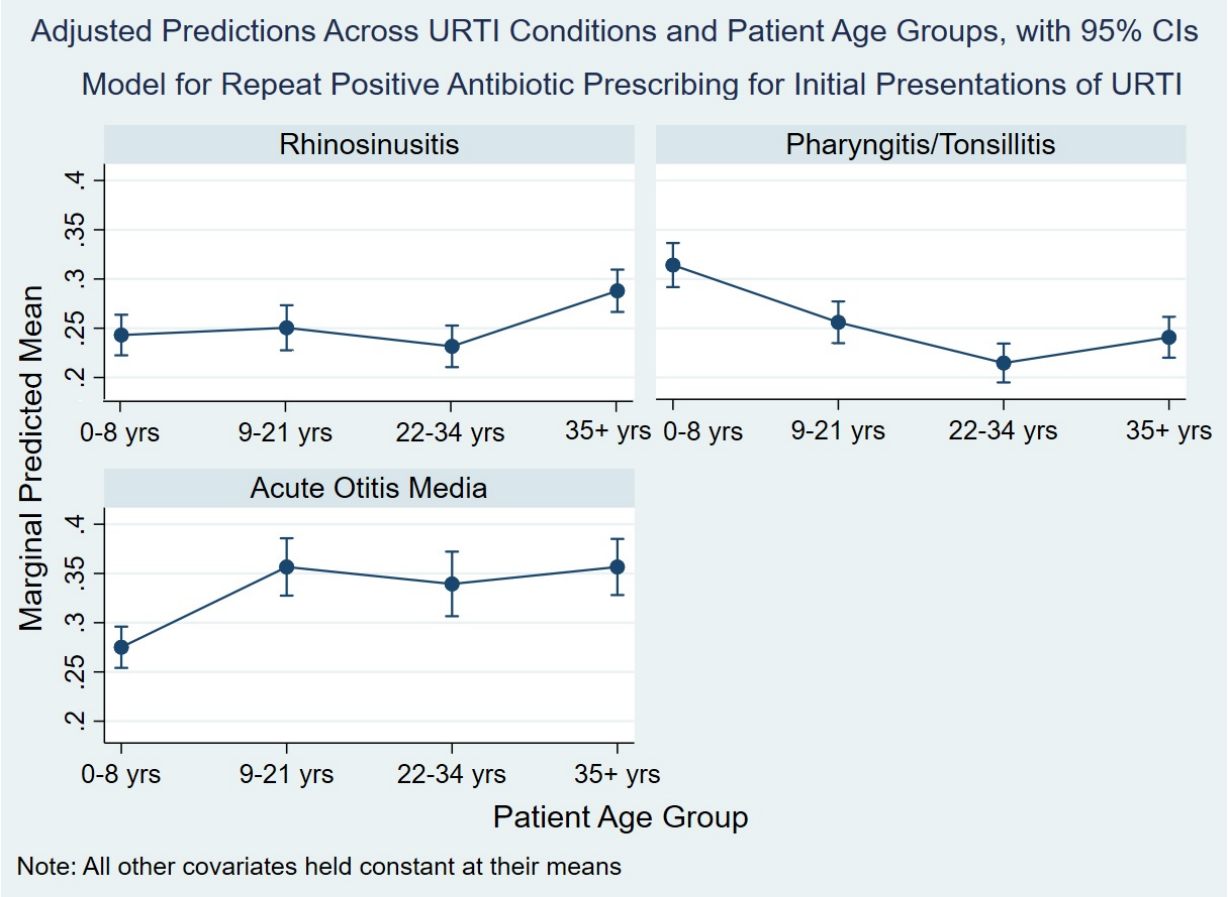
Patient age, URTI condition, comorbid condition status, temperature recording status, patient penicillin sensitivity status, and patient's PHN were found to affect the risk of repeat prescribing, in addition to ordinal line of choice of agent prescribed and unnecessary/necessary prescribing status (**Table C-24, Table C-25**). The line of antibiotic prescribed was found to have the most notable effect on the probability of repeats being prescribed, more so than unnecessary/necessary prescribing status. The following variables were insignificant: patient gender, disadvantage, concession status, mental health conditions, number of URTI episodes, remoteness and accessibility, practice size.

The probability of receiving a repeat was three percentage points less for patients receiving unnecessary prescriptions *(-0.026, p<0.001, 95%CI: -0.037, -0.015)* than patients receiving necessary prescriptions. In this context, unnecessary prescribing may potentially be considered to predispose patients to receiving prescriptions without repeats, and vice versa.

There was an effect modification between patient age group and the ordinal choice of antibiotic prescribed. When first-line antibiotics were prescribed, the probability of receiving a repeat was 25% for patients aged 0-8 years *(0.252, p<0.001, 95%CI: 0.233, 0.272),* 19% for patients aged 9-21 years *(0.194, p<0.001, 95%CI: 0.175, 0.214),* 14% for patients aged 22-34 years *(0.140, p<0.001, 95%CI: 0.123, 0.157)* and 19% for patients 35 years and over *(0.188, p<0.001, 95%CI: 0.169, 0.207).* Where second-line antibiotics were prescribed, the chance of receiving a repeat was 40% for patients 0-8 years (0.398, p<0.001, 95%CI: 0.371, 0.426*),* 44% for patients 9-21 years *(0.440, p<0.001, 95%CI: 0.407, 0.474),* and 42% for patients 22-34 years *(0.418, p<0.001, 95%CI: 0.387, 0.448)* and 45% for patients 35 years and over *(0.445, p<0.001, 95%CI: 0.418, 0.473).* Not recommended antibiotics being prescribed had a probability of 26% of a repeat being issued for patients aged 0-8 years *(0.257, p<0.001, 95%CI: 0.237, 0.277),* 31% for patients 9-21 years *(0.308, p<0.001, 95%CI: 0.284, 0.331),* 33% for patients 22-34 years *(0.325, p<0.001, 95%CI: 0.302, 0.349)* and 34% for patients 35 years and over *(0.338, p<0.001, 95%CI: 0.316, 0.361).*

There was an interaction identified between URTI condition and patient age group. Patients with rhinosinusitis were most likely to receive a repeat when aged 35 years and over *(0.288, p<0.001, 95%CI: 0.267, 0.310)* and least likely to receive a repeat at 22-34 years of age *(0.232, p<0.001, 95%CI: 0.210, 0.253).* Patients with pharyngitis aged 0-8 years were most

likely to receive a repeat on prescription *(0.314, p<0.001, 95%CI: 0.292, 0.337)* and least likely aged 22-34 years *(0.215, p<0.001, 95%CI: 0.195, 0.234).* For AOM, the risk of receiving a repeat was highest for patients aged 9-21 *(0.357, p<0.001, 95%CI: 0.327, 0.3863)* or 35 years and over *(0.357, p<0.001, 95%CI: 0.328, 0.385)* and lowest for patients 0-8 years *(0.275, p<0.001, 95%CI: 0.254, 0.296).*



C.9.2.1 Summary

Repeats on prescriptions were most likely for patients with AOM while patients with rhinosinusitis were least likely. For pharyngitis, the risk of repeat prescribing decreased with increasing patient age. For rhino, highest for patients 35 years and over and lowest for patients 22-34 years. For AOM, highest for 9-21 and 35+ and lowest for children 0-8years. The line of antibiotic prescribed was found to have the most notable effect on the probability of repeats being prescribed, more so than unnecessary/necessary prescribing status. Unnecessary prescribing appeared linked to receiving prescriptions without repeats on them. Of the variance not explained by fixed effects, the unique provider and practice combination was responsible for 44% of this variance.

C.9.3 Marginal effects for the repeats being issued on prescriptions model for upper respiratory tract infection

C.9.3.1 Average marginal effects

Table C-25: Average marginal effects for Model 4 – Repeats being issued on antibiotic prescriptions

Average Marginal Effects						
Repeat Positive Antibiotic Prescribing for Initial Presentations of URTI						
Independent Variable	**dy/dx**	**Std. Err.**	**z**	**P>z**	**[95% Conf.**	**Interval]**
Patient Age Group (ref. 0-8 years)						
9-21 yrs	0.003801	0.005181	0.73	0.463	-0.00635	0.013954
22-34 yrs	-0.01572	0.005234	-3.00	0.003	-0.02598	-0.00546
35+ yrs	0.014866	0.004921	3.02	0.003	0.005222	0.024511
URTI Condition (ref. Rhinosinusitis)						
Pharyngitis/Tonsillitis	0.007798	0.004622	1.69	0.092	-0.00126	0.016857
Acute Otitis Media	0.069954	0.005762	12.14	0.000	0.058662	0.081247
Unnecessary/Necessary Prescription Status (ref. Necessary)						
Unnecessary	-0.02619	0.005622	-4.66	0.000	-0.03721	-0.01517
Ordinal Line of Antibiotic Prescribed (ref. First-line)						
Second-line	0.219129	0.007865	27.86	0.000	0.203715	0.234544
Not Recommended	0.100171	0.004776	20.98	0.000	0.090811	0.109531
Patient Comorbid Condition Status (ref. Negative)						
Positive	0.020951	0.004794	4.37	0.000	0.011555	0.030347
Missing	-0.00488	0.048728	-0.10	0.920	-0.10038	0.09063
Penicillin Sensitivity (ref. Negative)						
Positive	0.028505	0.006935	4.11	0.000	0.014914	0.042097
Temperature Recording Status (ref. Negative)						
Positive	0.01364	0.005379	2.54	0.011	0.003098	0.024182
Patient Primary Health Network (ref. Perth North)						
Perth South	0.023514	0.010252	2.29	0.022	0.003422	0.043607
Country WA	0.009245	0.010809	0.86	0.392	-0.01194	0.03043
Interstate	0.01678	0.018807	0.89	0.372	-0.02008	0.053641
Missing	0.005863	0.014407	0.41	0.684	-0.02237	0.034099

C.9.3.2 Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in upper respiratory tract infection condition, across different values of patient age group

```
margins, dydx(condition_urti) at (agegrp_urti_new= (1 2 3 4))

Average marginal effects                        Number of obs     =     51,210
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 2.condition_urti 3.condition_urti

1._at        : agegrp_urti_new =           1       (0-8 yrs)
2._at        : agegrp_urti_new =           2       (9-21 yrs)
3._at        : agegrp_urti_new =           3       (22-34 yrs)
4._at        : agegrp_urti_new =           4       (35+ yrs)

------------------------------------------------------------------------------
                  |            Delta-method
                  |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------------
Rhinosinusitis    |  (base outcome)
------------------+-----------------------------------------------------------------
Pharyngitis       |
            _at   |
             1    |   .0703965   .0081609     8.63   0.000     .0544014    .0863917
             2    |   .0054493   .0095991     0.57   0.570    -.0133646    .0242631
             3    |  -.0164958    .008412    -1.96   0.050     -.032983   -8.59e-06
             4    |  -.0460829   .0079403    -5.80   0.000    -.0616455   -.0305203
------------------+-----------------------------------------------------------------
AOM               |
            _at   |
             1    |   .0317151   .0075594     4.20   0.000     .0168991    .0465312
             2    |   .1033712   .0125338     8.25   0.000     .0788054    .1279371
             3    |   .1035001   .0135503     7.64   0.000      .076942    .1300583
             4    |    .066282   .0106691     6.21   0.000     .0453709    .0871931
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

  Variables that uniquely identify margins: agegrp_urti_new _deriv
```

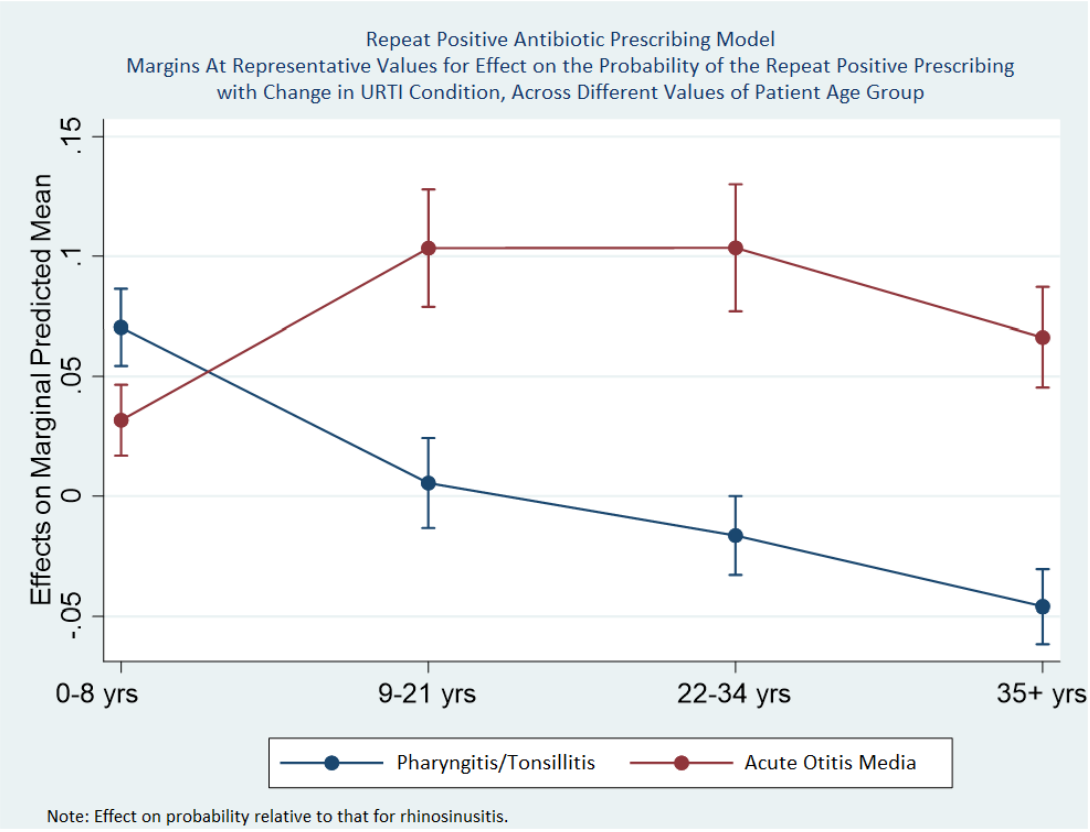


Figure C-12: Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in upper respiratory tract infection condition, across different values of patient age group, relative to the probability of repeats being issued on prescriptions for acute rhinosinusitis

C.9.3.2 Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in patient age group, across different values of upper respiratory tract infection condition,

```
. margins, dydx(agegrp_urti_new) at (condition_urti= (1 2 3 ))

Average marginal effects                        Number of obs     =     51,210
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 2.agegrp_urti_new 3.agegrp_urti_new 4.agegrp_urti_new

1._at        : condition_urti  =           1       (Rhinosinusitis)
2._at        : condition_urti  =           2       (Pharyngitis)
3._at        : condition_urti  =           3       (AOM)

------------------------------------------------------------------------------
                    |            Delta-method
                    |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------------+---------------------------------------------------------
0-8 years           |  (base outcome)
--------------------+---------------------------------------------------------
9-21 years          |
                _at |
                  1 |   .0123803   .0086986     1.42   0.155    -.0046685    .0294292
                  2 |  -.0525669   .0082694    -6.36   0.000    -.0687747   -.0363591
                  3 |   .0840365   .0115561     7.27   0.000     .0613869     .106686
--------------------+---------------------------------------------------------
22-34 years         |
                _at |
                  1 |   .0010992    .007724     0.14   0.887    -.0140396    .0162379
                  2 |  -.0857931   .0082588   -10.39   0.000    -.1019801   -.0696061
                  3 |   .0728842   .0135696     5.37   0.000     .0462882    .0994802
--------------------+---------------------------------------------------------
35+ years           |
                _at |
                  1 |   .0509757   .0072739     7.01   0.000     .0367191    .0652324
                  2 |  -.0655037   .0082535    -7.94   0.000    -.0816802   -.0493272
                  3 |   .0855426   .0111936     7.64   0.000     .0636036    .1074817
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

  Variables that uniquely identify margins: condition_urti _deriv
```

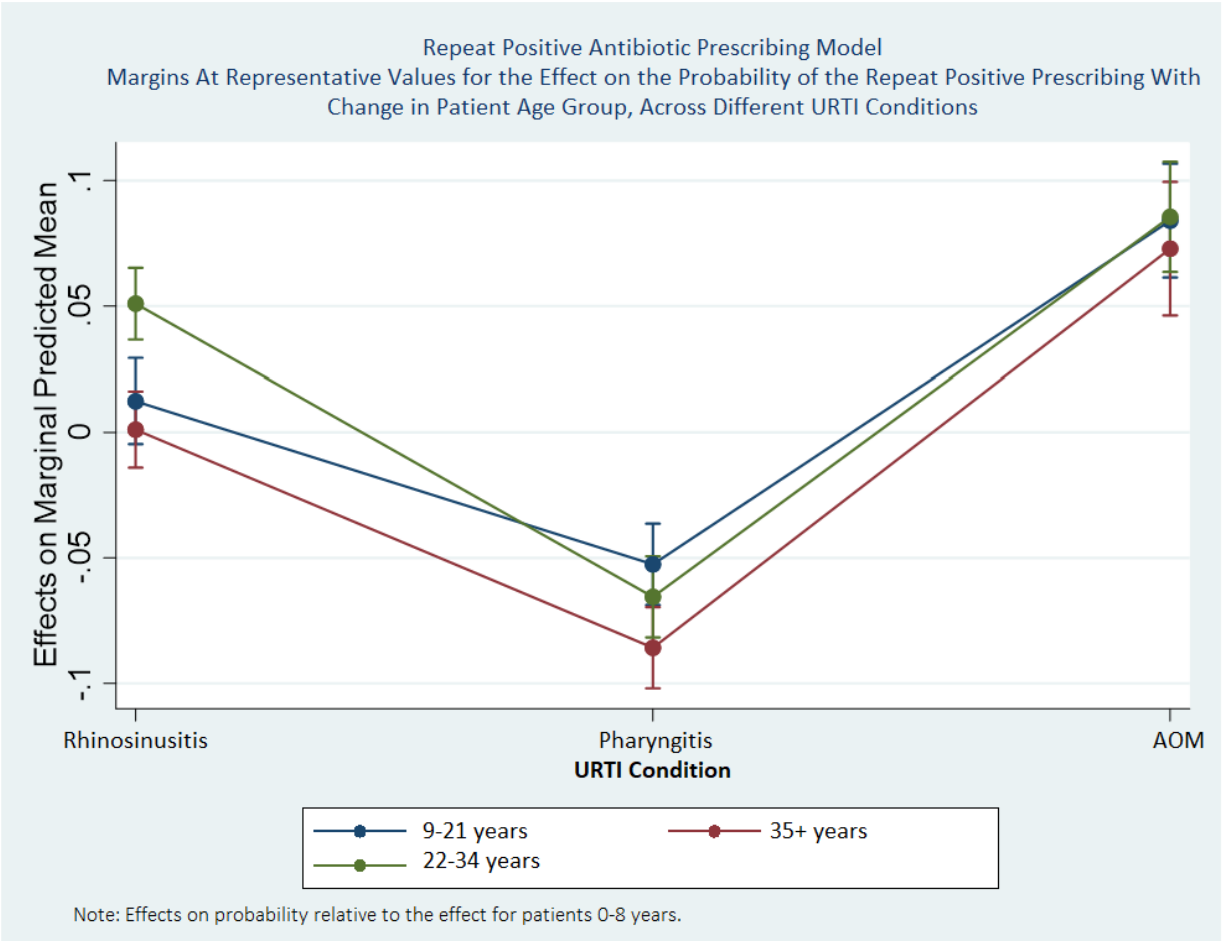


Figure C-13: Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in patient age group, across different values of upper respiratory tract infection condition, relative to the effect of repeats being issued on prescriptions for patients aged 0-8 years

C.9.3.2 Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in patient age group, across different values of ordinal choice of antibiotic prescribed

```
. margins, dydx(agegrp_urti_new) at (choice_urti_new= (1 2 3 ))

Average marginal effects                        Number of obs     =     51,210
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 2.agegrp_urti_new 3.agegrp_urti_new 4.agegrp_urti_new

1._at        : choice_urti_new =           1       (First-line)
2._at        : choice_urti_new =           2       (Second-line)
3._at        : choice_urti_new =           3       (Not Recommended)

------------------------------------------------------------------------------
                  |            Delta-method
                  |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
0-8 years         |  (base outcome)
------------------+-----------------------------------------------------------
9-21 years        |
              _at |
               1  |  -.0569828   .0073293    -7.77   0.000     -.071348   -.0426176
               2  |   .0418153   .0150563     2.78   0.005     .0123055    .0713251
               3  |   .0512712   .0083028     6.18   0.000     .0349981    .0675444
------------------+-----------------------------------------------------------
22-34 years       |
              _at |
               1  |  -.1105408   .0076258   -14.50   0.000    -.1254871   -.0955944
               2  |   .0193778   .0140068     1.38   0.167     -.008075    .0468306
               3  |   .0691983   .0083532     8.28   0.000     .0528262    .0855703
------------------+-----------------------------------------------------------
35+ years         |
              _at |
               1  |  -.0631149   .0074088    -8.52   0.000    -.0776358    -.048594
```

```
               2  |   .0467528   .0120535     3.88   0.000     .0231283    .0703772
               3  |   .0816938   .0075607    10.81   0.000      .066875    .0965126
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

  Variables that uniquely identify margins: choice_urti_new _deriv
```

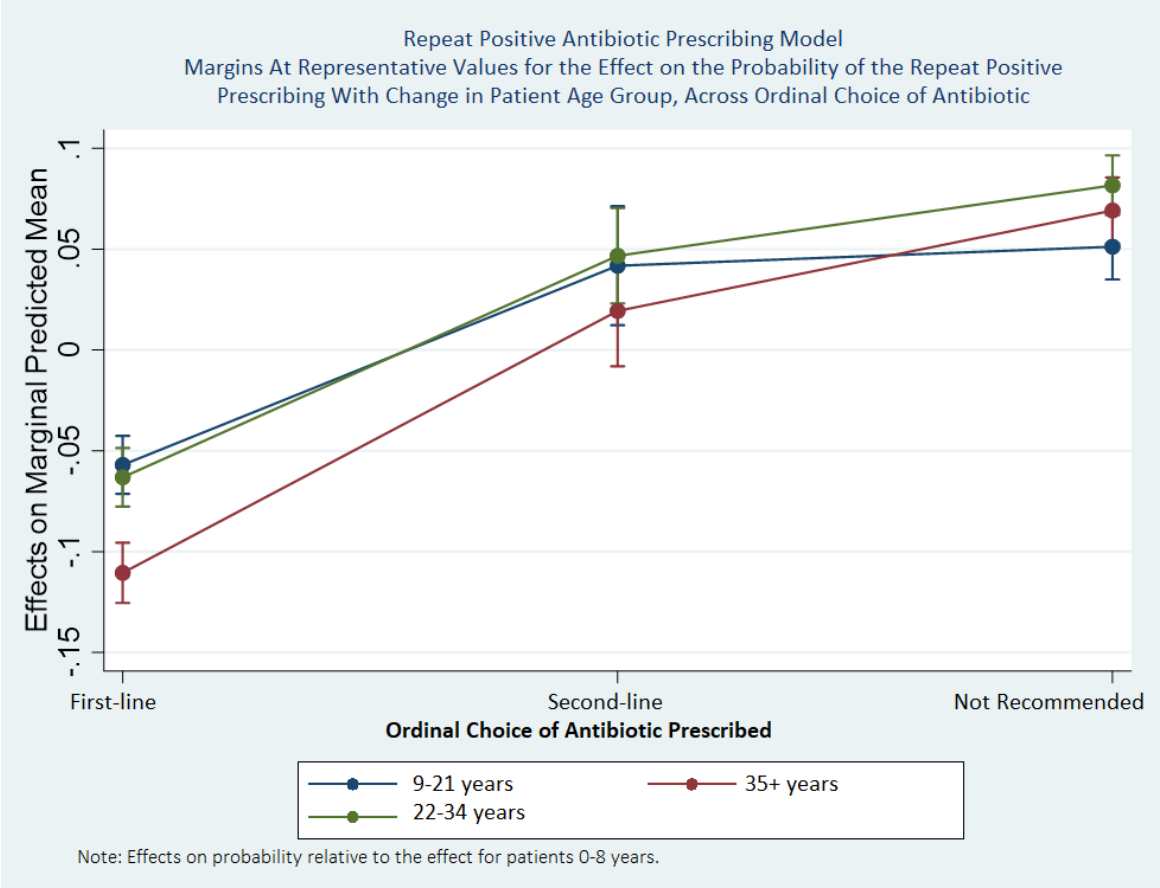


Figure C-14: Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in patient age group, across different values of ordinal choice of antibiotic prescribed, relative to the probability of repeats being issued on prescriptions for patients aged 0-8 years.

C.9.3.2 Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in ordinal choice of antibiotic prescribed, across patient age groups

```
margins, dydx(choice_urti_new) at (agegrp_urti_new = (1 2 3 4))


Average marginal effects                        Number of obs     =     51,210
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 2.choice_urti_new 3.choice_urti_new

1._at        : agegrp_urti_new =           1       (0-8 yrs)
2._at        : agegrp_urti_new =           2       (9-21 yrs)
3._at        : agegrp_urti_new =           3       (22-34 yrs)
4._at        : agegrp_urti_new =           4       (35+ yrs)

------------------------------------------------------------------------------
                     |            Delta-method
                     |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------------+--------------------------------------------------------------
First-line           |  (base outcome)
---------------------+--------------------------------------------------------------
Second-line          |
                 _at |
                  1  |   .1454059   .0103101    14.10   0.000     .1251985    .1656134
                  2  |    .244204   .0153667    15.89   0.000     .2140858    .2743223
                  3  |   .2753245   .0143587    19.17   0.000      .247182     .303467
                  4  |   .2552736   .0117135    21.79   0.000     .2323156    .2782317
---------------------+--------------------------------------------------------------
Not Recommended      |
```

```
                _at |
                  1 |   .0046243   .0067397     0.69   0.493    -.0085852    .0178338
                  2 |   .1128784   .0089875    12.56   0.000     .0952633    .1304935
                  3 |   .1843634   .0092161    20.00   0.000     .1663001    .2024266
                  4 |    .149433   .0084599    17.66   0.000      .132852    .1660141
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

  Variables that uniquely identify margins: agegrp_urti_new _deriv
```

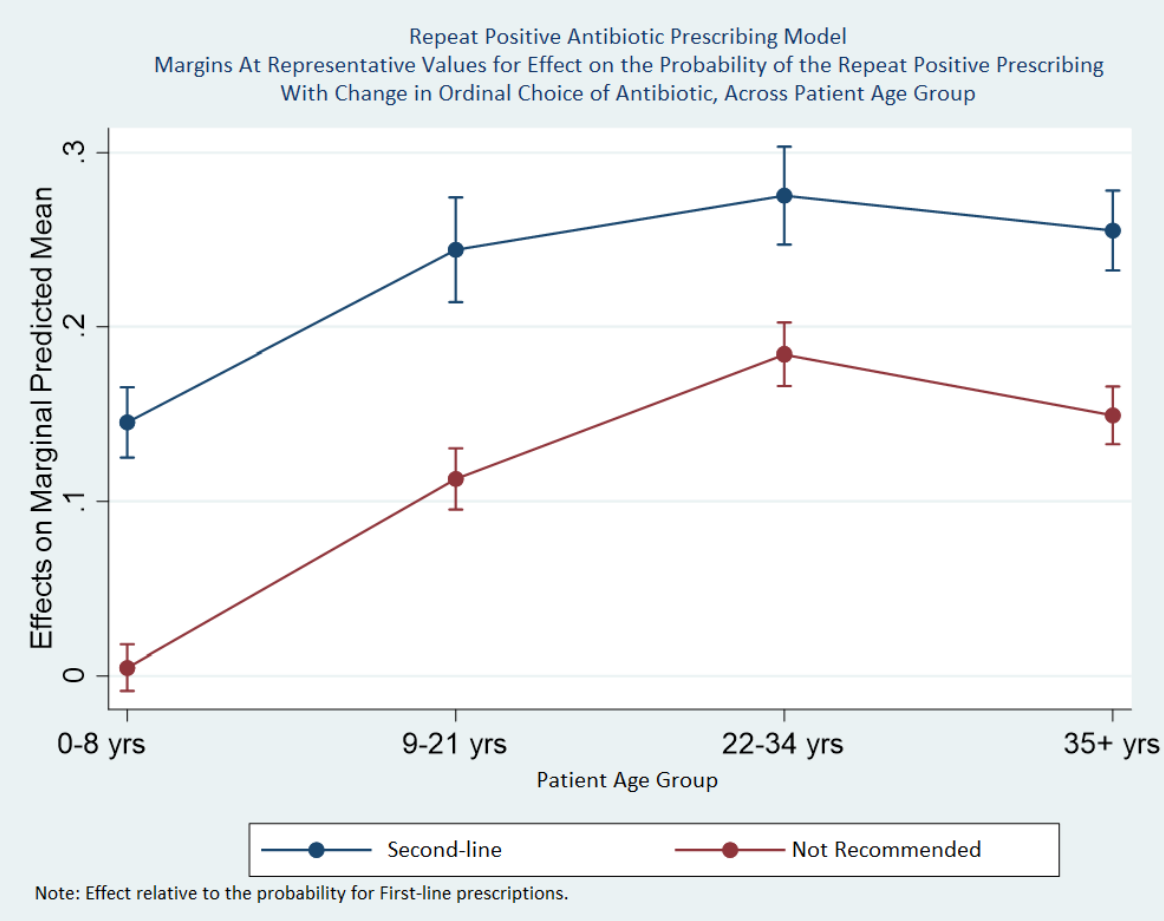


Figure C-15: Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in ordinal choice of antibiotic prescribed, across patient age groups, relative to the probability of repeats being issued on first-line prescriptions

C.10 Comparison with fixed-effects models

Table C-26: Three fixed-effects only comparisons for the inappropriate decision model

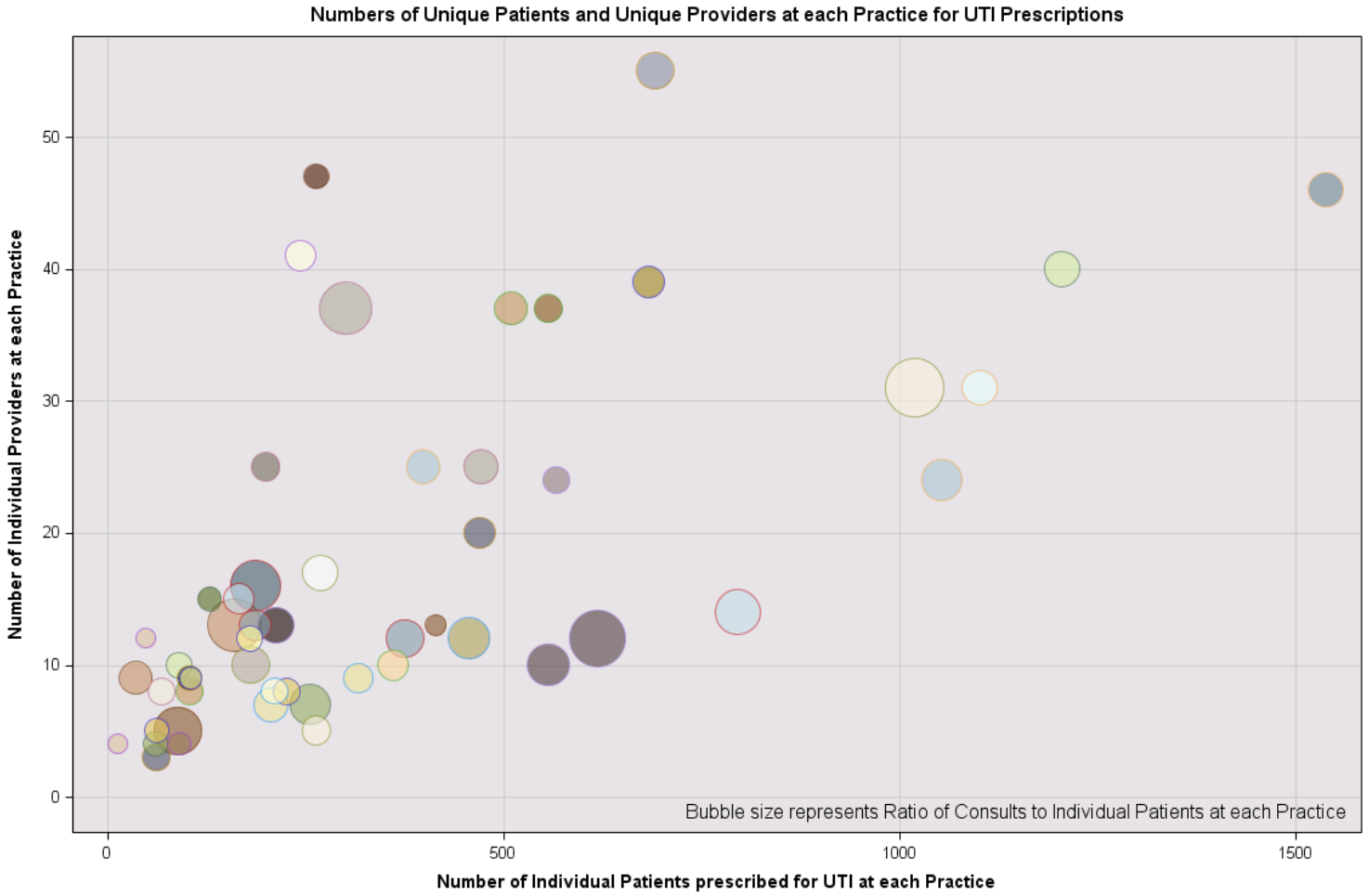
Inappropriate Decision Model	Mixed, two-level model (levels for patient and for unique combination of provider ID & practice ID)		Fixed model with dummies for practice		Fixed model with no practice	
	Exp. coeff.	t-statistic	Exp. coeff.	t-statistic	Exp. coeff.	t-statistic
Patient age group (ref. 0-8 yrs)						
	0.772***	-28.18	0.705***	-27.37	0.662***	-26.38
	0.797***	-30.31	0.689***	-27.83	0.590***	-24.64
	0.721***	-28.77	0.661***	-28.03	0.606***	-26.56
Patient gender (ref. female)						
Male	0.0500*	-2.11	0.0452*	-2.02	0.0479*	-2.19
Patient age group ## Gender (ref. # female)						
# Male	-0.207***	(-5.24)	-0.185***	(-4.96)	-0.181***	(-4.97)
# Male	-0.164***	(-4.32)	-0.179***	(-4.99)	-0.193***	(-5.50)
# Male	-0.0970**	(-2.74)	-0.0804*	(-2.42)	-0.0888**	(-2.73)
Patient penicillin sensitivity (ref. negative)						
Positive	0.351***	-11.85	0.330***	-11.85	0.327***	-12
Patient concessions status (ref. negative)						
Positive	0.0401*	-2.13	0.0483**	-2.74	0.0539**	-3.19
Patient mental health condition (ref. negative)						
Positive	0.0527*	-2.43	0.0616**	-3.03	0.0474*	-2.41
Missing	0.274	-1.25	0.747***	-5.16	0.499***	-13.64
Weekend consultation (ref. negative)						
Positive	0.216***	-8.81	0.300***	-14.08	0.238***	-11.66
Practice Size (ref. Medium/Large)						
Small	0.518***	-3.97	0.271*	-2.41	0.0761***	-3.92
Patient PHN (ref. Perth North)						
Perth South	-0.0472	(-1.16)	-0.407***	(-10.71)	-0.143***	(-9.58)
Country WA	0.0336	-0.73	-0.107*	(-2.24)	0.0272	-1.38
Interstate	0.190*	-2.47	0.0045	-0.06	0.156*	-2.32
Missing	0.125	-1.9	-0.0888	(-1.63)	0.139*	-1.99
Patient disadvantage status (ref. negative)						
Positive	0.0614*	-1.96			-0.174***	(-7.37)
Missing	-0.0817*	(-2.36)			-0.123***	(-5.83)
Patient with multiple URTI episodes (ref. negative)						
Positive			-0.0505**	(-3.18)		
Patient in remote area (ref. negative)						
Positive					0.215***	-6
Missing					-0.121	(-1.16)
_cons	-0.992***	(-19.50)	-0.763***	(-10.13)	-0.800***	(-42.34)
/						
var(_cons[~c	1.014***	-15.72				
N	111848		111848		111848	

Note: exponentiated coefficients, significance: * p<0.05, ** p<0.01, ***p<0.001

APPENDIX D – APPENDICES TO THE PREDICTORS OF INAPPROPRIATE PRESCRIBING FOR URINARY TRACT INFECTION CHAPTER (CHAPTER 5)

D.1 Clustering of patients and providers for initial presentations of urinary tract infection

Figure D-1: Bubble plot of clustering by inidividual patients, providers and practices for initial presentations of urinary tract infection



D.2 Antibiotic prescriptions

Table D-1: Frequency table of antibiotic prescriptions for initial presentations of urinary tract infection, by Anatomical Therapeutic Chemical classification

Anatomical Therapeutic Classification class	Frequency	Percent	Cumulative Percent
Beta-lactamase resistant penicillins	5	0.03	0.03
Beta-lactamase sensitive penicillins	8	0.04	0.07
Combinations of penicillins, incl. be..	1,402	7.8	7.87
Combinations of sulfonamides and trim..	336	1.87	9.74
First-generation cephalosporins	7,374	41.03	50.77
Fluoroquinolones	498	2.77	53.54
Lincosamides	3	0.02	53.56
Macrolides	46	0.26	53.81
Nitrofuran derivatives	702	3.91	57.72
Penicillins with extended spectrum	511	2.84	60.56
Second-generation cephalosporins	94	0.52	61.09
Tetracyclines	17	0.09	61.18
Third-generation cephalosporins	1	0.01	61.19
Trimethoprim and derivatives	6,976	38.81	100
Total	17,973	100	

Table D-2: Frequency table of antibiotic active ingredients prescribed but not recommended in the guidelines for initial presentations of urinary tract infection

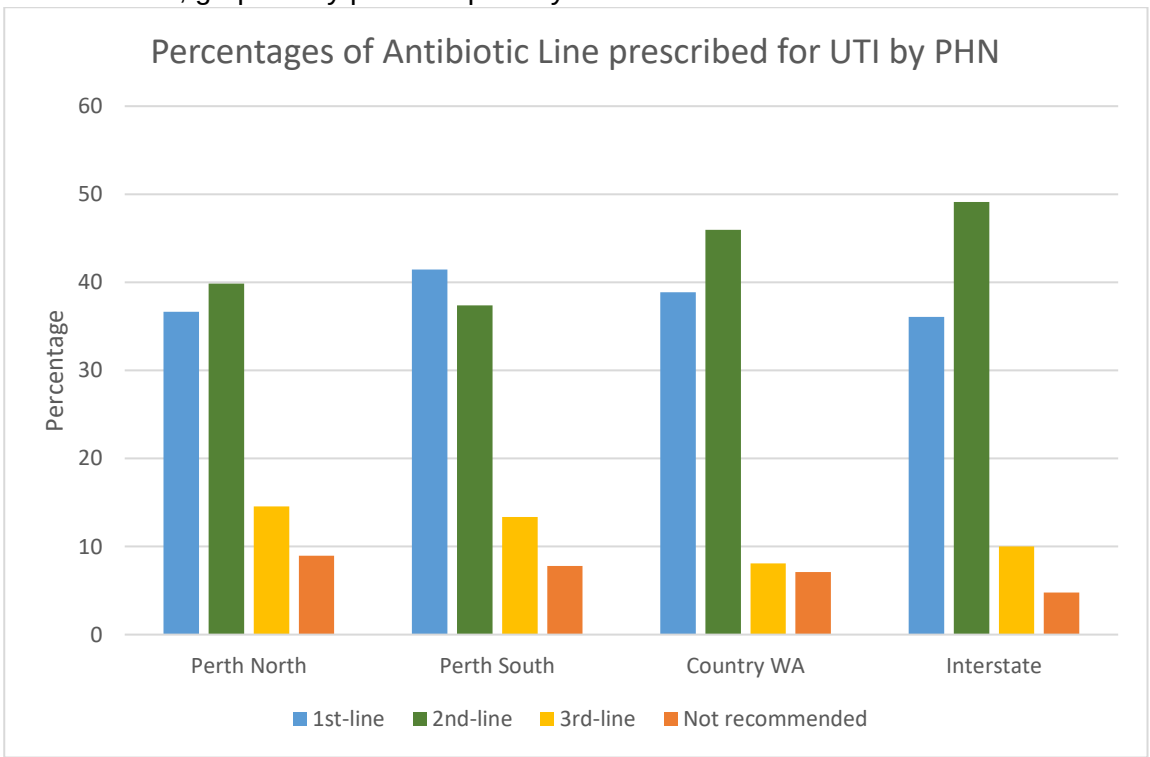
Active ingredient	Frequency	Percent
Amoxicillin	510	32.57
Ampicillin	1	0.06
Azithromycin	11	0.7
Cefaclor	83	5.3
Ceftriaxone	1	0.06
Cefuroxime	11	0.7
Ciprofloxacin	68	4.34
Clarithromycin	10	0.64
Clindamycin	3	0.19
Doxycycline	17	1.09
Erythromycin	16	1.02
Flucloxacillin	5	0.32
Nitrofurantoin	628	40.1
Phenoxymethylpenicillin	8	0.51
Roxithromycin	9	0.57
Trimethoprim with sulfamethoxazole	185	11.81
Total	1,566	100

Table D-3: Frequency table of ordinal choice of antibiotic prescribed, and primary health network, for antibiotic prescriptions for initial presentations of urinary tract infection

Primary Health Network	First-line	Second-line	Third-line	Not Recommended	Total
Perth North	2,603	2,804	787	724	6,918
	37.63	40.53	11.38	10.47	100
Perth South	2,413	2,219	652	535	5,819
	41.47	38.13	11.2	9.19	100
Country WA	1,904	2,125	406	269	4,704
	40.48	45.17	8.63	5.72	100
Interstate	93	108	21	6	228
	40.79	47.37	9.21	2.63	100
Missing	114	118	40	32	304
	37.5	38.82	13.16	10.53	100
Total	7,127	7,374	1,906	1,566	17,973
	39.65	41.03	10.6	8.71	100

Key
frequency
row percentage

Figure D-2: Bar graph of ordinal line of antibiotic prescribed for initial presentations of urinary tract infection, graphed by patient's primary health network



D.3 Ordinal choice of antibiotic prescribed for urinary tract infection

Table D-4: Frequency table of first-line and non-first-line antibiotic prescriptions, for initial presentations of urinary tract infection, by patient age group, including a ratio of non-first-line to first-line prescriptions

	First-line	Non-first-line	Ratio of non-first-line to first-line	Total
Patient age group				
45+ yrs, ref	3,565	4,582	1.3	8,147
16-44 yrs	3,229	4,724	1.5	7,953
6-15 yrs	215	779	3.6	994
0-5 yrs	118	761	6.4	879
Total	7,127	10,846	1.5	17,973

Table D-5: Frequency table of ordinal choice of antibiotic prescribed, for initial presentations of urinary tract infection, by patient age group

Patient Age Group	First-line	Second-line	Third-line/ Last Resort	Not Recommended	Total
45+ yrs	3,565	3,034	916	632	8,147
	43.76	37.24	11.24	7.76	100
16-44 yrs	3,229	3,288	697	739	7,953
	40.6	41.34	8.76	9.29	100
6-15 yrs	215	529	155	95	994
	21.63	53.22	15.59	9.56	100
0-5 yrs	118	523	138	100	879
	13.42	59.5	15.7	11.38	100
Total	7,127	7,374	1,906	1,566	17,973
	39.65	41.03	10.6	8.71	100

Key
frequency
row percentage

Table D-6: Frequency table of patient group by ordinal choice of antibiotic prescribed, for initial presentations of urinary tract infection

Patient Group	First-line	Second-line	Third-line	Not Recommended	Total
Women	6,290	5,746	1,234	1,258	14,528
	43.3	39.55	8.49	8.66	100
Men	504	576	379	113	1,572
	32.06	36.64	24.11	7.19	100
Children < 16yrs	333	1,052	293	195	1,873
	17.78	56.17	15.64	10.41	100
Total	7,127	7,374	1,906	1,566	17,973
	39.65	41.03	10.6	8.71	100

Key
frequency
row percentage

Table D-7: Frequency table of ordinal choice of antibiotic prescribed by patient primary health network, for patients with initial presentations of urinary tract infection

Choice of Antibiotic Prescribed	Perth North	Perth South	Country WA	Interstate	Missing	Total
First-line	2,603	2,413	1,904	93	114	7,127
	36.52	33.86	26.72	1.3	1.6	100
Second-line	2,804	2,219	2,125	108	118	7,374
	38.03	30.09	28.82	1.46	1.6	100
Third-line/Last Resort	787	652	406	21	40	1,906
	41.29	34.21	21.3	1.1	2.1	100
Not Recommended	724	535	269	6	32	1,566
	46.23	34.16	17.18	0.38	2.04	100
Total	6,918	5,819	4,704	228	304	17,973
	38.49	32.38	26.17	1.27	1.69	100

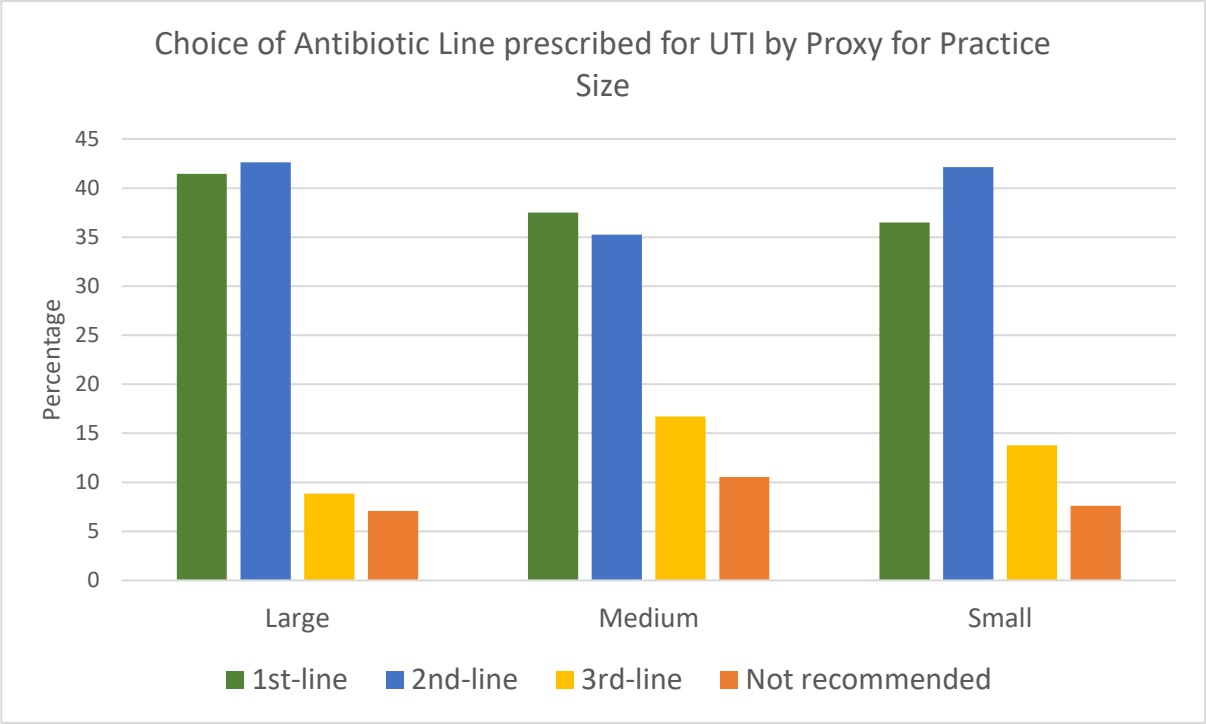
Key
frequency
row percentage

Table D-8: Frequency table of ordinal choice of antibiotic prescribed by patient primary health network, for patients with initial presentations of urinary tract infection

Ordinal Choice of Antibiotic Prescribed	Small Practice	Medium/Large Practice	Total
First-line	6,653	474	7,127
	93.35	6.65	100
Second-line	6,567	807	7,374
	89.06	10.94	100
Third-line/Last resor	1,759	147	1,906
	92.29	7.71	100
Not Recommended	1,432	134	1,566
	91.44	8.56	100
Total	16,411	1,562	17,973
	91.31	8.69	100

Key
frequency
row percentage

Figure D-3: Bar graph of ordinal choice of antibiotic prescribed for initial presentations of urinary tract infection, by (proxy for) practice size



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D.4 Whether repeats were issued on antibiotic prescriptions

D.4.1 Repeats issued on all antibiotic prescriptions for urinary tract infection

Table D-9: Frequency table for ordinal choice of antibiotic prescribed by patient's primary health network, for patients with initial presentations of urinary tract infection

Patient Age Group	Repeat Negative	Repeat Positive	Total
45+ yrs	5,701	2,446	8,147
	69.98	30.02	100
16-44 yrs	5,947	2,006	7,953
	74.78	25.22	100
6-15 yrs	630	364	994
	63.38	36.62	100
0-5 yrs	597	282	879
	67.92	32.08	100
Total	12,875	5,098	17,973
	71.64	28.36	100

Key
frequency
row percentage

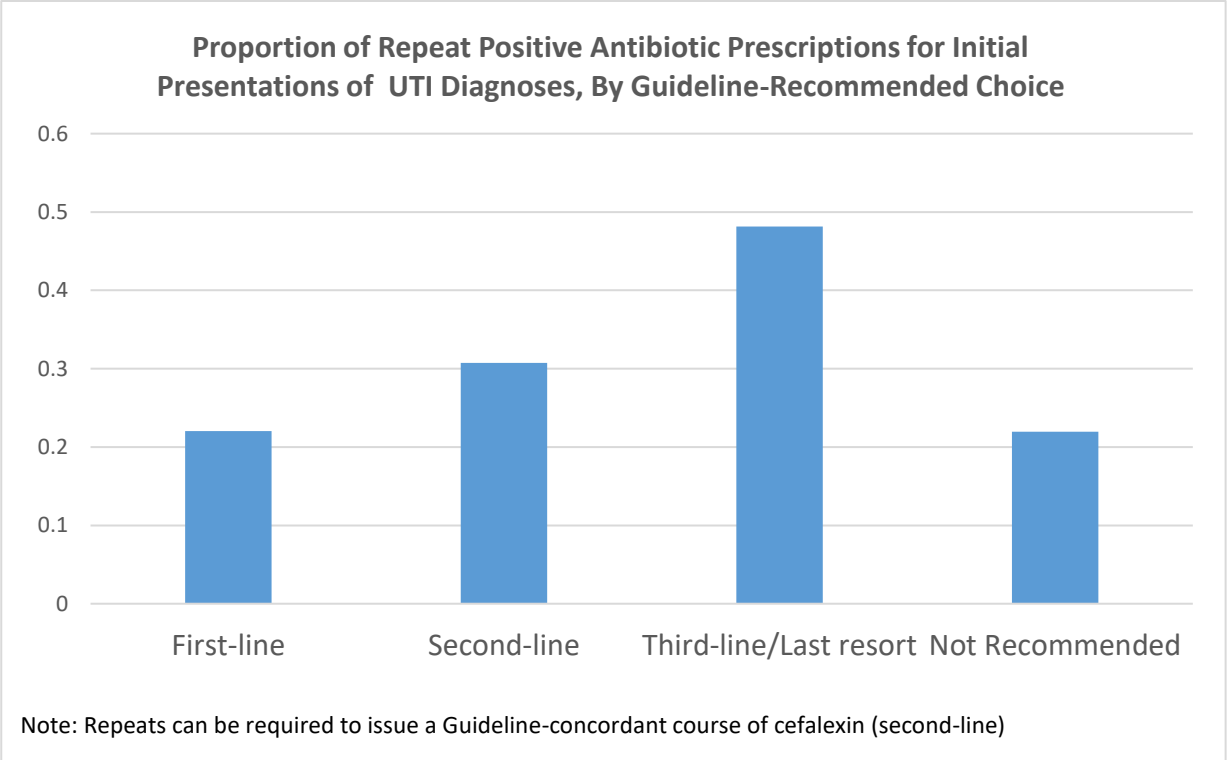
Table D-10: Frequency table of whether repeats were issued on antibiotic prescriptions for initial presentations of urinary tract infection, by Anatomical Therapeutic Chemical class

ATC class	Repeat Negative	Repeat Positive	Total
Beta-lactamase inhibitors	732	729	1,461
First-generation cephalosporins	4,934	2,083	7,017
Fluoroquinolones	280	235	515
Glycopeptides	1	0	1
Lincosamides	4	1	5
Macrolides	70	18	88
Nitrofurantoin	565	129	694
Penicillins	331	110	441
Second-generation cephalosporins	82	15	97
Tetracyclines	15	14	29
Third-generation cephalosporins	1	0	1
Trimethoprim	5,145	1,395	6,540
Trimethoprim – sulphonamide combinations	181	132	313
Total	12,341	4,861	17,202

Table D-11: Frequency table of whether repeats were issued on prescriptions, by ordinal choice of antibiotic prescribed, for initial presentations of urinary tract infection

Repeat Prescription Status	First-line	Second-line	Not Recommended	Total
Negative	17,701	4,171	13,138	35,010
	78.65	47.42	64.47	67.75
Positive	4,804	4,625	7,239	16,668
	21.35	52.58	35.53	32.25
Total	22,505	8,796	20,377	51,678
	100	100	100	100

Key
frequency
row percentage



Note: Repeats can be required to issue a Guideline-concordant course of cefalexin (second-line)

Figure D-4: Bar graph of antibiotic prescriptions with repeats issued on them, for initial presentations of urinary tract infection, by ordinal choice of antibiotic prescribed

Table D-12: Frequency table of patient age group by whether repeats were issued on the prescription, for initial presentations of urinary tract infection

	Repeat Prescription Status		
	Negative	Positive	Total
Patient Age Group			
45+ yrs, ref	5,701	2,446	8,147
	69.98	30.02	100
16-44 yrs	5,947	2,006	7,953
	74.78	25.22	100
6-15 yrs	630	364	994
	63.38	36.62	100
0-5 yrs	597	282	879
	67.92	32.08	100
Total	12,875	5,098	17,973
	71.64	28.36	100

Key
frequency
row percentage

D.4.2 Analysis of cefalexin prescriptions issued with repeats, for initial presentations of urinary tract infection

The recommendation for penicillin-sensitive patients with UTI is cephalexin. For adult females, the course recommended is five days' duration and 500mg strength, twelve-hourly, which amounts to a total of 5,000mg. Whereas adult males are recommended seven days' worth, i.e. 7,000mg. Children over one month in age required 12.5mg/kg up to 500mg orally, six-hourly (as opposed to twelve-hourly in adults), for five days, totalling a maximum of 10,000mg.

The liquid formulation five men received, would have required a repeat to take them from 5g course to 7g course. All five men receiving liquid formulation needed repeats but they were not needed for capsules (Table D-13).

Table D-13: Frequency table of medicine quantity and medicine strength, for male adults prescribed repeats for cephalexin with urinary tract infection

	Medicine quantity				
Medicine strength	1	100mL	20	40	Total
250mg	0	0	11	1	12
250mg/5mL	4	1	0	0	5
500mg	0	0	219	0	219
Total	4	1	230	1	236

The cefalexin prescriptions with repeats present provided to women at least sixteen years are listed in Table D-14. None of these women required repeats for cephalexin.

Table D-14: Frequency table of medicine quantity and medicine strength, for female adults prescribed repeats for cephalexin with urinary tract infection

	medicine quantity							
Medicine strength	1	10	100mL	15	2*20	20	40	Total
250mg	0	0	0	0	1	152	4	157
250mg/5mL	12	0	6	0	0	0	0	18
500mg	0	4	0	1	0	1,291	4	1,300
Total	12	4	6	1	1	1,443	8	1,475

Table D-15 provides a list of cephalexin prescriptions with repeats provided to children under eighteen years of age, for good measure, as GPs might work on this cutoff for children, unlike sixteen years used for the modelling in this thesis.

Table D-15: Frequency table of medicine quantity and medicine strength, for children under eighteen years issued repeats on cephalexin prescriptions for initial presentations of urinary tract infection

	Medicine quantity			
Medicine strength	1	100mL	20	Total
125mg/5mL	42	14	0	56
250mg	0	0	13	13
250mg/5mL	168	65	0	233
250mg/5ml	1	0	0	1
500mg	0	0	13	13
Total	211	79	26	316

For 16-17 year olds, both the 250mg and 250mg/5mL could have required repeats if treated as a child, or 500mg if treated as adult (Table D-16). This is the reason for examination of 16-17 year olds separately. However, the 500mg (n=10) did not require repeats as already a 10,000mg course.

Table D-16: Frequency table of medicine quantity and medicine strength, for 16-17 year olds issued repeats on cefalexin prescriptions for initial presentations of urinary tract infection

	Medicine quantity			
Medicine strength	1	100mL	20	Total
250mg	0	0	1	1
250mg/5mL	6	2	0	8
500mg	0	0	10	10
Total	6	2	11	19

For children under 16, those receiving 500mg x20 received a full course so did not require a repeat, as seen in Table D-17. Those receiving liquid formulations likely required repeats, as did the 250mg x20 course.

Table D-17: Frequency table of medicine quantity and medicine strength, for children under sixteen years issued repeats for cefalexin for initial presentations of urinary tract infection

	Medicine quantity			
Medicine strength	1	100mL	20	Total
125mg/5mL	42	14	0	56
250mg	0	0	12	12
250mg/5mL	162	63	0	225
250mg/5ml	1	0	0	1
500mg	0	0	3	3
Total	205	77	15	297

Therefore for UTI, of cephalexin scripts with repeats, 5/236 men, 0/2475 women, 10/19 16-17yrs, 294/297 children may have required repeats. Totalling 0.2% adults receiving repeats for cephalexin required them. 53% children 16-17 potentially required repeats, and 99% children under sixteen potentially required repeats. The strong majority of repeats were unnecessary for adults and the strong majority were potentially necessary for children.

For women 16 or over, the duration was variable, between 5 and 14 days as seen in Table D-18, and even “after sexual intercourse”. Overtreatment was common.

Table D-18: Frequency table of medicine instructions for adult females receiving cefalexin prescriptions with repeats issued on them for initial presentations of urinary tract infection

Medicine instructions	Frequency	Percent	Cumulative Percent
1 TDS	1	0.21	0.21
1 bd for 5 days	1	0.21	0.42
1 cap tds	11	2.33	2.75
1 capsule 6 hrly p/o	1	0.21	2.96
1 four times a day for 7 days	1	0.21	3.17
1 po BD for 5 days	1	0.21	3.38
1 qid for 10 days	1	0.21	3.59
1 tab bd	6	1.27	4.86
1 tab tds	37	7.82	12.68
1 tab tds for 5 days	2	0.42	13.11
1 tablet 6 hourly for 5 days	1	0.21	13.32
1 tds for 5 days	1	0.21	13.53
1/2 hr before food	1	0.21	13.74
10 days	2	0.42	14.16
10 mL three times daily for 7 days	1	0.21	14.38
10 ml four times a day	1	0.21	14.59
10-Jul	2	0.42	15.01
10mls 6hrly, for 5 days	1	0.21	15.22
10mls Twice a day	1	0.21	15.43
14 days	2	0.42	15.86
2 capsule stat then 1 cap twice daily	1	0.21	16.07
2 stat	30	6.34	22.41
2 stat then 1 tds	1	0.21	22.62
2 stat then 2 tonight then one three ..	1	0.21	22.83
2 stat, then 1 qid for 5 days	1	0.21	23.04
2 to start	2	0.42	23.47
2 weeks	1	0.21	23.68
250mg 6 hrly p/o	1	0.21	23.89
250mg six hourly for five days	1	0.21	24.1
5 days	6	1.27	25.37
5 days but can extend to 10 days	1	0.21	25.58
5-10 days	1	0.21	25.79
5-7 days	1	0.21	26
5-Jul	1	0.21	26.22
500mg BD for 5 days	2	0.42	26.64
500mg six hourly for five days	2	0.42	27.06
500mg six hourly for seven days	1	0.21	27.27
500mg*2 (1gm) 12 hrly p/o for 5 days	1	0.21	27.48
7 days	2	0.42	27.91
7 to 10 days	1	0.21	28.12

	7-Jul	1	0.21	28.33
7mls tds		1	0.21	28.54
After sexual intercourse as directed ..		1	0.21	28.75
Double dose first 4 doses		1	0.21	28.96
FOR 5 DAYS		9	1.9	30.87
FOR 6 DAYS		1	0.21	31.08
For 10 days		1	0.21	31.29
For 5 days		8	1.69	32.98
For 5 days, after food		1	0.21	33.19
For 7 days		2	0.42	33.62
For five days		1	0.21	33.83
For five days.		2	0.42	34.25
May be taken with or without food. Ad..		1	0.21	34.46
One capsule two times daily for 5 days		1	0.21	34.67
One capsule two times daily for 7 days		1	0.21	34.88
One tablet twice a day for 5 days		1	0.21	35.1
One tablet twice a day for seven days		1	0.21	35.31
One tablet twice daily for 5 days and..		1	0.21	35.52
Please take 2 tds for the 1st 1-2, th..		1	0.21	35.73
THEN 1 Q6 HRS		1	0.21	35.94
Take 2 initially and then 1 tds		1	0.21	36.15
Three times daily		1	0.21	36.36
To start if needed		1	0.21	36.58
a.c.		19	4.02	40.59
and 1 6 hourly		1	0.21	40.8
as directed		1	0.21	41.01
as required if gets a UTI on trip - 3..		1	0.21	41.23
complete course		1	0.21	41.44
delayed script		1	0.21	41.65
finish all		1	0.21	41.86
fo 10 days		1	0.21	42.07
for 3 to 5 days		1	0.21	42.28
for 1 week		1	0.21	42.49
for 10 days		26	5.5	47.99
for 10/7		1	0.21	48.2
for 14 days		1	0.21	48.41
for 1st script then one tab at night ..		1	0.21	48.63
for 2 weeks		1	0.21	48.84
for 24 hours then one bd for 4 days		1	0.21	49.05
for 3-5 days		1	0.21	49.26
for 5 days		76	16.07	65.33
for 5 days ONLY		1	0.21	65.54
for 5 days and review		1	0.21	65.75
for 5 days for acute infections		4	0.85	66.6
for 5 days for bladder infection		1	0.21	66.81
for 5 days for bladder infection .		1	0.21	67.02
for 5 days for urine infection		1	0.21	67.23
for 5 days with or without food.		1	0.21	67.44
for 5 days.		1	0.21	67.65
for 5 or up to 10 days		1	0.21	67.86
for 5-10 days		1	0.21	68.08
for 5-7		1	0.21	68.29
for 5-7 days		2	0.42	68.71
for 5/7		2	0.42	69.13
for 5d		1	0.21	69.34
for 6 days		1	0.21	69.56
for 7 days		21	4.44	74
for 7 days then clearance testing 7 ..		1	0.21	74.21
for 7 days.		1	0.21	74.42
for 7- 10 days		1	0.21	74.63
for 7-10 days		2	0.42	75.05
for 7days		1	0.21	75.26
for UTI		1	0.21	75.48
for about six days for UTI		1	0.21	75.69

for five days	6	1.27	76.96
for five days.	2	0.42	77.38
for one day then one bd total 5 days	1	0.21	77.59
for one week	1	0.21	77.8
for ten days	1	0.21	78.01
i tds	4	0.85	78.86
ii bd 7 days	1	0.21	79.07
ii stat then i tds	1	0.21	79.28
increase to 4 times daily if needed	1	0.21	79.49
m.d.u.	65	13.74	93.23
one bd for 7 days	1	0.21	93.45
one qid	5	1.06	94.5
one tab three times per day for one w..	1	0.21	94.71
one tds	1	0.21	94.93
one tds for 5 days	1	0.21	95.14
p.c.	2	0.42	95.56
p.r.n.	4	0.85	96.41
take one tablet every 8 hrs	2	0.42	96.83
take two to start and then one capsul..	1	0.21	97.04
two twice a day until finished	1	0.21	97.25
until all taken	1	0.21	97.46
until all taken.	2	0.42	97.89
until course complete	1	0.21	98.1
until finished	1	0.21	98.31
with lots of water	1	0.21	98.52
x 5 days	5	1.06	99.58
x 7 days	2	0.42	100
Total	473	100	

For men at least sixteen years of age, notable variation in duration also, there was under and over-treatment, ranging from between 5 to 14 days (Table D-19).

Table D-19: Frequency table of medicine instructions for adult males receiving cefalexin prescriptions with repeats issued on them, for initial presentations of urinary tract infection

Medicine instructions	**Frequency**	**Percent**	**Cumulative Percent**
1 BD	1	1	1
1 cap tds	3	3	4
1 tab bd	1	1	5
1 tab tds	17	17	22
10mls tds	1	1	23
for 14/7	1	1	24
2 stat	8	8	32
2 stat the 1 6hrly	1	1	33
2 stat then 1 tds until finished.	1	1	34
250mg six hourly for ten days	1	1	35
for 5/7	1	1	36
7mls tds	1	1	37
FOR 14 DAYS	1	1	38
Ffirst two doses 6 hours apart take t..	1	1	39
For 14 days	2	2	41
For 2 weeks	1	1	42
For fourteen days	1	1	43
UTI management	1	1	44
a.c.	2	2	46
for 10 days	8	8	54
for 10 days. Save repeat to use if ha..	1	1	55
for 14 days	7	7	62

for 2 weeks	1	1	63
for 2/7 ,1 td	1	1	64
for 5 days	7	7	71
for 7 days	3	3	74
for seven days	1	1	75
ii qid for infection for 5/7	1	1	76
m.d.u.	16	16	92
one table four times daily for three ..	1	1	93
one tds	1	1	94
take two capsule four times daily 24 ..	1	1	95
take two now and two tonight then one..	1	1	96
then 1 tds for 1 week for bladder inf..	1	1	97
two tabs stat then two tonight then o..	1	1	98
until finished.	1	1	99
x 5 days	1	1	100
Total	100	100	

For children under 16, the duration was also varied, ranging between 3 and 14 days, and most commonly 5 days, as per Table D-20 below:

Table D-20: Frequency table of medicine instructions for children under sixteen years of age receiving cefalexin prescriptions with repeats issued on them, for initial presentations of urinary tract infection

Medicine instructions	Frequency	Percent	Cumulative Percent
1 cap tds	1	0.62	0.62
1.2 mls	1	0.62	1.23
1/2 hr before food for 10 days	1	0.62	1.85
10 mls twice a day	1	0.62	2.47
10 days	1	0.62	3.09
10mL four times a day for 5 days	1	0.62	3.7
10ml stat	1	0.62	4.32
10mls, 6hrly for 5 days	1	0.62	4.94
12.5mg/kg 6hrly for 5 days orally	1	0.62	5.56
15kg	1	0.62	6.17
15ml (500mg) bd	1	0.62	6.79
250mg six hourly for five days	1	0.62	7.41
250mg/5mL QID for 5 days	1	0.62	8.02
3 mls 6 hourly for 1 week	1	0.62	8.64
3.75mL qid	1	0.62	9.26
300mg 6hourly 5 days	1	0.62	9.88
4 ml x 6 hrly	1	0.62	10.49
4.5ml six hourly for 5 days	1	0.62	11.11
4ml four times daily	1	0.62	11.73
5 days	5	3.09	14.81
5 ml every 6 hours for 5 days	1	0.62	15.43
5 ml four times a day, for 5-7 days. ..	1	0.62	16.05
5 ml orally three times a day for 7 d..	1	0.62	16.67
5-Jul	1	0.62	17.28
500 mg every 6 hours for 7 days.	1	0.62	17.9
5mls four times daily for five days	1	0.62	18.52
5mls tds	4	2.47	20.99
5mls, 6hrly for 5 days	1	0.62	21.6
6 mL two times daily for 7 days	1	0.62	22.22
6 ml (300mg) po qid	1	0.62	22.84
6.5 mls qid for 7 days	1	0.62	23.46
6mL qid	1	0.62	24.07
6ml 4 times a day for 5 days	1	0.62	24.69
7.5 ml tid for 5 days	1	0.62	25.31

7ml (175mg) PO TDS for 5d	1	0.62	25.93
9 days	1	0.62	26.54
9.5ml four times a day, 5 days	1	0.62	27.16
9ml twice a day for 5-7 days	1	0.62	27.78
FOR 5 DAYS	2	1.23	29.01
FOR 6 DAYS	2	1.23	30.25
For 1 week	1	0.62	30.86
For 3days	1	0.62	31.48
For 5 days	3	1.85	33.33
Give 2.7mls every 6 hours for 5 days	1	0.62	33.95
May be taken with or without food	1	0.62	34.57
Please dissolve one capsule in 5 mls ..	1	0.62	35.19
a.c.	2	1.23	36.42
by metric measure for 7 days	1	0.62	37.04
c.c.	2	1.23	38.27
for 10 days	6	3.7	41.98
for 10 days.	1	0.62	42.59
for 14 days	2	1.23	43.83
for 3 days	1	0.62	44.44
for 5 days	30	18.52	62.96
for 5 days only	1	0.62	63.58
for 5 days.	1	0.62	64.2
for 5- 7 days	1	0.62	64.81
for 5-7days	1	0.62	65.43
for 6 days	1	0.62	66.05
for 7 days	33	20.37	86.42
for 7 days.	1	0.62	87.04
for 7-10 day	1	0.62	87.65
fro 10 days	1	0.62	88.27
m.d.u.	18	11.11	99.38
x 5 days	1	0.62	100
Total	162	100	

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D.5 Marginal effects for the ordinal choice of antibiotic prescribing model for urinary tract infection

D.5.1 Average marginal effects

Table D-21: Average marginal effects for ordinal choice of antibiotic prescribed for initial presentations of urinary tract infection (Model 1)

Average Marginal Effects (Model 1) Ordinal Choice of Antibiotic Prescribed for Initial Presentations of UTI Model						
Variable	**dy/dx**	**Std. Err.**	**z**	**P>z**	**[95% Conf.**	**Interval]**
Patient Age Group						
45 years and over	(base outcome)					
16-44 years (predict Outcome:)						
First-line	-0.0299301	0.006937	-4.31	0.000	-0.0435263	-0.0163338
Second-line	0.0113018	0.0027619	4.09	0.000	0.0058885	0.0167151
Third-line	0.0089341	0.0021224	4.21	0.000	0.0047743	0.0130939
Not Recommended	0.0096942	0.0024878	3.9	0.000	0.0048183	0.0145702
6-15 years (predict Outcome:)						
First-line	-0.14676	0.0120251	-12.2	0.000	-0.1703287	-0.1231912
Second-line	0.0359399	0.0051579	6.97	0.000	0.0258306	0.0460492
Third-line	0.0488681	0.0045421	10.76	0.000	0.0399658	0.0577704
Not Recommended	0.0619519	0.0071379	8.68	0.000	0.047962	0.0759419
0-5 years (predict Outcome:)						
First-line	-0.1849305	0.0118474	-	0.000	-0.208151	-0.1617101
Second-line	0.0342046	0.0066219	5.17	0.000	0.0212259	0.0471833
Third-line	0.0637304	0.0047629	13.38	0.000	0.0543953	0.0730654
Not Recommended	0.0869956	0.0086858	10.02	0.000	0.0699717	0.1040194
Patient Gender						
Female	(base outcome)					
Male (predict Outcome:)						
First-line	-0.0892231	0.0099851	-8.94	0.000	-0.1087935	-0.0696527
Second-line	0.0234147	0.0033992	6.89	0.000	0.0167523	0.0300771
Third-line	0.0293018	0.0035705	8.21	0.000	0.0223037	0.0363
Not Recommended	0.0365066	0.0050462	7.23	0.000	0.0266162	0.0463969
Repeat on Prescription Status						
Negative	(base outcome)					
Positive (predict Outcome:)						
First-line	-0.0962027	0.0077177	-	0.000	-0.111329	-0.0810763
Second-line	0.0296811	0.0035305	8.41	0.000	0.0227615	0.0366006
Third-line	0.0306878	0.0026988	11.37	0.000	0.0253982	0.0359774
Not Recommended	0.0358338	0.0037132	9.65	0.000	0.0285561	0.0431115
Comorbid Condition Status						
Negative	(base outcome)					
Positive (predict Outcome:)						
First-line	-0.0369297	0.0080796	-4.57	0.000	-0.0527654	-0.0210939
Second-line	0.011216	0.0025104	4.47	0.000	0.0062957	0.0161364
Third-line	0.0116508	0.0026136	4.46	0.000	0.0065282	0.0167735
Not Recommended	0.0140628	0.0033004	4.26	0.000	0.0075942	0.0205314
Missing (predict Outcome:)						
First-line	-0.0928739	0.0543549	-1.71	0.088	-0.1994077	0.0136598
Second-line	0.0217922	0.0072047	3.02	0.002	0.0076713	0.0359131
Third-line	0.0307306	0.0192275	1.6	0.110	-0.0069545	0.0684158
Not Recommended	0.0403511	0.028641	1.41	0.159	-0.0157842	0.0964864
Culture Testing Status						
Negative	(base outcome)					
Positive (predict Outcome:)						
First-line	0.0598695	0.0195999	3.05	0.002	0.0214544	0.0982845
Second-line	-0.0225814	0.0085514	-2.64	0.008	-0.0393418	-0.0058209
Third-line	-0.0176727	0.0055061	-3.21	0.001	-0.0284645	-0.0068809
Not Recommended	-0.0196154	0.0057917	-3.39	0.001	-0.0309669	-0.008264

Average Marginal Effects (Model 1) continued						
Ordinal Choice of Antibiotic Prescribed for Initial Presentations of UTI Model						
Variable	**dy/dx**	**Std. Err.**	**z**	**P>z**	**[95% Conf.**	**Interval]**
Urine Dipstick Testing Status						
Negative	(base outcome)					
Positive (predict Outcome:)						
First-line	0.0653249	0.0210125	3.11	0.002	0.0241412	0.1065086
Second-line	-0.0248589	0.0093127	-2.67	0.008	-0.0431115	-0.0066062
Third-line	-0.0192277	0.0058638	-3.28	0.001	-0.0307205	-0.0077349
Not Recommended	-0.0212383	0.0061098	-3.48	0.001	-0.0332133	-0.0092633

Average Marginal Effects

The risk of higher-line prescribing decreased with increasing age. Children under six years were the least likely to receive first-line antibiotics *(-0.15, p<0.001, 95%CI: -0.208, -0.162)* and more likely to receive higher-line antibiotics than patients of the reference age, 45 years and over. Young children were six and nine percentage points respectively more likely to receive third-line *(0.064, p<0.001, 0.054, 0.073)* and not recommended *(0.087, p<0.001, 95%CI: 0.070, 0.104)* antibiotics than patients of reference age.

Children aged 6-15 years were less likely to receive first-line antibiotics than reference-age patients by fifteen percentage points *(-0.147, p<0.001, 95%CI: -0.170, -0.123)*. They were also five percentage points more likely to receive third line *(0.049, p<0.001, 95%CI: 0.040, 0.058)* and six percentage points more likely to receive not recommended antibiotics *(0.062, p<0.001, 95%CI: 0.048, 0.076).* Young adults sixteen to 44 years were three percentage points less likely to receive first-line antibiotics *(-0.029, p<0.001, 95%CI: -0.044, -0.016)*. They were also one percentage point more likely to receive second-line *(0.011, p<0.001, 95%CI: 0.006, 0.017)*, third-line *(0.009, p<0.001, 95%CI: 0.0048, 0.013),* or not recommended *(0.010, p<0.001, 95%CI: 0.0048, 0.015)* antibiotics than patients 45 years and over.

D.5.2 Margins at representative values for the effect on ordinal choice of antibiotic, with change in patient age group, across different values of whether repeats were issued on the prescription

```
. . margins, dydx(agegrp_uti_new) at (repeat_script= (1 0))

Average marginal effects                        Number of obs     =     17,973
Model VCE    : OIM

dy/dx w.r.t. : 2.agegrp_uti_new 3.agegrp_uti_new 4.agegrp_uti_new
1._predict   : Marginal predicted mean (1.choice_uti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_uti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_uti_new), predict(pr outcome(3))
4._predict   : Marginal predicted mean (4.choice_uti_new), predict(pr outcome(4))

1._at        : repeat_script   =           1        (Repeat Positive)

2._at        : repeat_script   =           0        (Repeat Negative)

------------------------------------------------------------------------------
                   |            Delta-method
                   |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
45+ years          |  (base outcome)
-------------------+----------------------------------------------------------------
16-44 years        |
     _predict#_at  |
              1 1  |  -.0289152   .0112113    -2.58   0.010    -.0508889   -.0069415
              1 2  |  -.0303206   .0082224    -3.69   0.000    -.0464362   -.0142049
              2 1  |   .0059848   .0024227     2.47   0.013     .0012365    .0107332
              2 2  |   .0133158   .0035409     3.76   0.000     .0063758    .0202558
              3 1  |   .0100159   .0039311     2.55   0.011     .0023112    .0177207
              3 2  |   .0085362   .0023855     3.58   0.000     .0038607    .0132118
              4 1  |   .0129144   .0052841     2.44   0.015     .0025577    .0232711
              4 2  |   .0084686   .0025025     3.38   0.001     .0035637    .0133735
-------------------+----------------------------------------------------------------
6-15 years         |
     _predict#_at  |
              1 1  |  -.0932033   .0176908    -5.27   0.000    -.1278766     -.05853
              1 2  |  -.1677995   .0148589   -11.29   0.000    -.1969225   -.1386765
              2 1  |   .0086763   .0042216     2.06   0.040     .0004021    .0169505
              2 2  |   .0461854   .0059019     7.83   0.000     .0346179    .0577529
              3 1  |   .0342076   .0068273     5.01   0.000     .0208263     .047589
              3 2  |   .0547683    .005543     9.88   0.000     .0439043    .0656324
              4 1  |   .0503194   .0115896     4.34   0.000     .0276041    .0730346
              4 2  |   .0668458   .0084949     7.87   0.000     .0501961    .0834955
-------------------+----------------------------------------------------------------
0-5 years          |
     _predict#_at  |
              1 1  |  -.0978473   .0195587    -5.00   0.000    -.1361816   -.0595129
              1 2  |  -.2191124   .0140971   -15.54   0.000    -.2467422   -.1914827
              2 1  |   .0087943   .0045555     1.93   0.054    -.0001343    .0177229
              2 2  |     .04347   .0078991     5.50   0.000      .027988     .058952
              3 1  |   .0360062   .0076336     4.72   0.000     .0210447    .0509678
              3 2  |   .0747738   .0056461    13.24   0.000     .0637076      .08584
              4 1  |   .0530467   .0132888     3.99   0.000     .0270011    .0790924
              4 2  |   .1008686   .0104645     9.64   0.000     .0803586    .1213786
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

Where 1=First=-line, 2=Second-line, 3=Third-line/Last Resort and 4=Not Recommended.
```

D.5.3 Margins at representative values for the effect on ordinal choice of antibiotic, with change in patient age group, across different values of patient gender

```
margins, dydx(agegrp_uti_new) at ((pat_sex)= (1 0))

Average marginal effects                        Number of obs     =     17,973
Model VCE    : OIM

dy/dx w.r.t. : 2.agegrp_uti_new 3.agegrp_uti_new 4.agegrp_uti_new
1._predict   : Marginal predicted mean (1.choice_uti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_uti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_uti_new), predict(pr outcome(3))
4._predict   : Marginal predicted mean (4.choice_uti_new), predict(pr outcome(4))

1._at        : pat_sex         =           1        (Male)

2._at        : pat_sex         =           0        (Female)

------------------------------------------------------------------------------
                  |            Delta-method
                  |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------------
45+ years         |  (base outcome)
------------------+-----------------------------------------------------------------
16-44 years       |
     _predict#_at |
             1 1  |  -.0059583   .0207157    -0.29   0.774    -.0465604    .0346437
             1 2  |  -.0326776   .0071719    -4.56   0.000    -.0467343    -.018621
             2 1  |   .0008494    .003271     0.26   0.795    -.0055616    .0072604
             2 2  |   .0123805   .0029695     4.17   0.000     .0065604    .0182006
             3 1  |   .0021195   .0073375     0.29   0.773    -.0122618    .0165008
             3 2  |   .0097537   .0021539     4.53   0.000     .0055321    .0139752
             4 1  |   .0029895   .0102435     0.29   0.770    -.0170874    .0230663
             4 2  |   .0105435   .0023975     4.40   0.000     .0058444    .0152425
------------------+-----------------------------------------------------------------
6-15 years        |
     _predict#_at |
             1 1  |  -.0933382   .0272528    -3.42   0.001    -.1467528   -.0399237
             1 2  |  -.1528324   .0128196   -11.92   0.000    -.1779585   -.1277064
             2 1  |   .0031006   .0061415     0.50   0.614    -.0089366    .0151377
             2 2  |   .0393095   .0053352     7.37   0.000     .0288527    .0497662
             3 1  |   .0350447   .0107605     3.26   0.001     .0139545    .0561349
             3 2  |   .0505613   .0048239    10.48   0.000     .0411067     .060016
             4 1  |    .055193   .0203603     2.71   0.007     .0152875    .0950984
             4 2  |   .0629617    .007448     8.45   0.000     .0483638    .0775595
------------------+-----------------------------------------------------------------
0-5 years         |
     _predict#_at |
             1 1  |  -.0951786   .0253827    -3.75   0.000    -.1449278   -.0454294
             1 2  |  -.1951013   .0127023   -15.36   0.000    -.2199973   -.1702052
             2 1  |   .0031816   .0060462     0.53   0.599    -.0086688     .015032
             2 2  |   .0371488   .0069853     5.32   0.000     .0234579    .0508396
             3 1  |   .0357668   .0100293     3.57   0.000     .0161096    .0554239
             3 2  |   .0670387   .0050991    13.15   0.000     .0570447    .0770327
             4 1  |   .0562302   .0189876     2.96   0.003     .0190153    .0934452
             4 2  |   .0909138   .0092933     9.78   0.000     .0726993    .1091283
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

Where 1=First=-line, 2=Second-line, 3=Third-line/Last Resort and 4=Not Recommended.
```

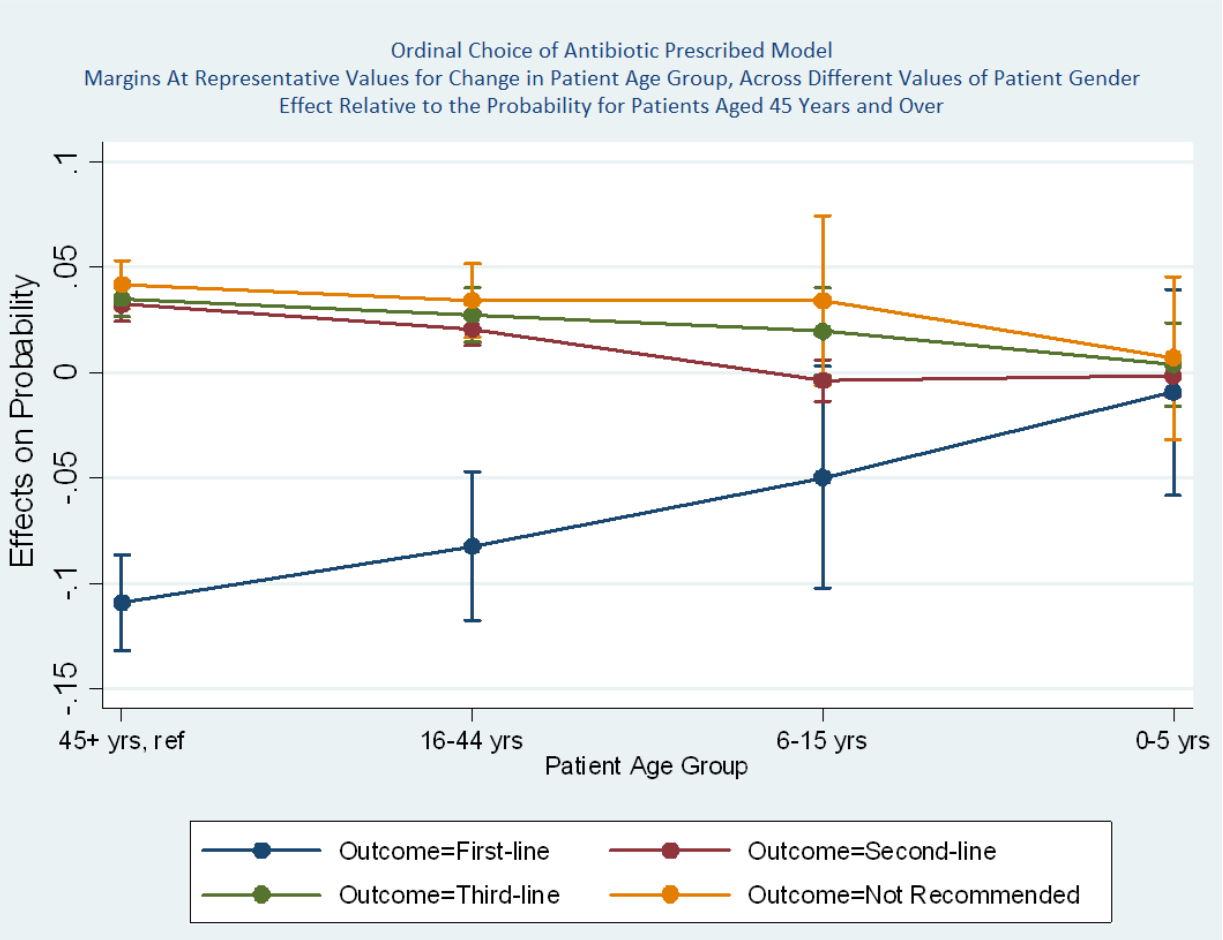


Figure D-5: Margins at representative values for the effect on the probability of each of the four ordinal choice of antibiotic outcomes occurring, with change in patient age group, across different values of patient gender

D.5.4 Margins at representative values for then effect on ordinal choice of antibiotic, with change in whether repeats were issued on the prescriptions, across different values of patient age group

```
Margins, dydx(repeat_script) at (agegrp_uti_new)=(1 2 3 4))


Average marginal effects                        Number of obs     =     17,973
Model VCE    : OIM

dy/dx w.r.t. : 1.repeat_script
1._predict   : Marginal predicted mean (1.choice_uti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_uti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_uti_new), predict(pr outcome(3))
4._predict   : Marginal predicted mean (4.choice_uti_new), predict(pr outcome(4))

1._at        : agegrp_uti_new  =           1        (45+ years)

2._at        : agegrp_uti_new  =           2        (16-44 years)

3._at        : agegrp_uti_new  =           3        (6-15 years)

4._at        : agegrp_uti_new  =           4        (0-5 years)

------------------------------------------------------------------------------
                 |            Delta-method
                 |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------------+------------------------------------------------------------
Repeat Negative  |  (base outcome)
-----------------+------------------------------------------------------------
Repeat Positive  |
    _predict#_at |
           1 1   |  -.1068389   .0104231   -10.25   0.000    -.1272678     -.08641
           1 2   |  -.1054335   .0106745    -9.88   0.000    -.1263552   -.0845118
           1 3   |  -.0322426   .0206348    -1.56   0.118     -.072686    .0082007
           1 4   |   .0144263   .0215547     0.67   0.503    -.0278202    .0566728
           2 1   |   .0367358   .0045039     8.16   0.000     .0279083    .0455634
           2 2   |   .0294049   .0042412     6.93   0.000     .0210922    .0377175
           2 3   |  -.0007733   .0019644    -0.39   0.694    -.0046235    .0030769
           2 4   |   .0020601   .0029606     0.70   0.487    -.0037426    .0078628
           3 1   |   .0330083   .0034517     9.56   0.000      .026243    .0397736
           3 2   |    .034488   .0037255     9.26   0.000     .0271861      .04179
           3 3   |   .0124476    .007996     1.56   0.120    -.0032243    .0281195
           3 4   |  -.0057593    .008585    -0.67   0.502    -.0225855     .011067
           4 1   |   .0370947   .0043699     8.49   0.000     .0285298    .0456596
           4 2   |   .0415405   .0050586     8.21   0.000      .031626    .0514551
           4 3   |   .0205683   .0134679     1.53   0.127    -.0058282    .0469648
           4 4   |  -.0107271   .0158046    -0.68   0.497    -.0417036    .0202494
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

Where 1=First=-line, 2=Second-line, 3=Third-line/Last Resort and 4=Not Recommended.


With a repeat, adults 11% less likely to receive first-line, and 3-4% more likely to receive each
of second-line, third-line, or not recommended agents. There was no significant difference in line
received for child age groups.
```

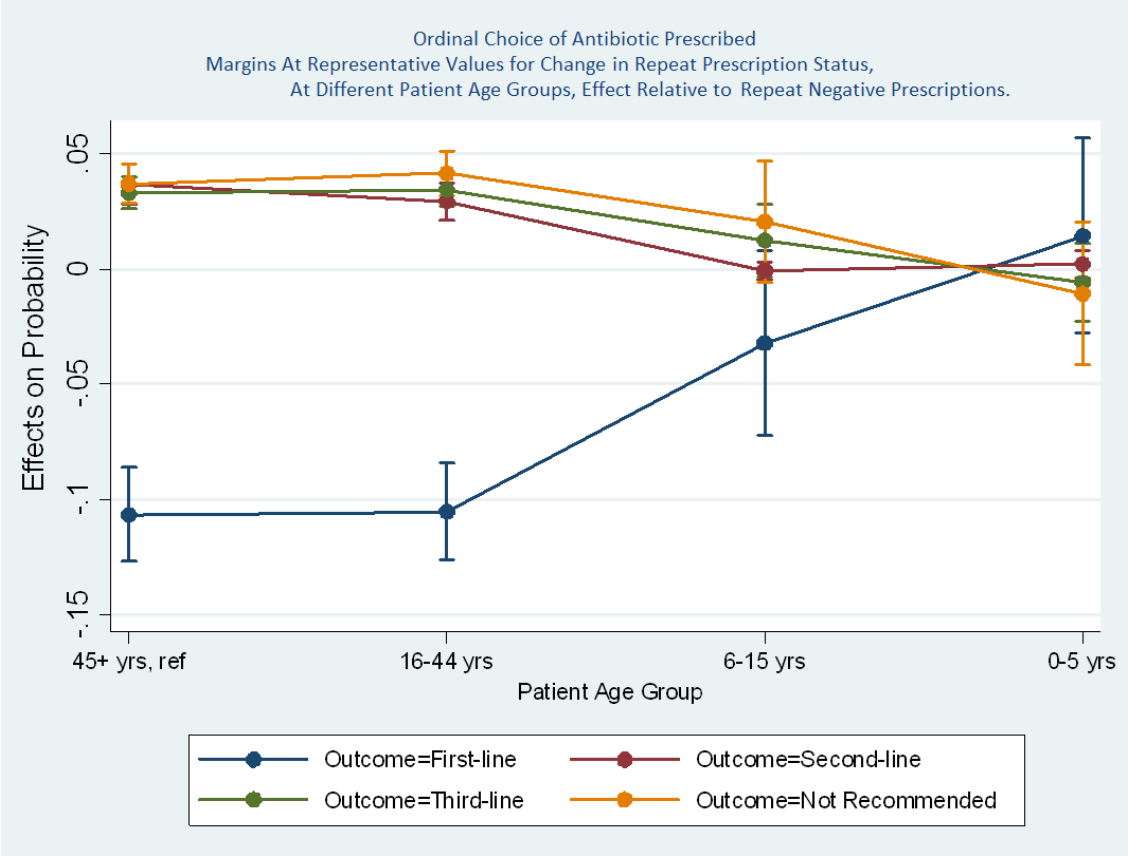


Figure D-6: Margins at representative values for the effect on the probability of the four ordinal choice of antibiotic outcomes occurring, with change in whether repeat were issued on the prescription, across different values of patient age group

D.5.5 Adjusted predictions for the effect on ordinal choice of antibiotic, at specific values of patient gender, patient age group and whether repeats were issued on the prescription

```
. margins, at(pat_sex=(0 1) agegrp_uti_new=(1 2 3 4) repeat_script=(1 0)) atmeans vsquish post

Adjusted predictions                            Number of obs     =     17,973
Model VCE    : OIM

1._predict   : Marginal predicted mean (1.choice_uti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_uti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_uti_new), predict(pr outcome(3))
4._predict   : Marginal predicted mean (4.choice_uti_new), predict(pr outcome(4))
1._at        : agegrp_uti_new  =           1        (45+ years)
               pat_sex         =           0        (Female)
               repeat_script   =           1        (Repeat Positive)
               0.pat_co~uti    =    .7753297 (mean)
               1.pat_co~uti    =    .1957381 (mean)
               2.pat_co~uti    =    .0289323 (mean)
               0.cult_tes~d    =    .9689534 (mean)
               1.cult_tes~d    =    .0310466 (mean)
               0.dipstick~d    =    .9545429 (mean)
               1.dipstick~d    =    .0454571 (mean)
               year            =    2014.602 (mean)
2._at        : agegrp_uti_new  =           1        (45+ years)
               pat_sex         =           0        (Female)
               repeat_script   =           0        (Repeat Negative)
               0.pat_co~uti    =    .7753297 (mean)
               1.pat_co~uti    =    .1957381 (mean)
               2.pat_co~uti    =    .0289323 (mean)
               0.cult_tes~d    =    .9689534 (mean)
               1.cult_tes~d    =    .0310466 (mean)
               0.dipstick~d    =    .9545429 (mean)
               1.dipstick~d    =    .0454571 (mean)
               year            =    2014.602 (mean)
3._at        : agegrp_uti_new  =           1        (45+ years)
               pat_sex         =           1        (Male)
               repeat_script   =           1        (Repeat Positive)
               0.pat_co~uti    =    .7753297 (mean)
               1.pat_co~uti    =    .1957381 (mean)
               2.pat_co~uti    =    .0289323 (mean)
```

```
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
4._at         : agegrp_uti_new  =           1         (45+ years)
                pat_sex         =           1         (Male)
                repeat_script   =           0         (Repeat Negative)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
5._at         : agegrp_uti_new  =           2         (16-44 years)
                pat_sex         =           0         (Female)
                repeat_script   =           1         (Repeat Positive)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
6._at         : agegrp_uti_new  =           2         (16-44 years)
                pat_sex         =           0         (Female)
                repeat_script   =           0         (Repeat Negative)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
7._at         : agegrp_uti_new  =           2         (16-44 years)
                pat_sex         =           1         (Male)
                repeat_script   =           1         (Repeat Positive)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
8._at         : agegrp_uti_new  =           2         (16-44 years)
                pat_sex         =           1         (Male)
                repeat_script   =           0         (Repeat Negative)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
9._at         : agegrp_uti_new  =           3         (6-15 years)
                pat_sex         =           0         (Female)
                repeat_script   =           1         (Repeat Positive)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
10._at        : agegrp_uti_new  =           3         (6-15 years)
                pat_sex         =           0         (Female)
                repeat_script   =           0         (Repeat Negative)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
11._at        : agegrp_uti_new  =           3         (6-15 years)
                pat_sex         =           1         (Male)
                repeat_script   =           1         (Repeat Positive)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
```

```
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
12._at        : agegrp_uti_new  =           3         (6-15 years)
                pat_sex         =           1         (Male)
                repeat_script   =           0         (Repeat Negative)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
13._at        : agegrp_uti_new  =           4         (0-5 years)
                pat_sex         =           0         (Female)
                repeat_script   =           1         (Repeat Positive)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
14._at        : agegrp_uti_new  =           4         (0-5 years)
                pat_sex         =           0         (Female)
                repeat_script   =           0         (Repeat Negative)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
15._at        : agegrp_uti_new  =           4         (0-5 years)
                pat_sex         =           1         (Male)
                repeat_script   =           1         (Repeat Positive)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)
16._at        : agegrp_uti_new  =           4         (0-5 years)
                pat_sex         =           1         (Male)
                repeat_script   =           0         (Repeat Negative)
                0.pat_co~uti    =    .7753297 (mean)
                1.pat_co~uti    =    .1957381 (mean)
                2.pat_co~uti    =    .0289323 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                year            =    2014.602 (mean)


------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_predict#_at |
        1  1 |   .3630471   .0145766    24.91   0.000     .3344775    .3916167
        1  2 |   .4714561   .0136237    34.61   0.000     .4447543     .498158
        1  3 |   .2618627   .0148832    17.59   0.000     .2326921    .2910333
        1  4 |   .3585672   .0167187    21.45   0.000     .3257991    .3913353
        1  5 |   .3314096   .0143658    23.07   0.000     .3032532    .3595659
        1  6 |   .4382159   .0134411    32.60   0.000     .4118717      .46456
        1  7 |   .2559369   .0193328    13.24   0.000     .2180454    .2938285
        1  8 |   .3525742   .0219831    16.04   0.000     .3094881    .3956603
        1  9 |    .264095   .0193907    13.62   0.000     .2260899    .3021001
        1 10 |   .2967566   .0177547    16.71   0.000      .261958    .3315551
        1 11 |   .2167674   .0274272     7.90   0.000     .1630112    .2705236
        1 12 |   .2459498   .0281826     8.73   0.000     .1907129    .3011867
        1 13 |   .2555769   .0210617    12.13   0.000     .2142967    .2968571
        1 14 |   .2410979    .016234    14.85   0.000     .2092797     .272916
        1 15 |   .2460119   .0292038     8.42   0.000     .1887736    .3032502
        1 16 |   .2318665   .0252929     9.17   0.000     .1822935    .2814396
        2  1 |   .4266171   .0064959    65.68   0.000     .4138854    .4393487
        2  2 |   .3863253   .0075834    50.94   0.000     .3714622    .4011884
        2  3 |   .4370537   .0058308    74.96   0.000     .4256256    .4484817
        2  4 |   .4277331    .006766    63.22   0.000      .414472    .4409941
        2  5 |   .4333535   .0060901    71.16   0.000     .4214171    .4452899
        2  6 |   .4010977   .0071601    56.02   0.000     .3870642    .4151313
        2  7 |   .4365131   .0060319    72.37   0.000     .4246908    .4483354
        2  8 |   .4291452   .0074012    57.98   0.000     .4146392    .4436512
        2  9 |   .4372177   .0058739    74.43   0.000      .425705    .4487305
        2 10 |   .4373354   .0058273    75.05   0.000     .4259141    .4487568
        2 11 |   .4286922   .0098878    43.36   0.000     .4093124     .448072
```

```
          2 12  |   .4352439   .0070513    61.73   0.000     .4214236    .4490642
          2 13  |   .4364753   .0061096    71.44   0.000     .4245007    .4484498
          2 14  |   .4344577   .0062602    69.40   0.000      .422188    .4467275
          2 15  |   .4352532   .0071181    61.15   0.000     .4213019    .4492045
          2 16  |   .4326395   .0078122    55.38   0.000     .4173278    .4479511
          3  1  |   .1154629   .0053544    21.56   0.000     .1049685    .1259573
          3  2  |    .082577   .0041257    20.02   0.000     .0744909    .0906632
          3  3  |   .1526643   .0064849    23.54   0.000     .1399542    .1653744
          3  4  |   .1169782   .0060682    19.28   0.000     .1050846    .1288717
          3  5  |   .1264341   .0055952    22.60   0.000     .1154677    .1374006
          3  6  |   .0919062   .0043509    21.12   0.000     .0833786    .1004338
          3  7  |   .1550175   .0081872    18.93   0.000     .1389708    .1710641
          3  8  |    .119025   .0078579    15.15   0.000     .1036238    .1344262
          3  9  |   .1517819   .0081004    18.74   0.000     .1359055    .1676583
          3 10  |   .1391603   .0071287    19.52   0.000     .1251883    .1531322
          3 11  |   .1708804   .0116732    14.64   0.000     .1480014    .1937594
          3 12  |   .1590167   .0116996    13.59   0.000     .1360859    .1819475
          3 13  |   .1551609   .0088272    17.58   0.000     .1378599     .172462
          3 14  |   .1609731    .007173    22.44   0.000     .1469144    .1750318
          3 15  |   .1589917   .0120813    13.16   0.000     .1353129    .1826706
          3 16  |    .164716   .0107148    15.37   0.000     .1437153    .1857167
          4  1  |   .0948729   .0065005    14.59   0.000     .0821321    .1076137
          4  2  |   .0596415   .0040445    14.75   0.000     .0517145    .0675686
          4  3  |   .1484194   .0104863    14.15   0.000     .1278666    .1689721
          4  4  |   .0967216   .0074107    13.05   0.000     .0821969    .1112462
          4  5  |   .1088028   .0073294    14.84   0.000     .0944376    .1231681
          4  6  |   .0687802    .004529    15.19   0.000     .0599036    .0776568
          4  7  |   .1525325   .0138758    10.99   0.000     .1253363    .1797286
          4  8  |   .0992556    .009761    10.17   0.000     .0801244    .1183868
          4  9  |   .1469054   .0133413    11.01   0.000     .1207568    .1730539
          4 10  |   .1267477    .010394    12.19   0.000      .106376    .1471195
          4 11  |    .18366   .0246282     7.46   0.000     .1353897    .2319303
          4 12  |   .1597896   .0212341     7.53   0.000     .1181715    .2014078
          4 13  |   .1527869   .0151353    10.09   0.000     .1231223    .1824515
          4 14  |   .1634713   .0127337    12.84   0.000     .1385137     .188429
          4 15  |   .1597432   .0219665     7.27   0.000     .1166896    .2027968
          4 16  |    .170778   .0206877     8.26   0.000      .130231    .2113251

Where 1=First=-line, 2=Second-line, 3=Third-line/Last Resort and 4=Not Recommended
```

D.5.6 Predictive margins for the effect on ordinal choice of antibiotic outcomes, across different values of patient age group and patient gender

```
margins, at(agegrp_uti_new=(1 2 3 4) pat_sex=(1 0))

Predictive margins                              Number of obs     =     17,973
Model VCE    : OIM

1._predict   : Marginal predicted mean (1.choice_uti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_uti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_uti_new), predict(pr outcome(3))
4._predict   : Marginal predicted mean (4.choice_uti_new), predict(pr outcome(4))

1._at        : agegrp_uti_new  =           1        (45+ years)
               pat_sex         =           1        (Male)

2._at        : agegrp_uti_new  =           1        (45+ years)
               pat_sex         =           0        (Female)

3._at        : agegrp_uti_new  =           2        (16-44 years)
               pat_sex         =           1        (Male)

4._at        : agegrp_uti_new  =           2        (16-44 years)
               pat_sex         =           0        (Female)

5._at        : agegrp_uti_new  =           3        (6-15 years)
               pat_sex         =           1        (Male)

6._at        : agegrp_uti_new  =           3        (6-15 years)
               pat_sex         =           0        (Female)

7._at        : agegrp_uti_new  =           4        (0-5 years)
               pat_sex         =           1        (Male)

8._at        : agegrp_uti_new  =           4        (0-5 years)
               pat_sex         =           0        (Female)
```

	Delta-method				
	Margin	Std. Err.	z	P>|z|	[95% Conf. Interval]
_predict#_at					
1 1	.3316927	.0156054	21.26	0.000	.3011068 .3622787
1 2	.4409312	.0130266	33.85	0.000	.4153997 .4664628
1 3	.3257344	.0207109	15.73	0.000	.2851418 .3663271
1 4	.4082536	.0127826	31.94	0.000	.3832002 .4333071
1 5	.2383545	.0266377	8.95	0.000	.1861456 .2905634
1 6	.2880988	.0155892	18.48	0.000	.2575445 .3186531
1 7	.2365142	.0246598	9.59	0.000	.1881818 .2848465
1 8	.24583	.0148047	16.60	0.000	.2168134 .2748466
2 1	.4291003	.0061144	70.18	0.000	.4171162 .4410844
2 2	.3967679	.0069648	56.97	0.000	.3831171 .4104186
2 3	.4299497	.0063217	68.01	0.000	.4175594 .4423401
2 4	.4091483	.0065648	62.32	0.000	.3962816 .4220151
2 5	.4322009	.0074873	57.72	0.000	.4175261 .4468756
2 6	.4360773	.0057658	75.63	0.000	.4247766 .447378
2 7	.4322819	.0073669	58.68	0.000	.4178431 .4467207
2 8	.4339166	.0060522	71.70	0.000	.4220545 .4457787
3 1	.1271292	.0059369	21.41	0.000	.1154932 .1387653
3 2	.0921171	.0042119	21.87	0.000	.0838619 .1003724
3 3	.1292487	.0077191	16.74	0.000	.1141194 .1443779
3 4	.1018708	.0044097	23.10	0.000	.093228 .1105136
3 5	.1621739	.0110977	14.61	0.000	.1404229 .183925
3 6	.1426785	.0064201	22.22	0.000	.1300953 .1552616
3 7	.162896	.0103635	15.72	0.000	.1425838 .1832082
3 8	.1591558	.0065775	24.20	0.000	.1462642 .1720474
4 1	.1120777	.0079551	14.09	0.000	.096486 .1276694
4 2	.0701838	.0044889	15.63	0.000	.0613857 .0789819
4 3	.1150672	.0106672	10.79	0.000	.0941599 .1359745
4 4	.0807272	.0050159	16.09	0.000	.0708962 .0905583
4 5	.1672707	.0210985	7.93	0.000	.1259183 .208623
4 6	.1331454	.0096206	13.84	0.000	.1142893 .1520016
4 7	.1683079	.0197431	8.52	0.000	.1296121 .2070038
4 8	.1610976	.0114358	14.09	0.000	.1386838 .1835114

Where 1=First=-line, 2=Second-line, 3=Third-line/Last Resort and 4=Not Recommended.

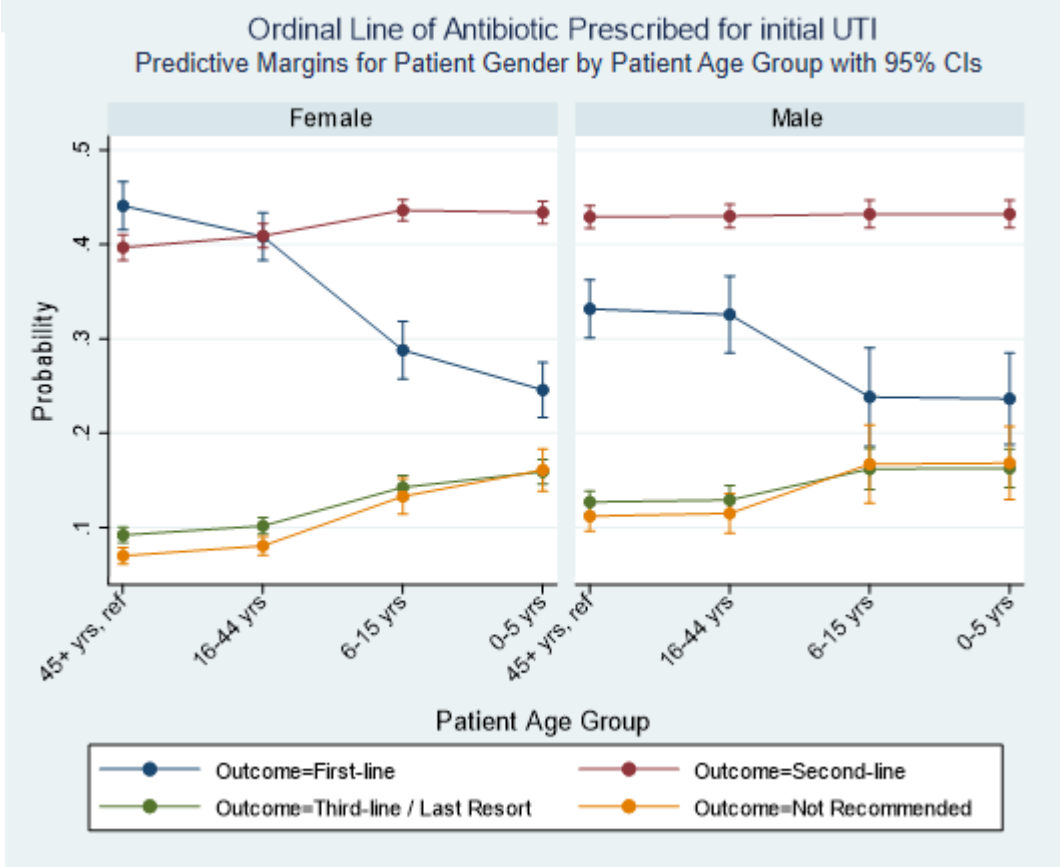


Figure D-7: Predictive margins for the effect on the probability of each of the four ordinal choice of antibiotic outcomes occurring, across different values of patient age group and patient gender, graphed by patient gender

D.5.7 Predictive margins for effect on the ordinal choice of antibiotic, across different values of patient age group and whether repeats were issued on the prescription

```
margins, at(agegrp_uti_new=(1 2 3 4) repeat_script=(1 0))

Predictive margins                              Number of obs     =     17,973
Model VCE    : OIM

1._predict   : Marginal predicted mean (1.choice_uti_new), predict(pr outcome(1))
2._predict   : Marginal predicted mean (2.choice_uti_new), predict(pr outcome(2))
3._predict   : Marginal predicted mean (3.choice_uti_new), predict(pr outcome(3))
4._predict   : Marginal predicted mean (4.choice_uti_new), predict(pr outcome(4))

1._at        : agegrp_uti_new  =           1        (45+ years)
               repeat_script   =           1        (Male)

2._at        : agegrp_uti_new  =           1        (45+ years)
               repeat_script   =           0        (Female)

3._at        : agegrp_uti_new  =           2        (16-44 years)
               repeat_script   =           1        (Male)

4._at        : agegrp_uti_new  =           2        (16-44 years)
               repeat_script   =           0        (Female)

5._at        : agegrp_uti_new  =           3        (6-15 years)
               repeat_script   =           1        (Male)

6._at        : agegrp_uti_new  =           3        (6-15 years)
               repeat_script   =           0        (Female)

7._at        : agegrp_uti_new  =           4        (0-5 years)
               repeat_script   =           1        (Male)

8._at        : agegrp_uti_new  =           4        (0-5 years)
               repeat_script   =           0        (Female)

------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_predict#_at |
         1 1 |   .3530734   .0142027    24.86   0.000     .3252366    .3809101
         1 2 |   .4599122   .0134321    34.24   0.000     .4335858    .4862387
         1 3 |   .3241582     .01408    23.02   0.000     .2965619    .3517545
         1 4 |   .4295917   .0133363    32.21   0.000     .4034529    .4557304
         1 5 |   .2598701    .018797    13.83   0.000     .2230287    .2967115
         1 6 |   .2921127   .0171227    17.06   0.000     .2585529    .3256726
         1 7 |   .2552261   .0205799    12.40   0.000     .2148903    .2955619
         1 8 |   .2407998   .0156506    15.39   0.000     .2101252    .2714744
         2 1 |   .4263751   .0062708    67.99   0.000     .4140846    .4386657
         2 2 |   .3896393   .0073387    53.09   0.000     .3752557    .4040229
         2 3 |     .43236   .0059538    72.62   0.000     .4206908    .4440291
         2 4 |   .4029551   .0069695    57.82   0.000     .3892952     .416615
         2 5 |   .4350514   .0059321    73.34   0.000     .4234247    .4466781
         2 6 |   .4358247    .005786    75.32   0.000     .4244844     .447165
         2 7 |   .4351694   .0060915    71.44   0.000     .4232303    .4471086
         2 8 |   .4331093   .0062033    69.82   0.000     .4209512    .4452675
         3 1 |   .1194041   .0052993    22.53   0.000     .1090176    .1297906
         3 2 |   .0863958   .0041611    20.76   0.000     .0782402    .0945513
         3 3 |     .12942   .0055513    23.31   0.000     .1185397    .1403003
         3 4 |    .094932   .0043986    21.58   0.000     .0863109    .1035531
         3 5 |   .1536117   .0078764    19.50   0.000     .1381742    .1690492
         3 6 |   .1411641   .0069235    20.39   0.000     .1275942     .154734
         3 7 |   .1554103   .0086091    18.05   0.000     .1385368    .1722838
         3 8 |   .1611696   .0069302    23.26   0.000     .1475867    .1747525
         4 1 |   .1011474   .0066827    15.14   0.000     .0880495    .1142453
         4 2 |   .0640527    .004233    15.13   0.000     .0557561    .0723493
         4 3 |   .1140618    .007523    15.16   0.000      .099317    .1288066
         4 4 |   .0725213   .0047316    15.33   0.000     .0632475     .081795
         4 5 |   .1514668   .0133165    11.37   0.000      .125367    .1775665
         4 6 |   .1308985   .0103419    12.66   0.000     .1106287    .1511682
         4 7 |   .1541941   .0148905    10.36   0.000     .1250092     .183379
         4 8 |   .1649213   .0123457    13.36   0.000     .1407241    .1891185
------------------------------------------------------------------------------
Where 1=First=-line, 2=Second-line, 3=Third-line/Last Resort and 4=Not Recommended.
```

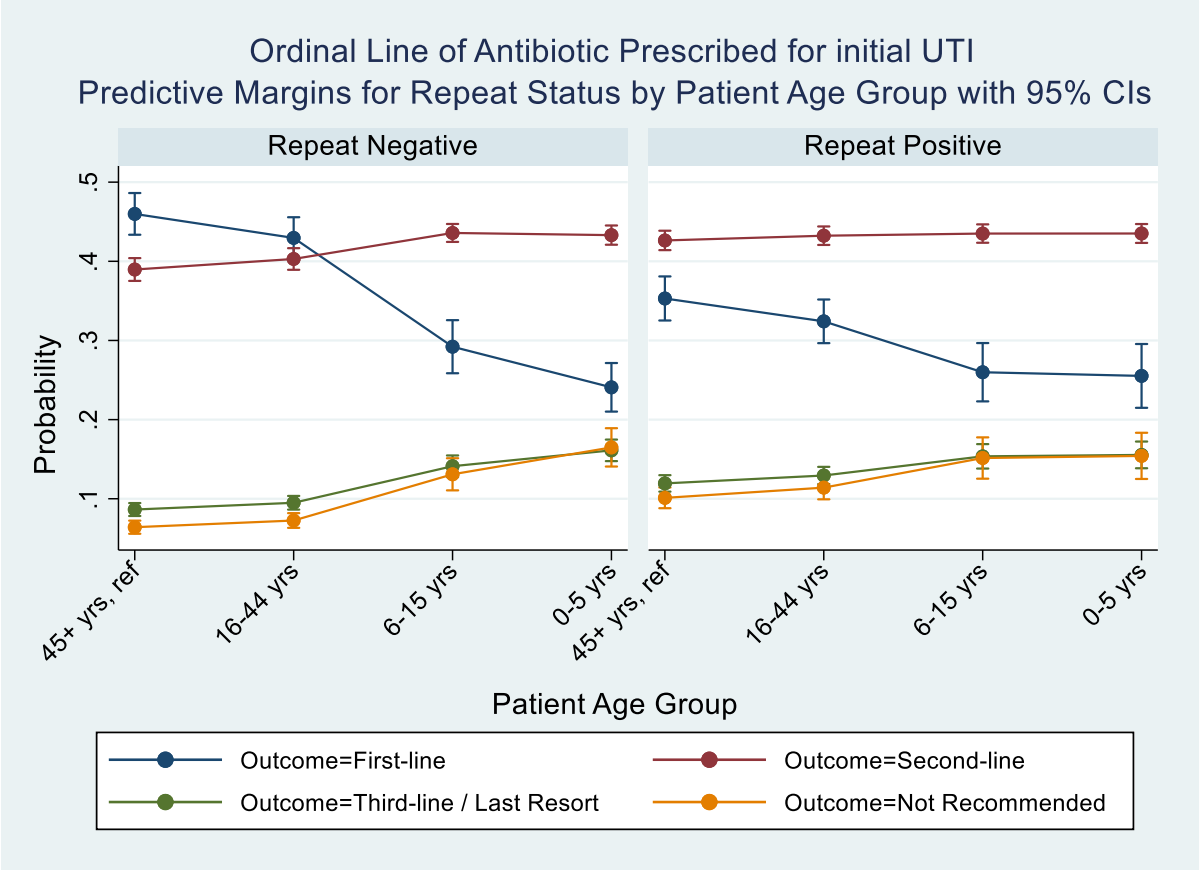


Figure D-8: Predictive margins for the effect on the probability of each of the four ordinal choice of antibiotic outcomes occurring, across different values of patient age group and whether repeats were issued on the prescription, graphed by repeat on prescription status

D.6 Marginal effects for the model for repeats being issued on antibiotic prescriptions for initial presentations of urinary tract infection

D.6.1 Average marginal effects

Table D-22: Average marginal effects for repeat positive antibiotic prescribing for initial presentations of urinary tract infection (Model 3)

Average Marginal Effects (Model 3) Repeat Positive Antibiotic Prescribing for Initial Presentations of UTI Model						
Variable	**dy/dx**	**Std. Err.**	**z**	**P>z**	**[95% Conf.**	**Interval]**
Patient Age Group, ref. 45 years and over						
16-44 yrs	-0.0154515	0.0063311	-2.44	0.015	-0.0278602	-0.0030429
6-15 yrs	0.0541286	0.0132175	4.1	0.000	0.0282227	0.0800346
0-5 yrs	0.0035729	0.013635	0.26	0.793	-0.0231513	0.0302971
Patient Gender, ref. Female						
Male	0.0827534	0.0109402	7.56	0.000	0.061311	0.1041959
Ordinal Choice of Antibiotic Prescribed, ref. First-line						
Second-line	0.0795068	0.0076602	10.38	0.000	0.064493	0.0945206
Third-line	0.187035	0.0121971	15.33	0.000	0.1631291	0.210941
Not Recommended	0.0112022	0.0110261	1.02	0.310	-0.0104085	0.032813
Culture Testing Status, ref. Negative						
Positive	0.0499152	0.0189255	2.64	0.008	0.012822	0.0870084
Urine Dipstick Testing Status, ref. Negative						
Positive	-0.0493777	0.0193114	-2.56	0.011	-0.0872273	-0.011528
Temperature Testing Status, ref. Negative						
Positive	0.0215037	0.009648	2.23	0.026	0.0025941	0.0404134
Multiple UTI Episodes, ref. Negative						
Positive	0.056751	0.0083593	6.79	0.000	0.0403671	0.073135

Average Marginal Effects

When patient age is considered solely, patients aged 16-44 were 2% less likely (-0.015, p=0.015, 95%CI: -0.028,-0.003), while older children were 5-6% more likely (0.054, p<0.001, 95%CI: 0.028, 0.080), to receive a repeat positive prescription that patients of 45 years and over. There was no significant difference in probability for young children than that of patients 45 years and over (0.004, p=0.793, 95%CI: -0.023, 0.030). When considered alone, male gender is associated with 8 percentage points higher risk of repeat positive prescribing (0.083, p<0.001, 95%CI: 0.061, 0.104).

D.6.2 Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in patient gender, across different values of patient age group

```
margins, dydx(pat_sex) at (agegrp_uti_new = (1 2 3 4))

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 1.pat_sex

1._at        : agegrp_uti_new  =           1        (45+ years)
2._at        : agegrp_uti_new  =           2        (16-44 years)
3._at        : agegrp_uti_new  =           3        (6-15 years)
4._at        : agegrp_uti_new  =           4        (0-5 years)

------------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Female       |  (base outcome)
-------------+----------------------------------------------------------------
Male         |
         _at |
          1  |   .0996745   .0126512     7.88   0.000     .0748785    .1244704
          2  |   .0928677   .0196783     4.72   0.000     .0542989    .1314365
          3  |   -.020989   .0344754    -0.61   0.543    -.0885595    .0465815
          4  |  -.0397436    .031382    -1.27   0.205    -.1012511     .021764
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

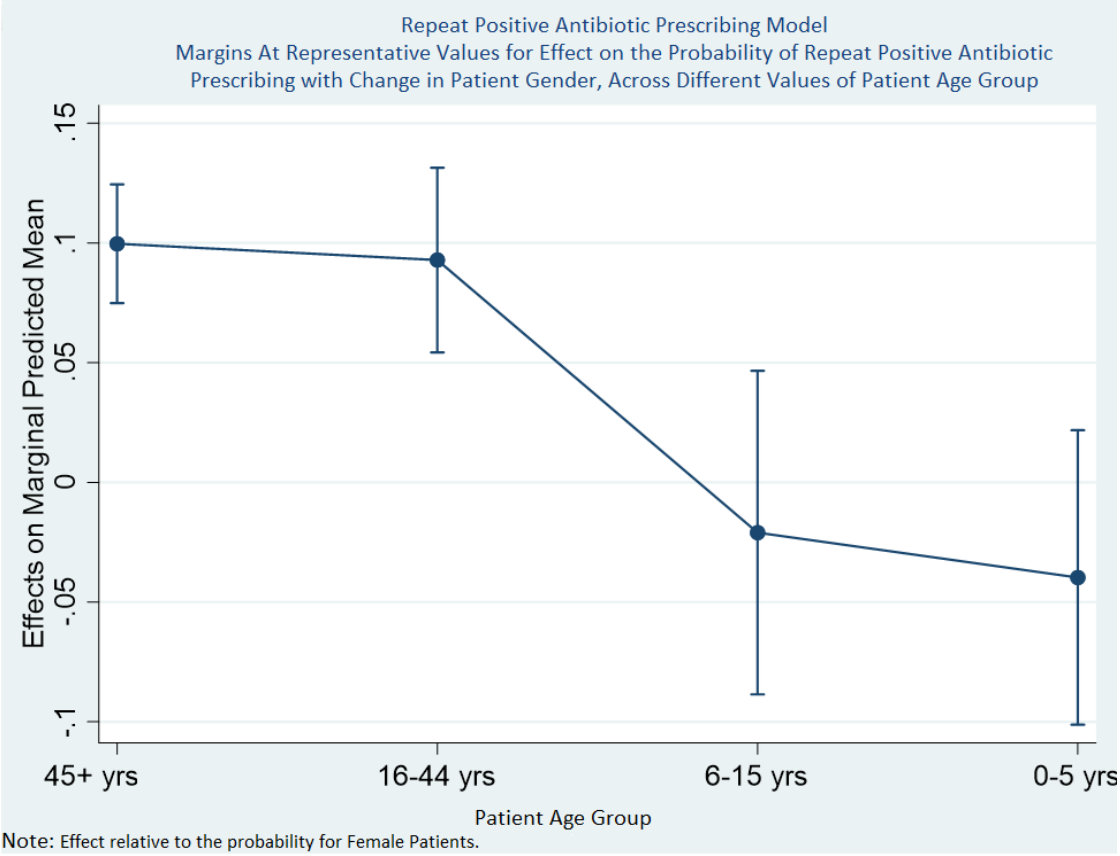


Figure D-9: Margins at representative values for the effect on the probability of repeats being issued on prescriptions with change in patient gender, across different values of patient age group, relative to the effect on the probability for female patients

D.6.3 Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions, with change in patient age group, across different values of patient gender

```
margins, dydx(agegrp_uti_new) at (pat_sex= (1 0))

Average marginal effects                        Number of obs     =     17,973
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 2.agegrp_uti_new 3.agegrp_uti_new 4.agegrp_uti_new

1._at        : pat_sex         =           1        (Male)
2._at        : pat_sex         =           0        (Female)
------------------------------------------------------------------------------
                  |            Delta-method
                  |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
45+ years         |  (base outcome)
------------------+-----------------------------------------------------------
16-44 years       |
              _at |
               1  |  -.0215669   .0220748    -0.98   0.329    -.0648328     .021699
               2  |  -.0147601   .0065122    -2.27   0.023    -.0275239   -.0019964
------------------+-----------------------------------------------------------
6-15 years        |
              _at |
               1  |  -.0537118   .0340187    -1.58   0.114    -.1203872    .0129636
               2  |   .0669517   .0141598     4.73   0.000      .039199    .0947045
------------------+-----------------------------------------------------------
0-5 years         |
              _at |
               1  |  -.1209867   .0307346    -3.94   0.000    -.1812254    -.060748
               2  |   .0184314   .0147607     1.25   0.212    -.0104991    .0473619
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

  Variables that uniquely identify margins: pat_sex _deriv
```

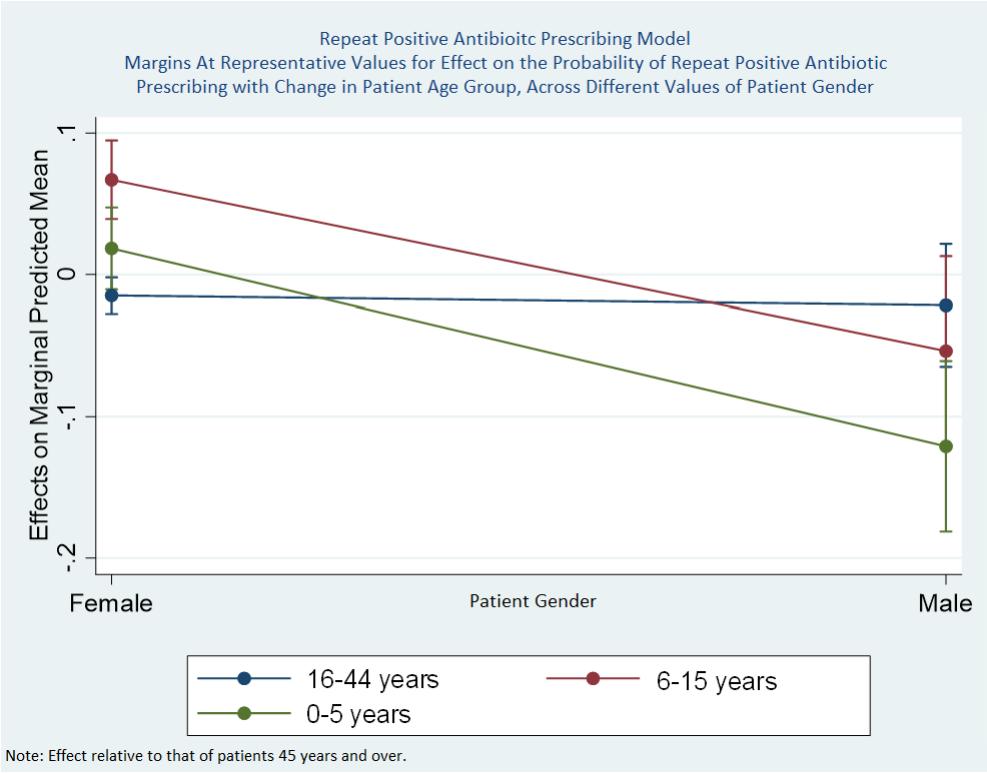


Figure D-10: Margins at representative values for the effect on the probability of repeats being issued on antibiotic prescriptions with change in patient age group, across different values of patient gender, relative to the effect on the probability for patients aged 45 years and over

D.6.4 Predictive margins for the probability of repeats being issued on antibiotic prescriptions, across different values of patient age group and patient gender

```
margins, at(agegrp_uti_new=(1 2 3 4) pat_sex=(1 0))

Predictive margins                              Number of obs     =     17,973
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()

1._at        : agegrp_uti_new  =           1        (45+ years)
               pat_sex         =           1        (Male)

2._at        : agegrp_uti_new  =           1        (45+ years)
               pat_sex         =           0        (Female)

3._at        : agegrp_uti_new  =           2        (16-44 years)
               pat_sex         =           1        (Male)

4._at        : agegrp_uti_new  =           2        (16-44 years)
               pat_sex         =           0        (Female)

5._at        : agegrp_uti_new  =           3        (6-15 years)
               pat_sex         =           1        (Male)

6._at        : agegrp_uti_new  =           3        (6-15 years)
               pat_sex         =           0        (Female)

7._at        : agegrp_uti_new  =           4        (0-5 years)
               pat_sex         =           1        (Male)

8._at        : agegrp_uti_new  =           4        (0-5 years)
               pat_sex         =           0        (Female)


------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         _at |
          1  |   .3791592   .0212501    17.84   0.000     .3375097    .4208087
          2  |   .2794847   .0165451    16.89   0.000      .247057    .3119125
          3  |   .3575923   .0258736    13.82   0.000     .3068811    .4083036
          4  |   .2647246   .0161805    16.36   0.000     .2330113    .2964379
          5  |   .3254474   .0362973     8.97   0.000     .2543061    .3965888
          6  |   .3464364   .0217938    15.90   0.000     .3037214    .3891515
          7  |   .2581725   .0321624     8.03   0.000     .1951354    .3212097
          8  |   .2979161   .0214567    13.88   0.000     .2558618    .3399704
------------------------------------------------------------------------------

. marginsplot, bydim(pat_sex) byopt(rows(1))

  Variables that uniquely identify margins: agegrp_uti_new pat_sex
```

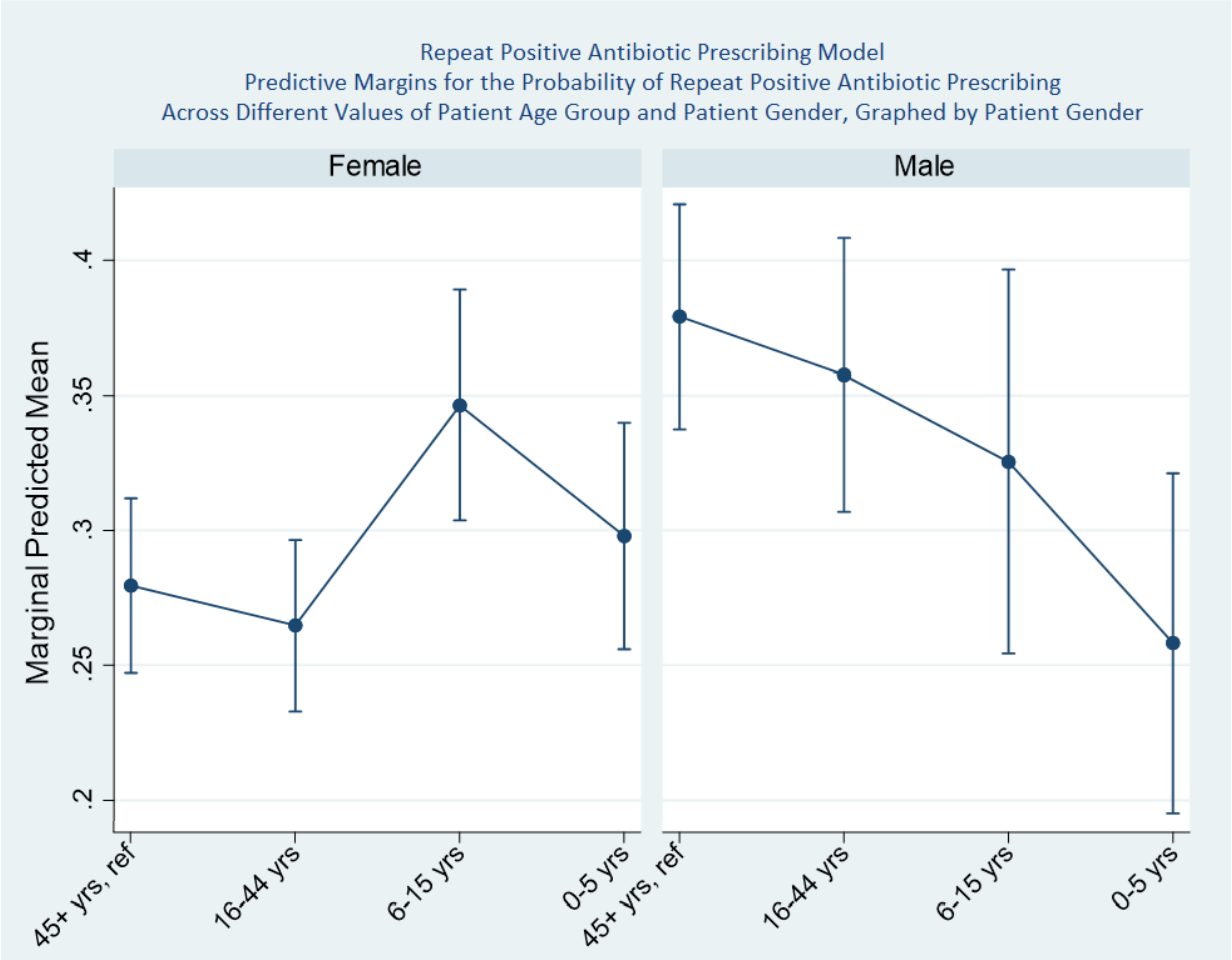


Figure D-11: Predictive margins for the probability of repeats being issued on antibiotic prescriptions. across different values of patient age group and patient gender, graphed by patient gender

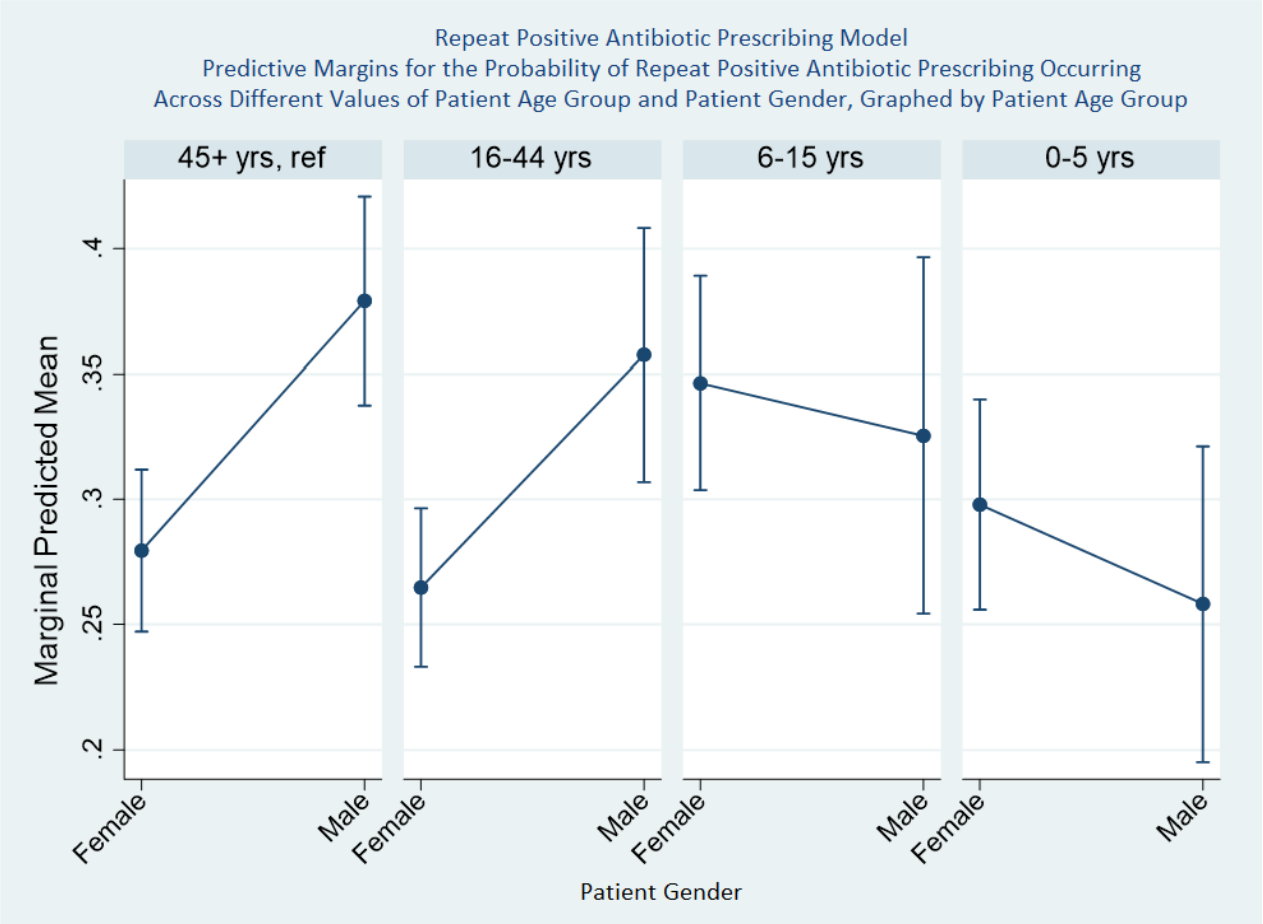


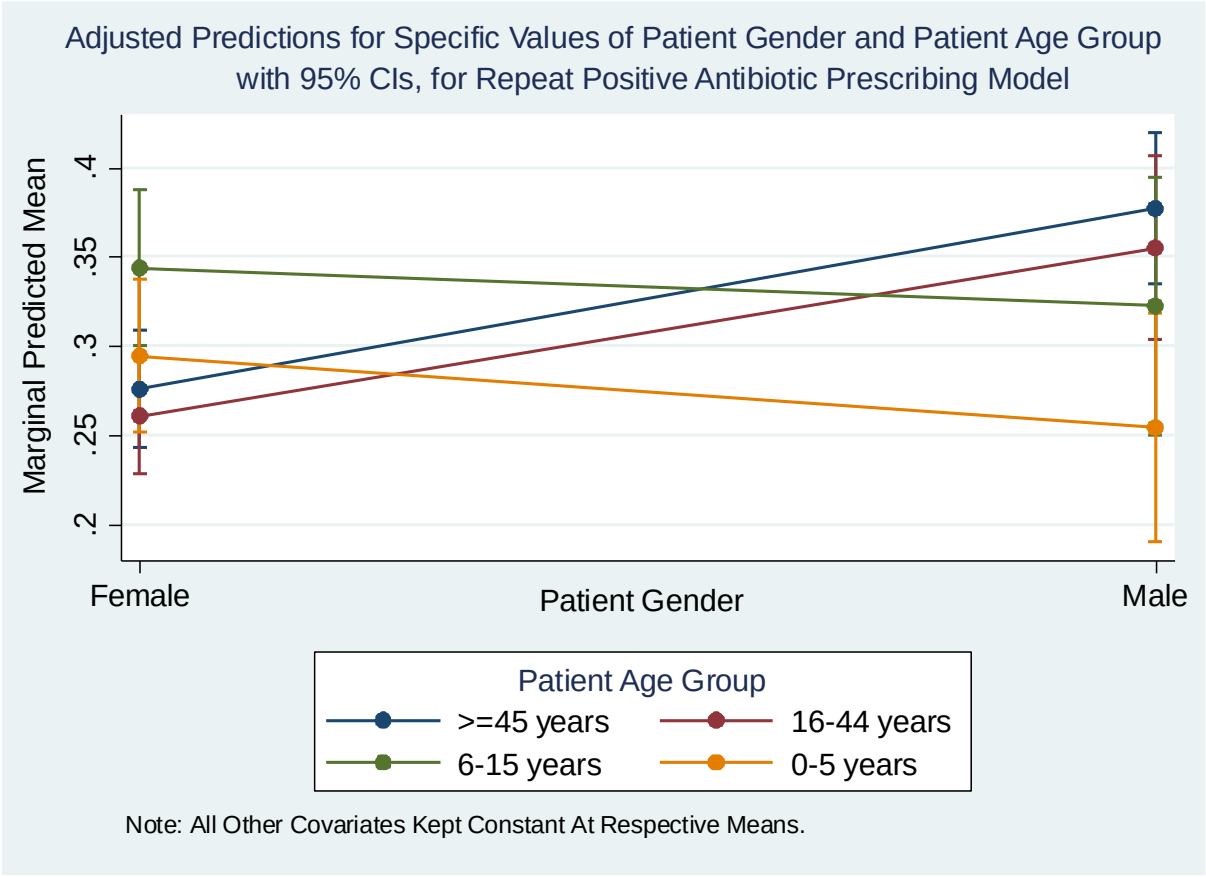
Figure D-12: Predictive margins for the probability of repeats being issued on antibiotic prescriptions, across different values of patient age group and patient gender, graphed by patient age group

D.6.5 Adjusted predictions for the effect on the probability of repeats being issued on antibiotic prescribing, at specific values of patient gender and age group

```
margins, at(pat_sex=(0 1) agegrp_uti_new=(1 2 3 4)) atmeans vsquish post

Adjusted predictions                            Number of obs     =     17,973
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
1._at        : agegrp_uti_new  =           1         (45+ years)
               pat_sex         =           0         (Female)
               1.choice_u~w    =    .3965393 (mean)
               2.choice_u~w    =    .4102821 (mean)
               3.choice_u~w    =     .106048 (mean)
               4.choice_u~w    =    .0871307 (mean)
               0.cult_tes~d    =    .9689534 (mean)
               1.cult_tes~d    =    .0310466 (mean)
               0.dipstick~d    =    .9545429 (mean)
               1.dipstick~d    =    .0454571 (mean)
               0.temp_tes~d    =    .8366995 (mean)
               1.temp_tes~d    =    .1633005 (mean)
               0.multip~UTI    =    .8304123 (mean)
               1.multip~UTI    =    .1695877 (mean)
               year            =    2014.602 (mean)
2._at        : agegrp_uti_new  =           1         (45+ years)
               pat_sex         =           1         (Male)
               1.choice_u~w    =    .3965393 (mean)
               2.choice_u~w    =    .4102821 (mean)
               3.choice_u~w    =     .106048 (mean)
               4.choice_u~w    =    .0871307 (mean)
               0.cult_tes~d    =    .9689534 (mean)
               1.cult_tes~d    =    .0310466 (mean)
               0.dipstick~d    =    .9545429 (mean)
               1.dipstick~d    =    .0454571 (mean)
               0.temp_tes~d    =    .8366995 (mean)
```

```
                1.temp_tes~d    =    .1633005 (mean)
                0.multip~UTI    =    .8304123 (mean)
                1.multip~UTI    =    .1695877 (mean)
                year            =    2014.602 (mean)
3._at           : agegrp_uti_new  =           2         (16-44 years)
                pat_sex         =           0         (Female)
                1.choice_u~w    =    .3965393 (mean)
                2.choice_u~w    =    .4102821 (mean)
                3.choice_u~w    =     .106048 (mean)
                4.choice_u~w    =    .0871307 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                0.temp_tes~d    =    .8366995 (mean)
                1.temp_tes~d    =    .1633005 (mean)
                0.multip~UTI    =    .8304123 (mean)
                1.multip~UTI    =    .1695877 (mean)
                year            =    2014.602 (mean)
4._at           : agegrp_uti_new  =           2         (16-44 years)
                pat_sex         =           1         (Male)
                1.choice_u~w    =    .3965393 (mean)
                2.choice_u~w    =    .4102821 (mean)
                3.choice_u~w    =     .106048 (mean)
                4.choice_u~w    =    .0871307 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                0.temp_tes~d    =    .8366995 (mean)
                1.temp_tes~d    =    .1633005 (mean)
                0.multip~UTI    =    .8304123 (mean)
                1.multip~UTI    =    .1695877 (mean)
                year            =    2014.602 (mean)
5._at           : agegrp_uti_new  =           3         (6-15 years)
                pat_sex         =           0         (Female)
                1.choice_u~w    =    .3965393 (mean)
                2.choice_u~w    =    .4102821 (mean)
                3.choice_u~w    =     .106048 (mean)
                4.choice_u~w    =    .0871307 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                0.temp_tes~d    =    .8366995 (mean)
                1.temp_tes~d    =    .1633005 (mean)
                0.multip~UTI    =    .8304123 (mean)
                1.multip~UTI    =    .1695877 (mean)
                year            =    2014.602 (mean)
6._at           : agegrp_uti_new  =           3         (6-15 years)
                pat_sex         =           1         (Male)
                1.choice_u~w    =    .3965393 (mean)
                2.choice_u~w    =    .4102821 (mean)
                3.choice_u~w    =     .106048 (mean)
                4.choice_u~w    =    .0871307 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                0.temp_tes~d    =    .8366995 (mean)
                1.temp_tes~d    =    .1633005 (mean)
                0.multip~UTI    =    .8304123 (mean)
                1.multip~UTI    =    .1695877 (mean)
                year            =    2014.602 (mean)
7._at           : agegrp_uti_new  =           4         (0-5 years)
                pat_sex         =           0         (Female)
                1.choice_u~w    =    .3965393 (mean)
                2.choice_u~w    =    .4102821 (mean)
                3.choice_u~w    =     .106048 (mean)
                4.choice_u~w    =    .0871307 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                0.temp_tes~d    =    .8366995 (mean)
                1.temp_tes~d    =    .1633005 (mean)
                0.multip~UTI    =    .8304123 (mean)
                1.multip~UTI    =    .1695877 (mean)
                year            =    2014.602 (mean)
8._at           : agegrp_uti_new  =           4         (0-5 years)
                pat_sex         =           1         (Male)
                1.choice_u~w    =    .3965393 (mean)
                2.choice_u~w    =    .4102821 (mean)
                3.choice_u~w    =     .106048 (mean)
                4.choice_u~w    =    .0871307 (mean)
                0.cult_tes~d    =    .9689534 (mean)
                1.cult_tes~d    =    .0310466 (mean)
                0.dipstick~d    =    .9545429 (mean)
                1.dipstick~d    =    .0454571 (mean)
                0.temp_tes~d    =    .8366995 (mean)
                1.temp_tes~d    =    .1633005 (mean)
```

```
                0.multip~UTI    =     .8304123 (mean)
                1.multip~UTI    =     .1695877 (mean)
                year            =     2014.602 (mean)

------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         _at |
          1  |   .2758586   .0167564    16.46   0.000     .2430167    .3087004
Men       2  |   .3770028   .0216522    17.41   0.000     .3345653    .4194403
          3  |   .2609397   .0163752    15.94   0.000     .2288449    .2930345
Men       4  |   .3550592   .0263203    13.49   0.000     .3034723     .406646
          5  |   .3437207    .022166    15.51   0.000     .3002761    .3871654
Men       6  |    .322412   .0368394     8.75   0.000     .2502081    .3946159
          7  |    .294509   .0217623    13.53   0.000     .2518556    .3371623
Men       8  |   .2543218   .0325081     7.82   0.000     .1906071    .3180364
------------------------------------------------------------------------------
```



.

Figure D-13: Adjusted predictions for the effect on the probability of repeats being issued on antibiotic prescriptions, at specific values of patient gender and age group, with all other covariates kept constant at sample means

D.7 Marginal effects for the binary model of non-first-line antibiotic prescribing for upper respiratory tract infection

D.7.1 Average marginal effects

Table D-23: Average marginal effects for non-first-line antibiotic prescribing for initial presentations of urinary tract infection (Model 2)

Average Marginal Effects (Model 2) Non-first-line Antibiotic Prescribing for Initial Presentations of UTI Model						
Variable	**dy/dx**	**Std. Err.**	**z**	**P>z**	**[95% Conf.**	**Interval]**
Patient Age Group, ref. 45 years and over						
16-44 yrs	-0.0154515	0.0063311	-2.44	0.015	-0.0278602	-0.0030429
6-15 yrs	0.0541286	0.0132175	4.1	0.000	0.0282227	0.0800346
0-5 yrs	0.0035729	0.013635	0.26	0.793	-0.0231513	0.0302971
Patient Gender, ref. Female						
Male	0.0827534	0.0109402	7.56	0.000	0.061311	0.1041959
Ordinal Choice of Antibiotic Prescribed, ref. First-line						
Second-line	0.0795068	0.0076602	10.38	0.000	0.064493	0.0945206
Third-line	0.187035	0.0121971	15.33	0.000	0.1631291	0.210941
Not Recommended	0.0112022	0.0110261	1.02	0.310	-0.0104085	0.032813
Culture Testing Status, ref. Negative						
Positive	0.0499152	0.0189255	2.64	0.008	0.012822	0.0870084
Urine Dipstick Testing Status, ref. Negative						
Positive	-0.0493777	0.0193114	-2.56	0.011	-0.0872273	-0.011528
Temperature Testing Status, ref. Negative						
Positive	0.0215037	0.009648	2.23	0.026	0.0025941	0.0404134
Multiple UTI Episodes, ref. Negative						
Positive	0.056751	0.0083593	6.79	0.000	0.0403671	0.073135

D.7.2 Margins at representative values for the effect on non-first-line antibiotic prescribing with change in patient gender, across different values of patient age group

```
margins, dydx(pat_sex) at (agegrp_uti_new = (1 2 3 4))


Average marginal effects                        Number of obs     =     17,973
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 1.pat_sex

1._at        : agegrp_uti_new  =           1        (45+ years)
2._at        : agegrp_uti_new  =           2        (16-44 years)
3._at        : agegrp_uti_new  =           3        (6-15 years)
4._at        : agegrp_uti_new  =           4        (0-5 years)

------------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Female       |  (base outcome)
-------------+----------------------------------------------------------------
Male         |
         _at |
          1  |   .1051625   .0136892     7.68   0.000     .0783322    .1319928
          2  |   .0666988   .0216411     3.08   0.002     .0242831    .1091146
          3  |   .0539348   .0316631     1.70   0.088    -.0081238    .1159933
          4  |   .0084262   .0279886     0.30   0.763    -.0464304    .0632828
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.

  Variables that uniquely identify margins: agegrp_uti_new
(note: file nonfirst_uti_pat_sex_age.gph not found)
(file nonfirst_uti_pat_sex_age.gph saved)
```

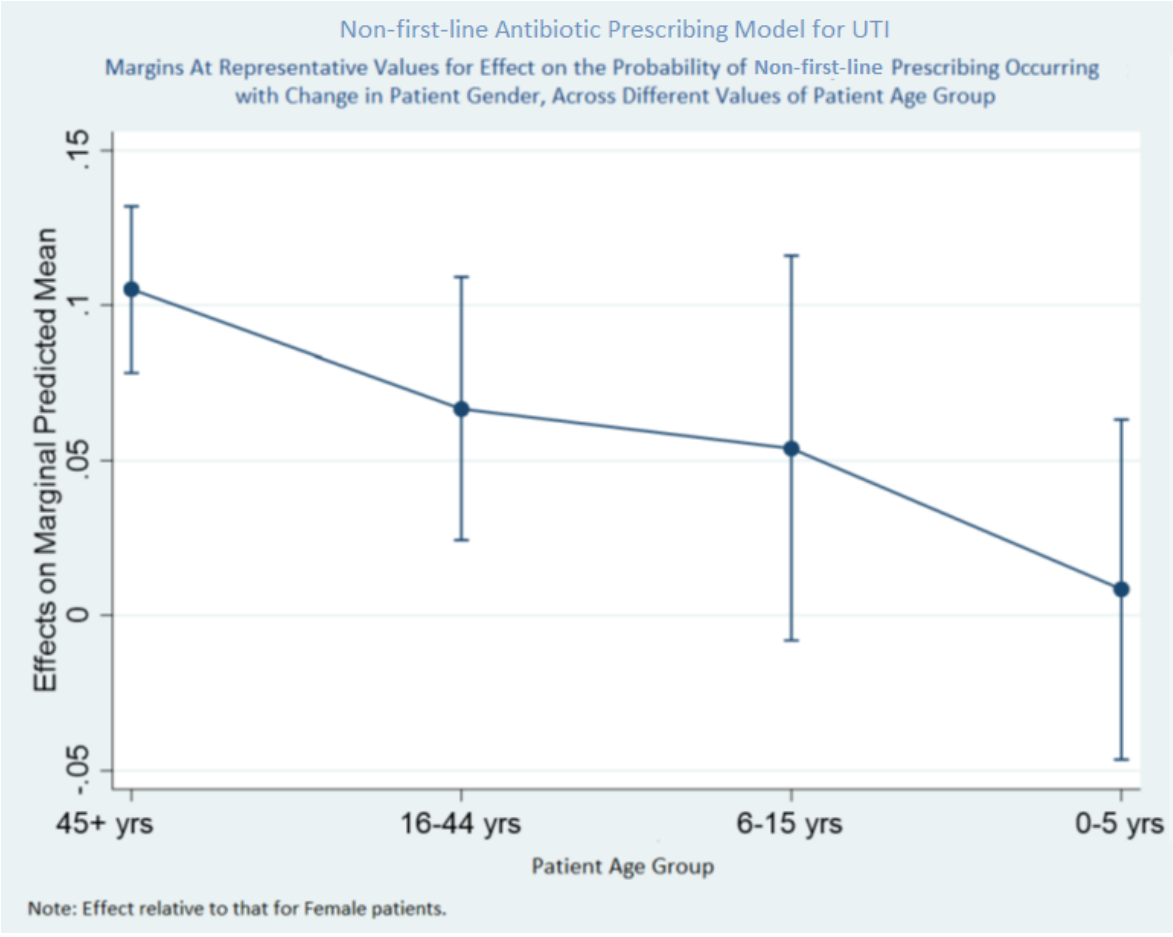


Figure D-14: Margins at representative values for the effect on the probability of non-first-line antibiotic prescribing occurring with change in patient gender, across different values of patient age group, relative to the effect for female patients

D.7.3 Margins at representative values for the effect on non-first-line antibiotic prescribing occurring with change in patient age group, across different values of patient gender

```
margins, dydx(agegrp_uti_new) at (pat_sex= (1 0))

Average marginal effects                        Number of obs     =     17,973
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()
dy/dx w.r.t. : 2.agegrp_uti_new 3.agegrp_uti_new 4.agegrp_uti_new

1._at        : pat_sex         =           1        (Male)
2._at        : pat_sex         =           0        (Female)

------------------------------------------------------------------------------
                  |            Delta-method
                  |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------------
45+ years         |  (base outcome)
------------------+-----------------------------------------------------------------
16-44 years       |
              _at |
               1  |   .0076189   .0247123     0.31   0.758    -.0408163    .0560541
               2  |   .0460826   .0078067     5.90   0.000     .0307818    .0613833
------------------+-----------------------------------------------------------------
6-15 years        |
              _at |
               1  |   .1630435   .0319727     5.10   0.000     .1003782    .2257089
               2  |   .2142713   .0146911    14.59   0.000     .1854773    .2430653
------------------+-----------------------------------------------------------------
0-5 years         |
              _at |
               1  |   .2006749   .0287321     6.98   0.000     .1443611    .2569887
               2  |   .2974113   .0151943    19.57   0.000      .267631    .3271916
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

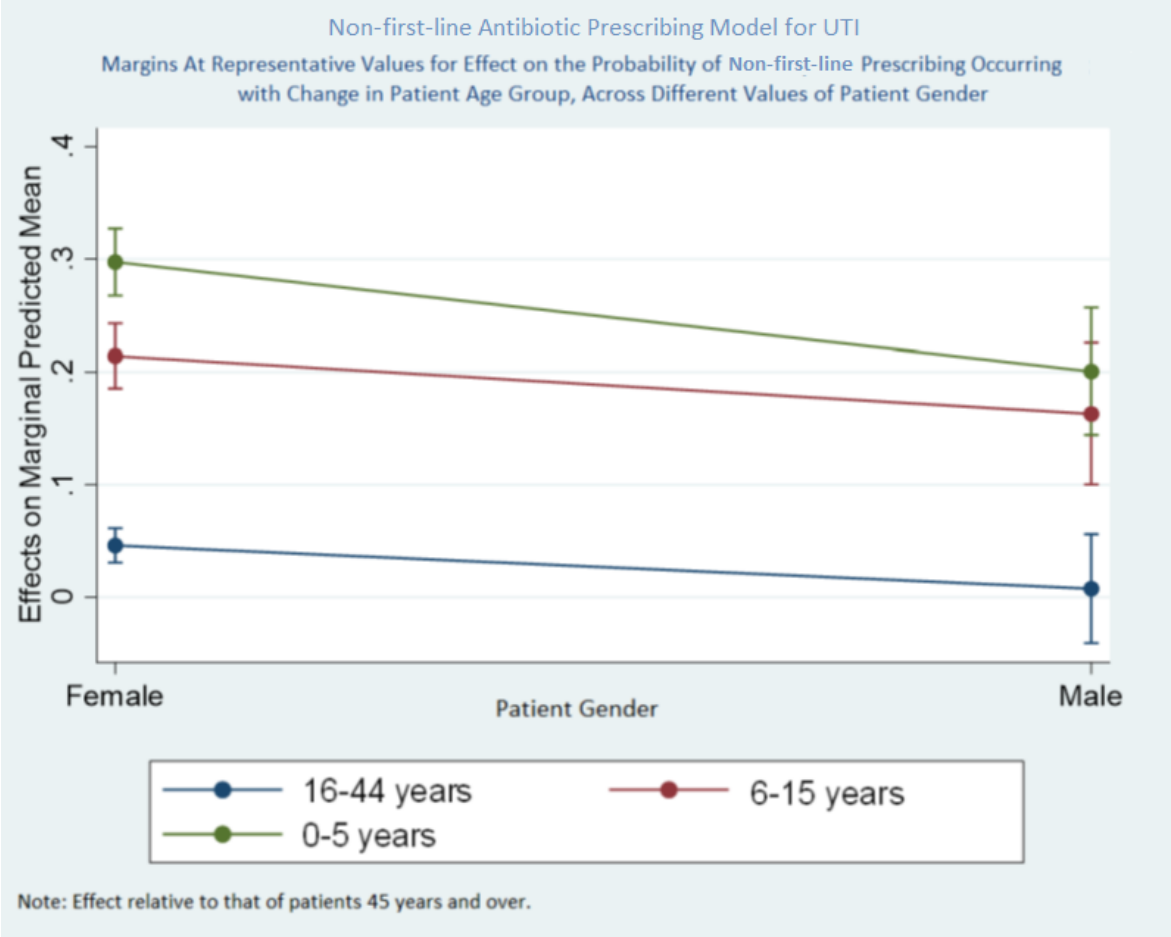


Figure D-15: Margins at representative values for the effect on the probability of non-first-line antibiotic prescribing occurring with change in patient age group, across different values of patient gender, relative to the effect on the probability for patients aged 45 years and over

D.7.4 Predictive margins for the effect on non-first-line antibiotic prescribing occurring at different values of patient age group and patient gender

```
. margins, at(agegrp_uti_new==(4 3 2 1) pat_sex==(1 0))

Predictive margins                              Number of obs     =     17,973
Model VCE    : OIM

Expression   : Marginal predicted mean, predict()

1._at        : agegrp_uti_new  =           4        (0-5 years)
               pat_sex         =           1        (Male)

2._at        : agegrp_uti_new  =           4        (0-5 years)
               pat_sex         =           0        (Female)

3._at        : agegrp_uti_new  =           3        (6-15 years)
               pat_sex         =           1        (Male)

4._at        : agegrp_uti_new  =           3        (6-15 years)
               pat_sex         =           0        (Female)

5._at        : agegrp_uti_new  =           2        (16-44 years)
               pat_sex         =           1        (Male)

6._at        : agegrp_uti_new  =           2        (16-44 years)
               pat_sex         =           0        (Female)

7._at        : agegrp_uti_new  =           1        (45+ years)
               pat_sex         =           1        (Male)

8._at        : agegrp_uti_new  =           1        (45+ years)
               pat_sex         =           0        (Female)
```

	Delta-method				
	Margin	Std. Err.	z	P>|z|	[95% Conf. Interval]
_at					
1	.8563983	.0262223	32.66	0.000	.8050036 .907793
2	.8479721	.0148427	57.13	0.000	.818881 .8770632
3	.8187669	.0302957	27.03	0.000	.7593884 .8781453
4	.7648321	.0164496	46.50	0.000	.7325914 .7970728
5	.6633422	.024193	27.42	0.000	.6159248 .7107597
6	.5966434	.0136835	43.60	0.000	.5698242 .6234626
7	.6557234	.0175349	37.40	0.000	.6213555 .6900912
8	.5505608	.0139861	39.36	0.000	.5231487 .577973

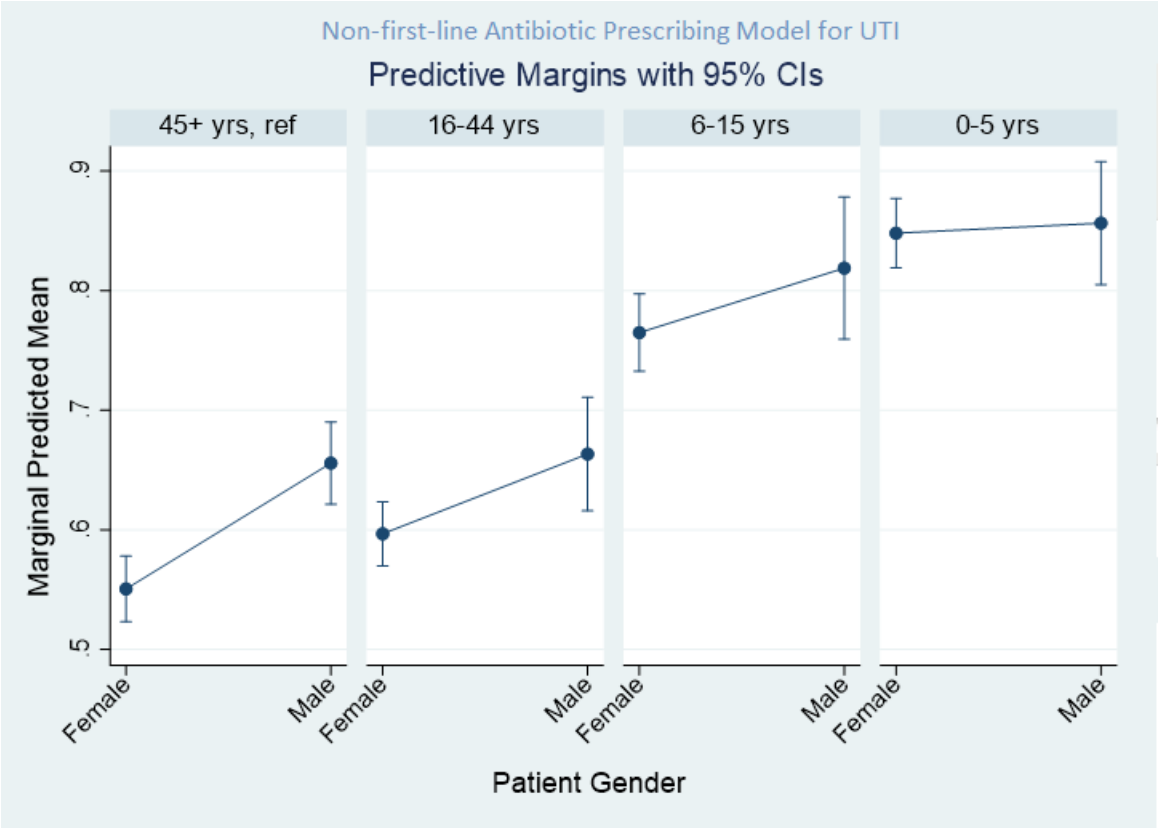


Figure D-16: Predictive margins for the effect on the probability of non-first-line antibiotic prescribing occurring at different values of patient age group and patient gender, graphed by patient age group

D.8 Comparison of final mixed-effects models with fixed-effects models

Table D-24: Summary of fixed-effects models compared against mixed model for choice of antibiotic prescribed for initial presentations of urinary tract infection

Ordinal Choice of Antibiotic Prescribed Model	**Mixed, three-level model (patient, provider, practice levels)**		**Fixed model with dummies for practice**		**Fixed model with no practice**	
	Exp. coeff.	t-statistic	Exp. coeff.	t-statistic	Exp. coeff.	t-statistic
Patient age group (ref. 45+ yrs)						
16-44 yrs	0.165***	-3.98	0.172***	-4.36	0.185***	-4.8
6-15 yrs	0.916***	-10.49	0.862***	-10.45	0.862***	-10.63
0-5 yrs	1.257***	-13.91	1.173***	-13.84	1.177***	-14.15
Patient gender (ref. female)						
Male	0.574***	-8.99	0.550***	-9.14	0.540***	-9.06
Patient age group ## Gender (ref. 45+ yrs # female)						
16-44 yrs # Male	-0.133	(-1.13)	-0.0862	(-0.76)	-0.0824	(-0.73)
6-15 yrs # Male	-0.265	(-1.43)	-0.333	(-1.88)	-0.309	(-1.78)
0-5 yrs # Male	-0.514**	(-2.91)	-0.383*	(-2.29)	-0.474**	(-2.90)
Repeat Prescription Stats (ref. negative)						
Positive	0.551***	-10.11	0.524***	-10.99	0.469***	-10.28
Patient age group ## Repeat prescription status (ref. 45+ yrs 1 # negative)						
16-44 yrs # Positive	0.00502	-0.07	0.00526	-0.08	-0.00855	(-0.13)
6-15 yrs # Positive	-0.356**	(-2.66)	-0.359**	(-2.84)	-0.284*	(-2.28)
0-5 yrs # Positive	-0.643***	(-4.45)	-0.627***	(-4.63)	-0.447***	(-3.37)
Patient comorbid condition (ref. negative)						
Positive	0.195***	-4.53	0.165***	-4.03	0.146***	-3.62
Missing	0.504	-1.63	-0.212	(-0.86)	0.591***	-7.01
Culture testing status (ref. negative)						
Positive	-0.309**	(-3.09)	-0.336***	(-3.60)	-0.457***	(-5.43)
Dipstick testing status (ref. negative)						
Positive	-0.336**	(-3.15)	-0.166	(-1.77)	-0.184*	(-2.57)
Year (unit increase)	0.0274*	-2.15	0.0217*	-2.24	0.0199*	-2.23
Prescribing reason recorded (ref. negative)						
Positive			0.428***	-5.05	-0.0942*	(-2.33)
Weekend consultation (ref. negative)						
Positive			0.117*	-2.33		
Patient in remote area (ref. negative)						
Positive					0.332***	-5.03
Missing					-0.488*	(-2.23)
Patient PHN (ref. Perth North)						
Perth South					-0.241***	(-6.86)
Country WA					-0.309***	(-7.75)
Interstate					-0.247*	(-1.98)
Missing					0.361*	-2.13
Practice Size (ref. Medium/large)						
Small					0.150**	-3.02

	Mixed, three-level model (patient, provider, practice levels)		**Fixed model with dummies for practice**		**Fixed model with no practice**	
	Exp. coeff.	t-statistic	Exp. coeff.	t-statistic	Exp. coeff.	t-statistic
/						
cut1	55.17*	-2.14	43.71*	-2.24	39.98*	-2.22
cut2	57.47*	-2.23	45.73*	-2.35	41.91*	-2.33
cut3	58.54*	-2.27	46.70*	-2.4	42.85*	-2.38
var(_cons[~)	0.0622	-1.63				
var(_cons[~]	1.075***	-12.19				
N	17973		17973		17973	

Note: exponentiated coefficients, significance: * p<0.05, ** p<0.01, *** p<0.001

1

APPENDIX E – APPENDICES TO TRENDS IN PRESCRIBING FOR UPPER RESPIRATORY TRACT INFECTION CHAPTER (CHAPTER 6)

E.1 Tables

E.1.1 Upper respiratory tract infection conditions excluding influenza / influenza-like illness

Table E-1: Linear chi-squared tests for trend using linear regression for upper respiratory tract infection conditions

Linear Regression Model for:	All URTI excl. Influenza/ILI			Rhinosinusitis			Pharyngitis			AOM		
	Coef.	[95% Conf. Interval]		Coef.	[95% Conf. Interval]		Coef.	[95% Conf. Interval]		Coef.	[95% Conf. Interval]	
Likely Unnecessary Antibiotic Prescribing rate												
Month	-0.00092	-0.001041	-0.000803	-0.00185	-0.001984	-0.00172	-0.00118	-0.001368	-0.001001	0.000168	-6.04E-05	0.0003958
Constant	1.461116	1.383122	1.539111	2.125135	2.038259	2.212011	1.632775	1.512335	1.753215	0.661007	0.5112001	0.810813
Antibiotic Prescribing rate												
Month	-0.00232	-0.002478	-0.002165	-0.02	-0.00225	-0.001753	-0.00064	-0.000774	-0.000503	-0.00265	-0.002741	-0.002555
Constant	2.005439	1.902623	2.108255	1.65027	1.487045	1.813494	1.130649	1.041434	1.219863	2.325499	2.264192	2.386807
Prescribing of Second-line antibiotic agent												
Month	0.001139	0.0008867	0.0013912	0.003066	0.0027845	0.0033484	n/a	n/a	n/a	0.001456	0.0008301	0.0020819
Constant	-0.5856	-0.751273	-0.419931	-1.76975	-1.954933	-1.584575	n/a	n/a	n/a	-0.62812	-1.03921	-0.217021
Prescribing of antibiotic Not Recommended in Guidelines												
Month	-0.00138	-0.001527	-0.001231	-0.00025	-0.000513	6.61E-06	-0.00425	-0.004463	-0.00404	0.000114	-0.00013	0.0003571
Constant	1.301287	1.204303	1.398271	0.595765	0.4251143	0.7664154	3.272015	3.133117	3.410913	0.132159	-0.027742	0.2920594
Non-first-line antibiotic prescribing												
Month	-0.00024	-0.000592	0.0001121	0.002813	0.0023695	0.0032569	-0.00425	-0.004463	-0.00404	0.00157	0.0010925	0.0020467
Constant	0.715685	0.4843257	0.9470449	-1.17399	-1.465379	-0.882599	3.272015	3.133117	3.410913	-0.49596	-0.809316	-0.182597
Repeat(s) issued on antibiotic prescription												
Month	0.000181	-0.000237	0.0005978	0.002034	0.0014403	0.0026271	-0.00105	-0.001406	-0.000685	6.06E-05	-0.000298	0.0004195
Constant	0.201558	-0.072546	0.4756627	-0.98178	-1.371488	-0.592079	0.948381	0.7116284	1.185133	0.334132	0.0984428	0.5698209

Antibiotic prescription as Private prescription												
month	-0.00052	-0.000662	-0.000384	0.000257	-0.000375	0.0008892	-0.00129	-0.001706	-0.000877	-0.00062	-0.000929	-0.000317
constant	0.372086	0.2808433	0.463328	-0.06276	-0.477817	0.3523042	0.887227	0.6147981	1.159655	0.440756	0.2397699	0.6417414
Temperature recording during consultation												
month	0.003928	0.0034422	0.0044142	0.006449	0.0045486	0.0083493	0.016029	0.0115158	0.0205422	0.029648	0.0240738	0.0352214
constant	-2.25469	-2.573873	-1.935503	-3.59128	-4.839355	-2.343196	-9.27212	-12.23628	-6.307953	-17.8002	-21.46092	-14.13946

1

Table E-2: Linear chi-squared tests for trend using linear regression for acute rhinosinusitis

Linear Regression Model for Antibiotic agent Prescribing Rate:	Acute Rhinosinusitis Coef.	[95% Conf.	Interval]	
Amoxicillin				
Month	-0.002824	-0.003273	-0.002375	***
Constant	2.180083	1.885295	2.474871	
Amoxicillin with clavulanate				
Month	0.003009	0.002723	0.003295	***
Constant	-1.736256	-1.924167	-1.548345	
Cefalexin				
Month	0.000238	0.000076	0.000400	**
Constant	-0.032350	-0.139006	0.074307	
Cefuroxime				
Month	0.0000569	0.000000	0.0000411	***
Constant	-0.033401	-0.0437467	-0.0230554	
Clarithromycin				
Month	-0.000573	-0.000636	-0.000509	***
Constant	0.437955	0.396501	0.479409	
Doxycycline				
Month	0.0003996	0.000321	0.0004781	***
Constant	-.2432993	-0.29488	-0.1917186	
Roxithromycin				
Month	-0.000678	-0.000881	-0.000474	***
Constant	0.547367	0.413765	0.680970	

Table E-3: Linear chi-squared tests for trend using linear regression for acute pharyngitis / tonsillitis

Linear Regression Model for Antibiotic agent Prescribing Rate:	Acute Pharyngitis / Tonsillitis Coef.	[95% Conf.	Interval]	
Amoxicillin				
Month	-0.003214	-0.003517	-0.002911	***
Constant	2.266512	2.067375	2.465650	
Amoxicillin with clavulanate				
Month	0.000669	0.000193	0.001144	**
Constant	-0.293364	-0.605802	0.019074	
Benzathine benzylpenicillin				
Month	4.58e-06	3.52e-06	5.64e-06	***
Constant	-0.0029229	-0.0036208	-0.0022249	
Cefalexin				
Month	0.000837	0.000707	0.000966	***
Constant	-0.444656	-0.529916	-0.359396	
Procaine benzylpenicillin				
Month	-0.001130	-0.001324	-0.000936	***
Constant	0.799339	0.672098	0.926581	
Phenoxymethlypenicillin				
Month	0.003621	0.003438	0.003803	***
Constant	-1.974824	-2.094704	-1.854944	
Trimethoprim with sufamethoxazole				
Month	-.0000599	0.000	-.0000771	***
Constant	.0435457	.0322898	.0548015	

Table E-4: Linear chi-squared tests for trend using linear regression for acute otitis media

Linear Regression Model for Antibiotic agent Prescribing Rate:	Acute Otitis Media Coef.	[95% Conf.	Interval]	
Amoxicillin				
Month	-0.001656	-0.002131	-0.001182	***
Constant	1.548973	1.237216	1.860730	
Amoxicillin with clavulanate				
Month	0.001402	0.000772	0.002032	***
Constant	-0.596382	-1.010298	-0.182466	
Cefalcor				
Month	-0.000505	-0.000597	-0.000412	***
Constant	0.358851	0.297827	0.419876	
Cefalexin				
Month	0.000652	0.000494	0.000810	***
Constant	-0.336478	-0.440348	-0.232608	
Cefuroxime				
Month	0.0001984	0.0001742	0.0002226	***
Constant	-0.1212103	-0.137125	-0.1052957	
Erythromycin				
Month	-0.000074	-0.000128	-0.000020	**
Constant	0.070903	0.035490	0.106317	
Trimethoprim with sulfamethoxazole				
Month	0.0001058	0.0000567	0.000155	***
Constant	-0.0519367	-0.0842254	-0.019648	

E.1.2 Influenza / influenza-like illness

There were 253 antibiotic prescriptions among 2,175 initial presentations for influenza/ILI, a prescribing rate of 12%. This ranged from 0 to 26 prescriptions per month.

Table E-5: Antibiotic prescribing rate and prescribing rates for individual antibiotic agents prescribed for influenza / influenza-like illness.

Prescribing Outcomes for All Patients with initial presentations of Influenza/ILI												
URTI Condition	**Dependent Variable**	**a) Descriptive Statistics (Moving Average Data)**			**b) Linear Regression Model for Trend**							
	Prescribing Outcome Monthly Rate	**Mean prop.**	**Jan 2012 prop.**	**Jun 2017 prop.**	**Coefficient (unit increase per month)**	**[95% Conf.**	**Interval]**	**p-value**	**R-squared**	**Jan 2012 predicted value**	**Jun 2017 predicted value**	**Percentage Point Difference ***
Influenza	**Overall Antibiotic Prescribing Rate +**	0.11	0.09	0.11	-0.00045	-0.00075	-0.00015	0.004	0.1243	0.097008	0.013366	1
	amoxicillin	0.19	0.18	0.56	0.005098	0.003431	0.006765	0.000	0.3684	0.564242	0.497576	50
	amoxicillin with clavulanate	0.23	0.01	0.02	-0.0008	-0.003	0.001413	0.474	0.008	0.018182	0.018182	2
	cefalexin	0.11	0.00	0.20	0.002353	0.001764	0.002943	0.000	0.4986	0.071515	0.071515	7
	clarithromycin	0.22	0.38	0.06	-0.004	-0.00516	-0.00283	0.000	0.4231	0.112727	-0.52061	-52

Note +: The rate calculation for overall antibiotic prescribing was calculated with the numerator being all patients with initial presentations of influenza/ILI, who were prescribed an antibiotic. The denominator is all patients with initial presentations of influenza/ILI.
Note *: The percentage point difference uses predicted values for first and last months of the study period, January 2012 to June 2017 inclusive.
Note: The rate calculation for each individual antibiotic agent was calculated with the numerator being all patients with initial presentations of influenza/ILI who were prescribed the particular antibiotic. The denominator is all patients with initial presentations of the influenza/ILI who were prescribed any antibiotic agent.

Table E-6: Linear chi-squared tests for trend using linear regression for influenza / influenza-like illness

Linear Regression Model for:	Influenza/ILI Coef.	[95% Conf.	Interval]	
Overall Antibiotic Prescribing rate				
month	-0.00045	-0.000750	-0.000152	**
constant	0.416904	0.220684	0.613125	
Repeat(s) issued on antibiotic prescription				
month	-0.00282	-0.003577	-0.002065	***
constant	2.203313	1.706657	2.699969	
Antibiotic prescription written as Private prescription				
month	-0.00359	-0.005208	-0.001972	***
constant	2.492115	1.429445	3.554786	
Temperature recording during consultation				
month	0.003194	0.002156	0.004231	***
constant	-1.76863	-2.449972	-1.087284	

Table E-7: Linear chi-squared tests for trend using linear regression for influenza / influenza-like illness

Linear Regression Model for:	Influenza/ILI Coef.	[95% Conf.	Interval]	
Amoxicillin prescribing rate				
Month	0.005098	0.003431	0.006765	***
Constant	-3.15986	-4.254730	-2.064993	
Amoxicillin with clavulanate prescribing rate				
Month	-0.0008	-0.003004	0.001413	
Constant	0.74856	-0.701690	2.198811	
Azithromycin prescribing rate				
Month	0.000063	0.000859	0.875000	
Constant	0.021824	0.544591	0.934000	
Cefalexin prescribing rate				
month	0.002353	0.001764	0.002943	***
Constant	-1.43917	-1.826245	-1.052097	
Clarithromycin prescribing rate				
Month	-0.004	-0.005160	-0.002830	***
Constant	2.843512	2.078337	3.608688	
Flucloxacillin prescribing rate				
Month	-0.0010289	-0.0013899	-0.0006678	***
Constant	0.6882292	0.451111	0.9253474	
Roxithryomycin prescribing rate				
Month	-0.0006743	-0.0010638	-0.0002847	***
Constant	0.4781669	0.2223176	0.7340161	

E.1.3 Mean prescribing rates for all upper respiratory tract infection conditions including influenza / influenza-like illness

Table E-8: Mean prescribing rates of individual antibiotics, by upper respiratory tract infection condition, January 2012 to June 2017 inclusive.

	Acute Rhinosinusitis	Acute Pharyngitis/ Tonsillitis	AOM	Influenza/ILI
Antibiotic				
amoxicillin	0.33	0.16	0.46	0.19
amoxicillin with clavulanate	0.24	0.15	0.32	0.23
azithromycin	0.03	0.01	0.01	0.06
benzathine penicillin	0.00	0.00	0.00	0.00
cefaclor	0.02	0.01	0.03	0.02
cefalexin	0.12	0.10	0.09	0.11
ceftriaxone	0.00	0.00	0.00	0.00
cefuroxime	0.00	0.00	0.01	0.01
ciprofloxacin	0.00	0.00	0.01	0.00
clarithromycin	0.06	0.02	0.01	0.22
clindamycin	0.00	0.00	0.00	0.00
dicloxacillin	0.00	0.00	0.00	0.00
doxycyline	0.02	0.00	0.00	0.04
erythromycin	0.03	0.03	0.02	0.03
flucloxacillin	0.00	0.00	0.00	0.01
gentamycin	0.00	0.00	0.00	0.00
minocycline	0.00	0.00	0.00	0.00
moxifloxacin	0.00	0.00	0.00	0.00
nitrofurantoin	0.00	0.00	0.00	0.00
norfloxacin	0.00	0.00	0.00	0.00
phenoxymethylpenicillin	0.03	0.40	0.00	0.03
procaine penicillin	0.00	0.06	0.00	0.01
roxithromycin	0.10	0.05	0.01	0.04
tobramycin	0.00	0.00	0.00	0.00
trimethoprim	0.00	0.00	0.00	0.00
trimethoprim with sulfamethoxazole	0.01	0.00	0.02	0.00

E.2 Additional time series plots

E.2.1 All upper respiratory tract infection conditions excluding influenza / influenza-like illness

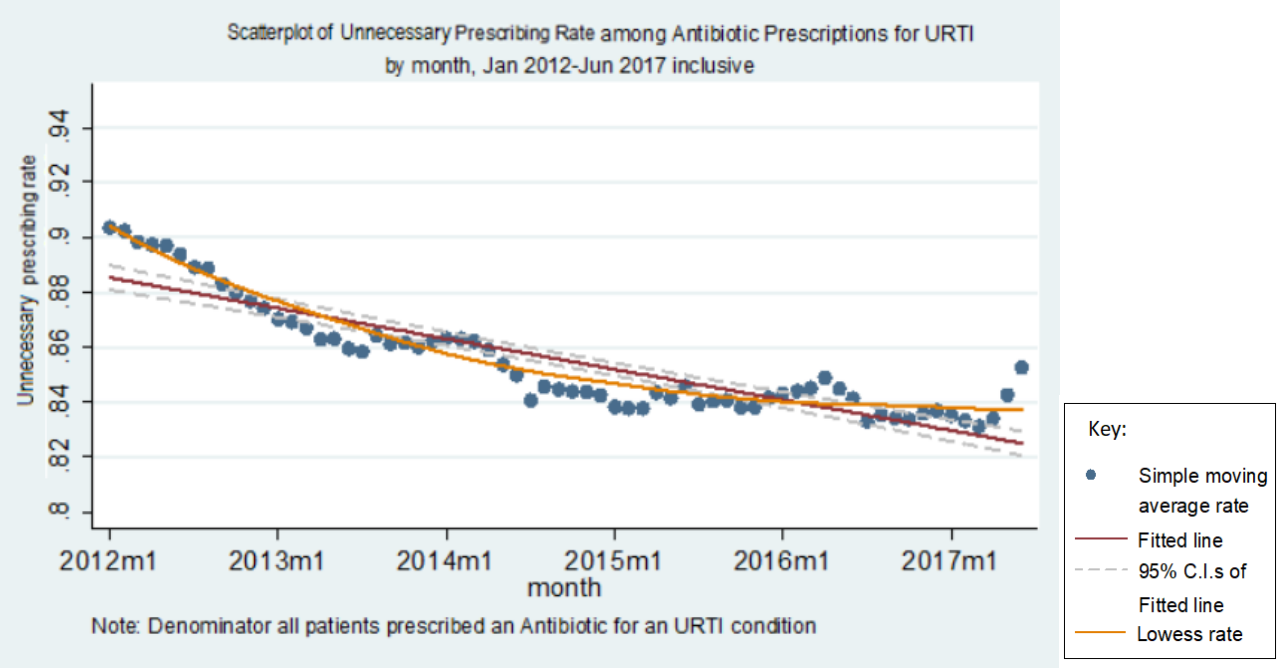


Figure E-1: Time Series Plot of Unnecessary Antibiotic Prescribing rates for all URTI diagnoses, Jan 2012-Jun 2017 inclusive, by month

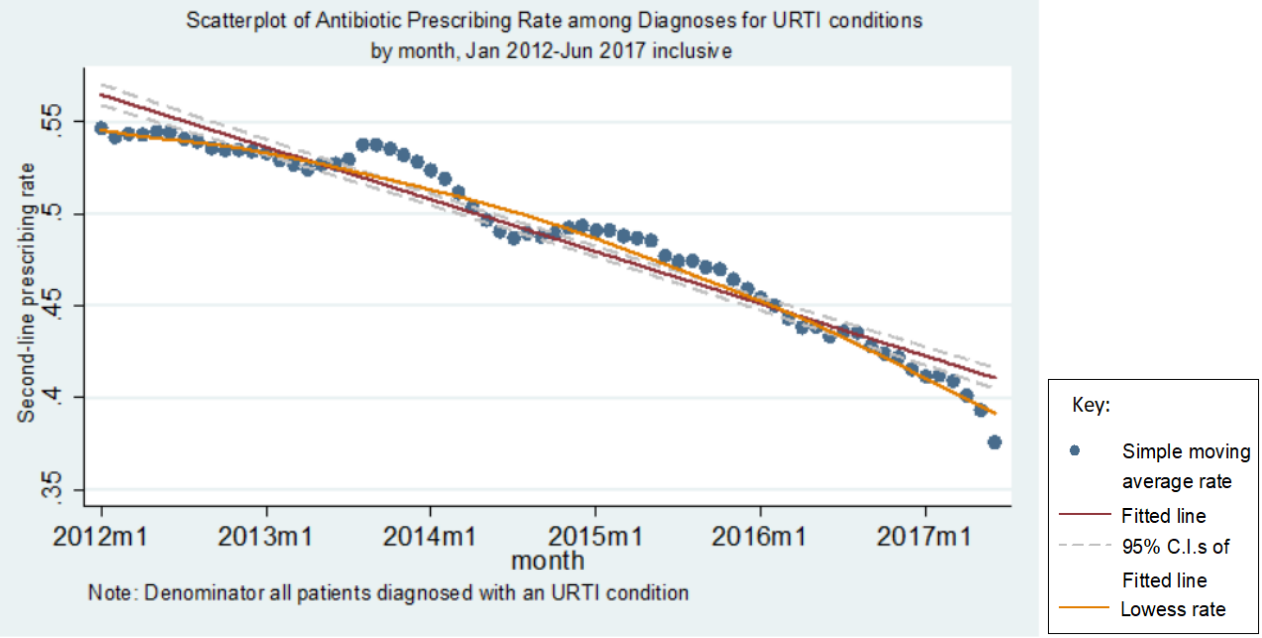


Figure E-2: Time series plot of antibiotic prescribing rates for antibiotics for all initial presentations of upper respiratory tract infection, Jan 2012-Jun 2017 inclusive, by month

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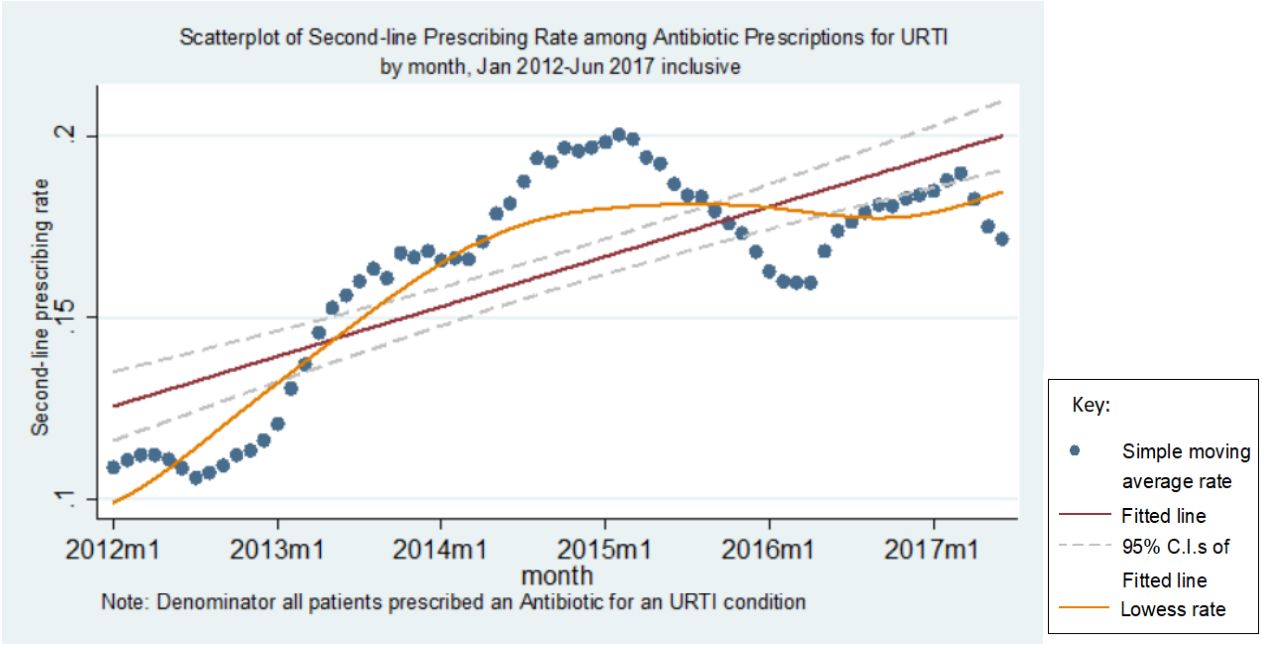


Figure E-3: Time series plot of second-line antibiotic prescribing rates for all initial presentations of upper respiratory tract infection, Jan 2012-Jun 2017 inclusive, by month

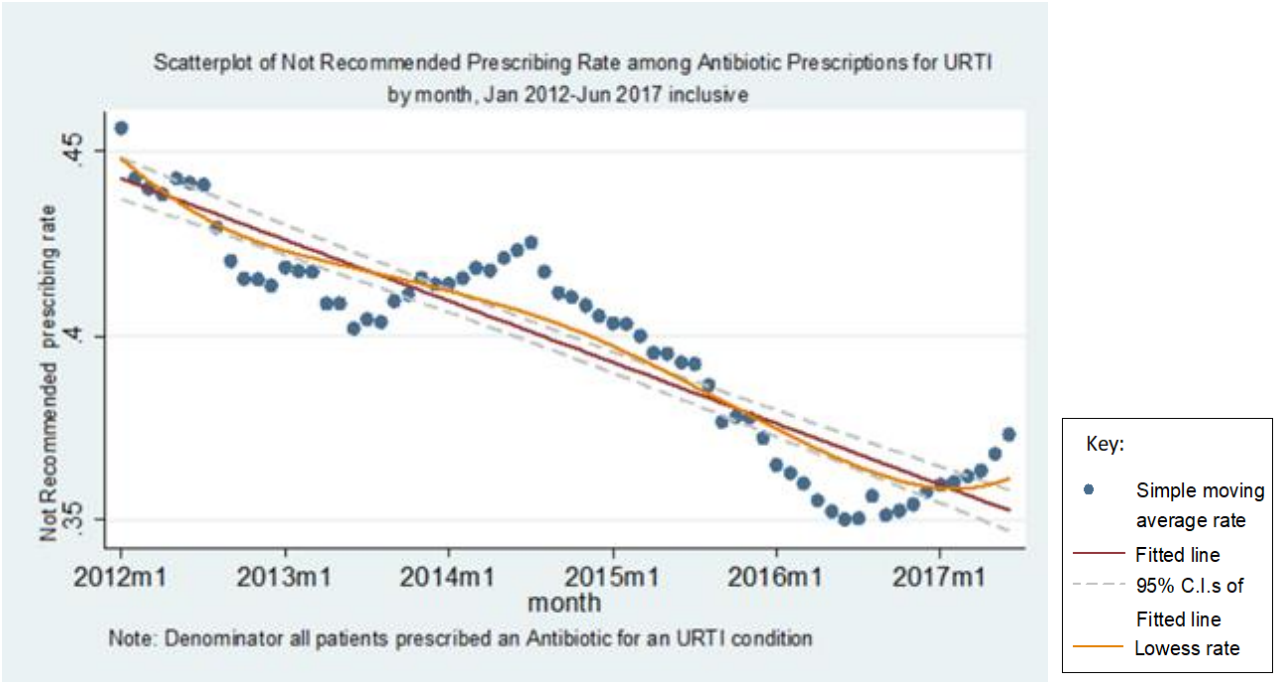


Figure E-4: Time series plot of antibiotic prescribing rates for antibiotics not recommended in the guidelines for all initial presentations of upper respiratory tract infection, Jan 2012-Jun 2017 inclusive, by month

E.2.1 By specific condition

E.2.1.1 Acute rhinosinusitis

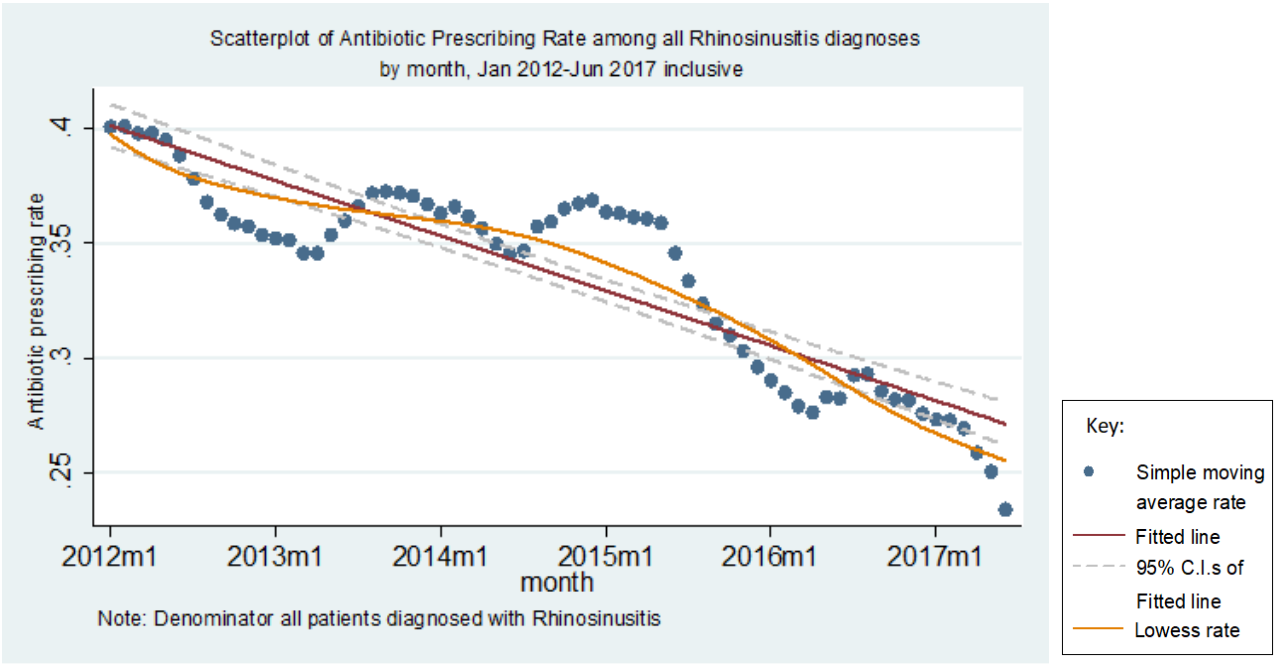


Figure E-5: Time series plot of antibiotic prescribing rates for initial presentations of acute rhinosinusitis, January 2012 to June 2017, inclusive, by month

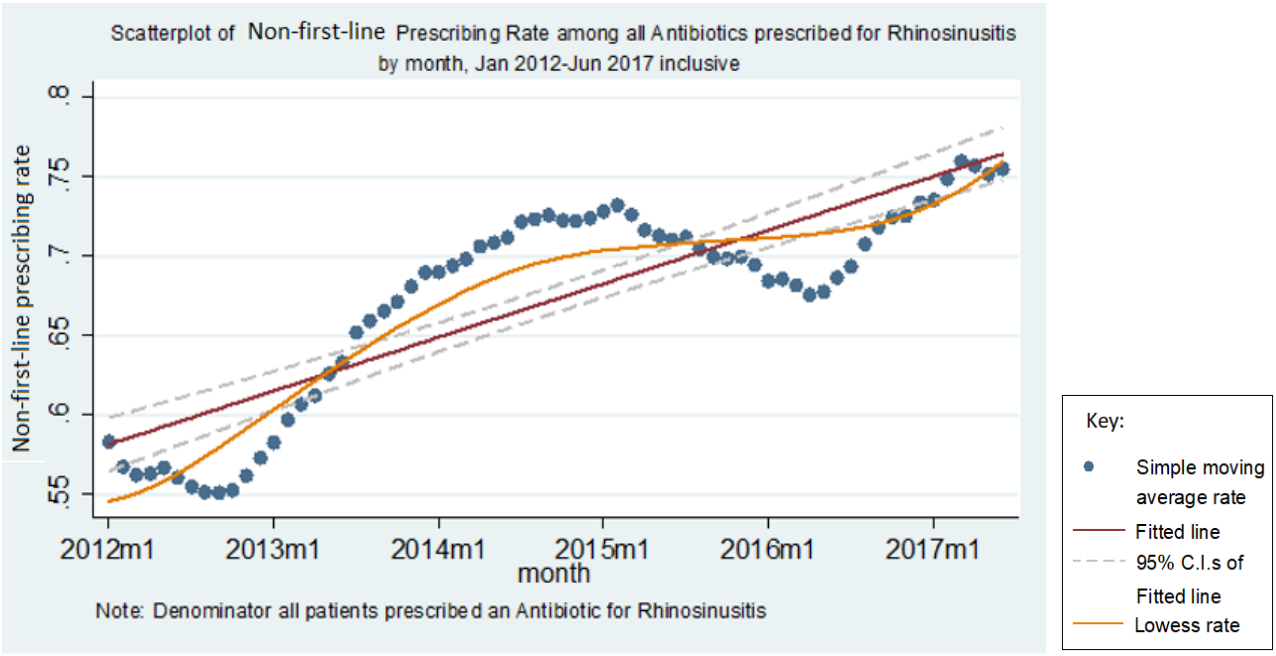


Figure E-6: Time series plot of non-first-line antibiotic prescribing rates for initial presentations of acute rhinosinusitis, January 2012 to June 2017, inclusive, by month

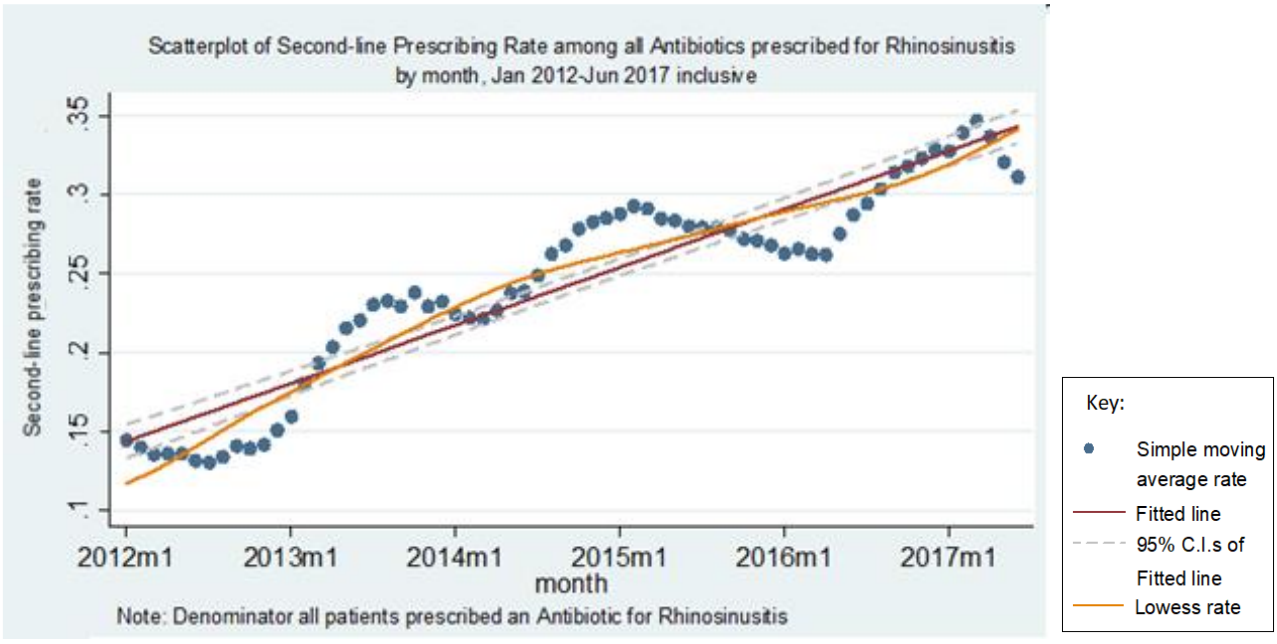


Figure E-7: Time series plot of second-line antibiotic prescribing rates for initial presentations of acute rhinosinusitis, January 2012 to June 2017, inclusive, by month

E.2.1.2 Acute pharyngitis / tonsillitis

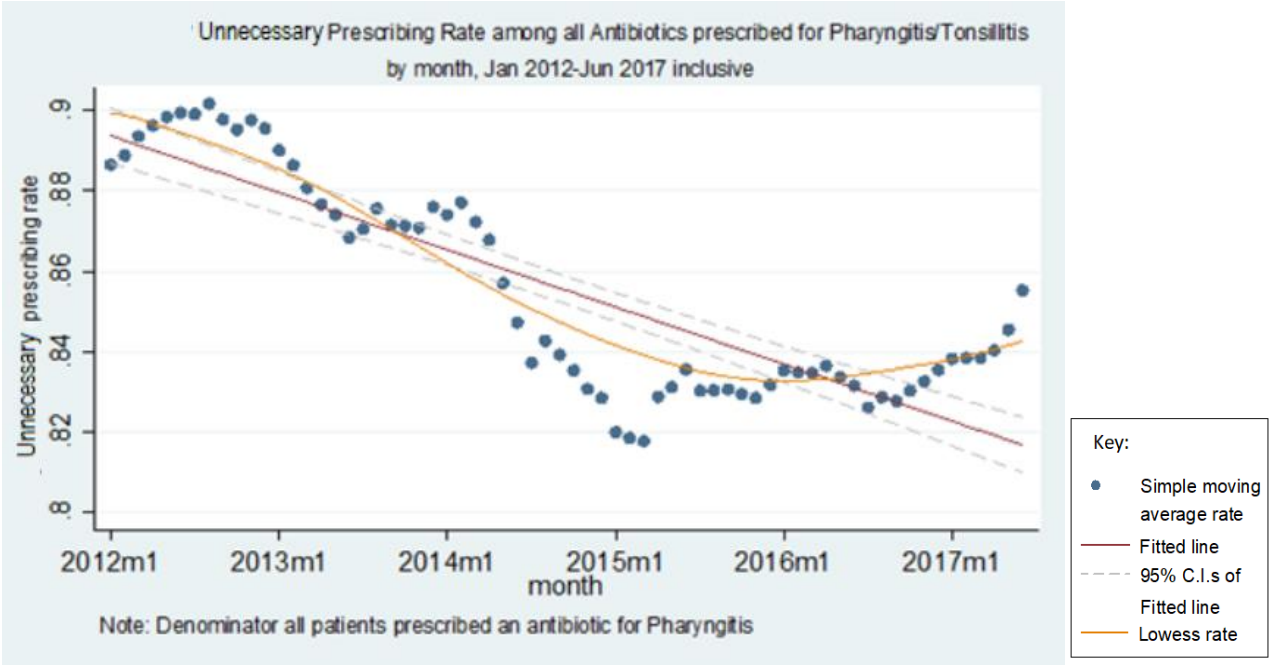


Figure E-8: Time series plot of unnecessary antibiotic prescribing rates for initial presentations of acute pharyngitis / tonsillitis, January 2012 to June 2017, inclusive, by month

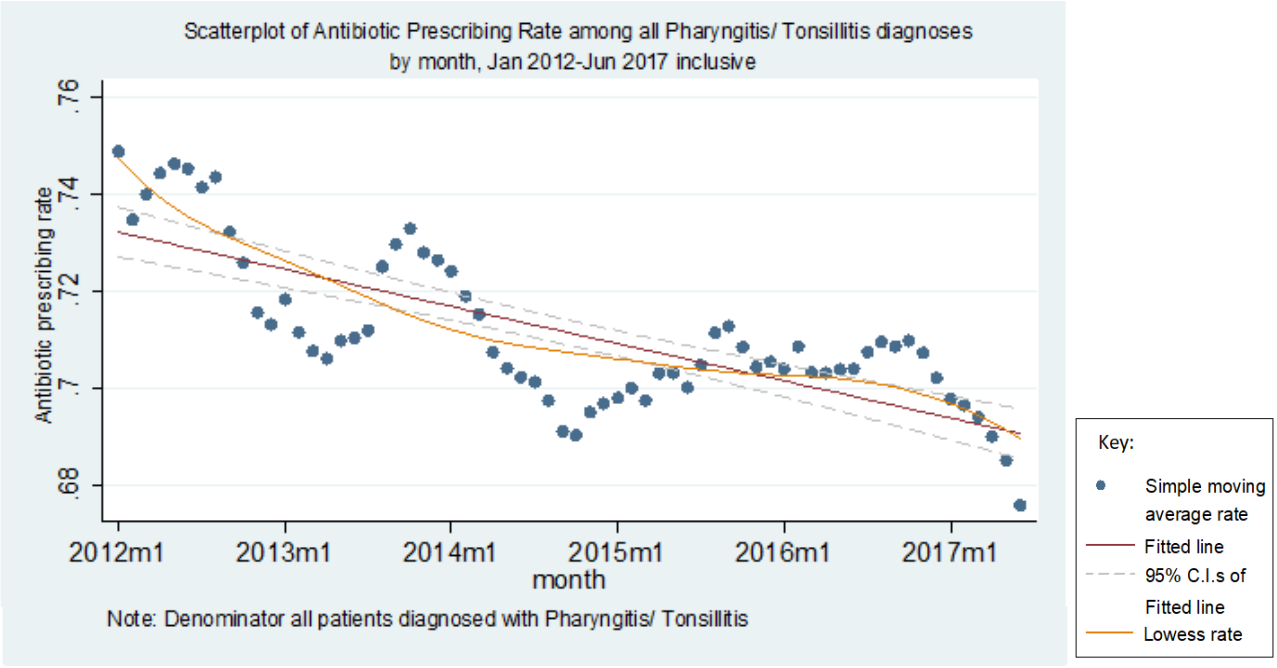


Figure E-9: Time series plot of antibiotic prescribing rates for initial presentations of acute pharyngitis / tonsillitis, January 2012 to June 2017, inclusive, by month

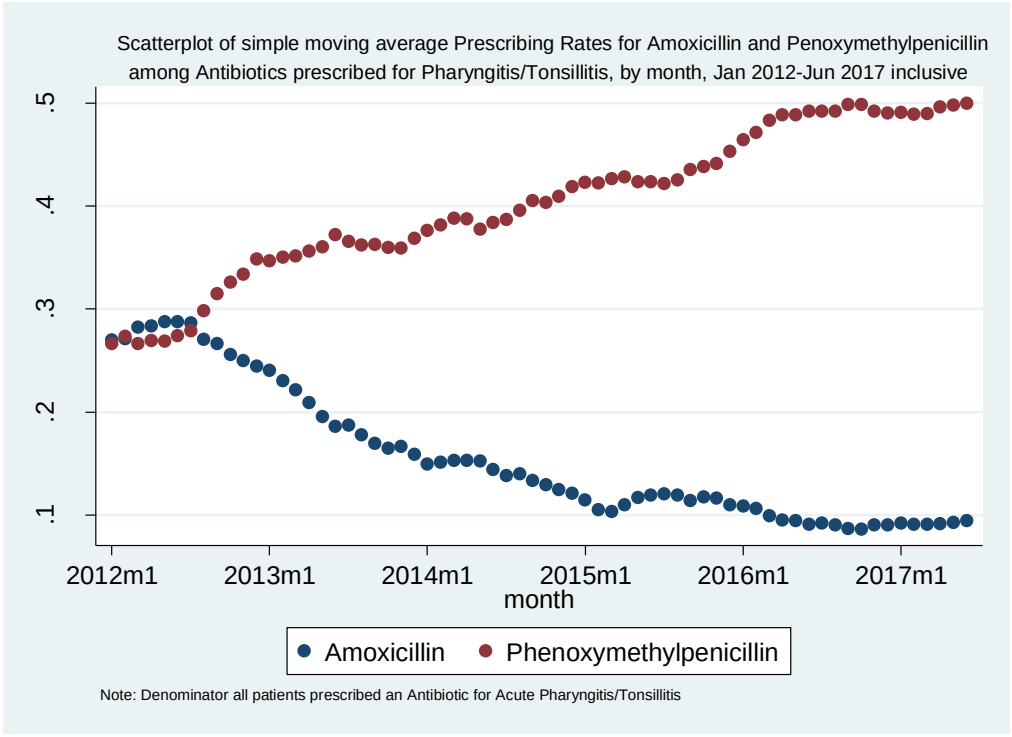


Figure E-10: Time series plot of amoxicillin and phenoxymethylpenicillin prescribing rates for initial presentations of acute pharyngitis / tonsillitis, January 2012 to June 2017, inclusive, by month

E.2.1.3 Acute otitis media

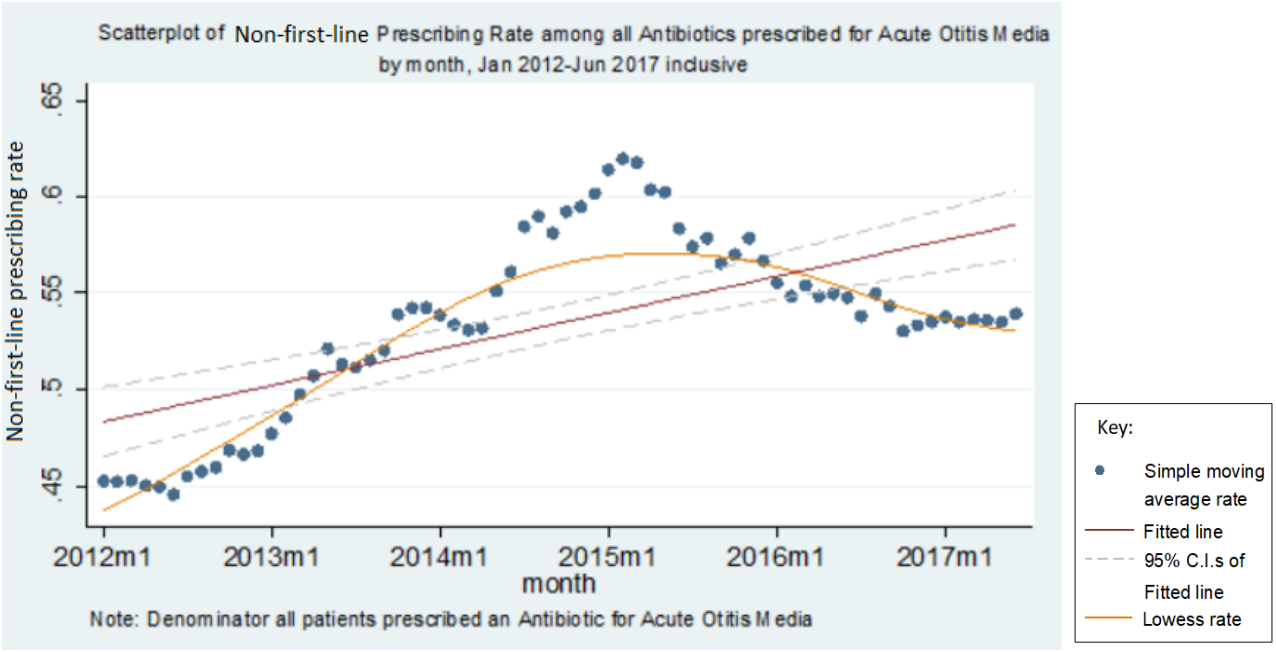


Figure E-11: Time series plot of non-first-line antibiotic prescribing rates for initial presentations of acute otitis media, January 2012 to June 2017, inclusive, by month

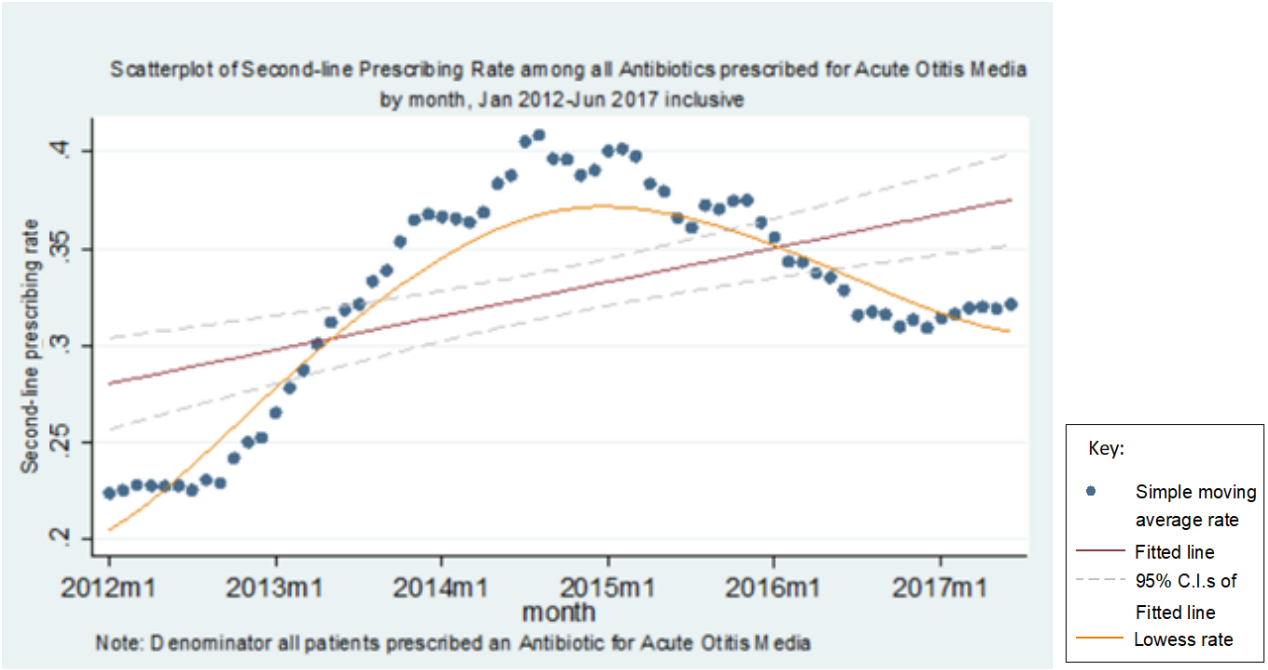


Figure E-12: Time series plot of second-line antibiotic prescribing rates for initial presentations of acute otitis media, January 2012 to June 2017, inclusive, by month

APPENDIX F – APPENDICES TO TRENDS IN PRESCRIBING FOR URINARY TRACT INFECTION CHAPTER (CHAPTER 7)

F.1 Tables

Table F-1: Summary of multiple, bivariable linear regression models / Chi-squared linear test for trend for patients with urinary tract infection

Linear Regression Model for:	Coef.	Std. Err.	t	P>t	[95% Conf.	Interval]	Num.	F(1, 64)	Prob > F	R-squared	Adj R-squared	Root MSE
antibiotic prescribing rate												
Month	0.000765	5.51E-05	13.87	0.0000	0.0006544	0.0008746	66	192.5	0.0000	0.7505	0.7466	0.00853
_cons	0.342587	0.03619	9.47	0.0000	0.2702891	0.4148852						
first-line agent												
Month	-0.00091	8.61E-05	-10.5	0.0000	-0.001079	-0.000735	66	111.07	0.0000	0.6344	0.6287	0.01332
_cons	0.995734	0.056537	17.61	0.0000	0.8827877	1.10868						
second-line agent												
Month	0.001555	0.000073	21.31	0.0000	0.0014094	0.001701	66	453.95	0.0000	0.8764	0.8745	0.0113
_cons	-0.61706	0.04794	-12.9	0.0000	-0.712835	-0.521293						
third-line agent												
Month	-0.0002	0.000116	-1.7	0.0940	-0.00043	0.0000346	66	2.89	0.0939	0.0432	0.0283	0.018
_cons	0.237212	0.076367	3.11	0.0030	0.084651	0.3897735						
not recommended agent												
Month	-0.00045	7.22E-05	-6.24	0.0000	-0.000595	-0.000306	66	38.9	0.0000	0.378	0.3683	0.01117
_cons	0.384118	0.047418	8.1	0.0000	0.289389	0.4788471						
non-first-line agent												
Month	0.000907	8.61E-05	10.54	0.0000	0.0007352	0.0010792	66	111.07	0.0000	0.6344	0.6287	0.01332
_cons	0.004266	0.056537	0.08	0.9400	-0.10868	0.1172121						
repeat(s) issued on script												
month	-0.00175	0.000078	-22.5	0.0000	-0.001907	-0.001596	66	504.65	0.0000	0.8875	0.8857	0.01206
_cons	1.44066	0.051199	28.14	0.0000	1.338379	1.54294						
private script												
month	-0.00084	5.62E-05	-14.9	0.0000	-0.000949	-0.000725	66	222.11	0.0000	0.7763	0.7728	0.00869
_cons	0.574207	0.036887	15.57	0.0000	0.5005167	0.6478969						
urine dipstick requested & performed												
month	0.000122	6.81E-05	1.78	0.0790	-1.46E-05	0.0002575	66	3.18	0.0792	0.0474	0.0325	0.01054
_cons	0.874982	0.044726	19.56	0.0000	0.7856307	0.9643334						
temperature recorded during consult												
month	0.001978	0.000138	14.35	0.0000	0.0017029	0.0022538	66	205.85	0.0000	0.7628	0.7591	0.02134
_cons	-1.14707	0.090562	-12.7	0.0000	-1.327988	-0.96615						

Table F-2: Summary of multiple, bivariable linear regression models / Chi-squared linear test for trend for women with initial presentations of urinary tract infection

Linear Regression Model for:	Coef.	Std. Err.	t	P>t	[95% Conf.	Interval]	Num. obs.	F(1, 64)	Prob > F	R-squared	Adj R-squared	Root MSE
antibiotic prescribing rate												
month	0.000753	5.81E-05	12.96	0.0000	0.000637	0.000869	66	167.9	0.0000	0.724	0.7197	0.00899
_cons	0.373134	0.038146	9.78	0.0000	0.296929	0.449339						
first-line agent												
month	-0.00102	0.000091	-11.16	0.0000	-0.0012	-0.00083	66	124.48	0.0000	0.6604	0.6551	0.01408
_cons	1.103023	0.05975	18.46	0.0000	0.983658	1.222387						
second-line agent												
month	0.001626	7.76E-05	20.96	0.0000	0.001471	0.001782	66	439.29	0.0000	0.8728	0.8709	0.01201
_cons	-0.6787	0.050966	-13.32	0.0000	-0.78052	-0.57689						
third-line agent												
month	-0.00022	0.000107	-2.06	0.0440	-0.00044	-6.48E-06	66	4.24	0.0437	0.0621	0.0474	0.01663
_cons	0.231226	0.070557	3.28	0.0020	0.090273	0.372178						
not recommended agent												
month	-0.00039	6.41E-05	-6.09	0.0000	-0.00052	-0.00026	66	37.04	0.0000	0.3666	0.3567	0.00993
_cons	0.344456	0.042124	8.18	0.0000	0.260305	0.428608						
non-first-line agent												
month	0.001015	0.000091	11.16	0.0000	0.000833	0.001197	66	124.48	0.0000	0.6604	0.6551	0.01408
_cons	-0.10302	0.05975	-1.72	0.0890	-0.22239	0.016342						
repeat(s) issued on script												
month	-0.00191	7.52E-05	-25.37	0.0000	-0.00206	-0.00176	66	643.52	0.0000	0.9095	0.9081	0.01164
_cons	1.521096	0.049386	30.8	0.0000	1.422437	1.619755						
private script												
month	-0.00088	5.72E-05	-15.4	0.0000	-0.001	-0.00077	66	237.09	0.0000	0.7874	0.7841	0.00886
_cons	0.603302	0.037587	16.05	0.0000	0.528214	0.678391						
urine dipstick requested &												
month	8.17E-05	7.94E-05	1.03	0.3070	-7.7E-05	0.00024	66	1.06	0.3070	0.0163	0.0009	0.01228
_cons	0.897667	0.052126	17.22	0.0000	0.793534	1.001799						
temperature recorded during												
month	0.001867	0.000127	14.74	0.0000	0.001614	0.00212	66	217.32	0.0000	0.7725	0.7689	0.0196
_cons	-1.08301	0.083169	-13.02	0.0000	-1.24916	-0.91686						

Table F-3: Summary of multiple, bivariable linear regression models / Chi-squared linear test for trend for men with initial presentations of urinary tract infection

Linear Regression Model for:	Coef.	Std. Err.	t	P>t	[95% Conf.	Interval]	Num. obs.	F(1, 64)	Prob > F	R-squared	Adj R-squared	Root MSE
antibiotic prescribing rate												
month	0.001107	0.0001	11.03	0.0000	0.000906	0.001307	66	121.66	0.0000	0.6553	0.6499	0.01553
_cons	0.049941	0.065884	0.76	0.4510	-0.08168	0.181559						
first-line agent												
month	-0.00197	0.000325	-6.05	0.0000	-0.00262	-0.00132	66	36.65	0.0000	0.3642	0.3542	0.05034
_cons	1.622798	0.213636	7.6	0.0000	1.196011	2.049586						
second-line agent												
month	0.001421	0.000169	8.4	0.0000	0.001083	0.00176	66	70.48	0.0000	0.5241	0.5167	0.0262
_cons	-0.57416	0.111191	-5.16	0.0000	-0.79629	-0.35203						
third-line agent												
month	0.000643	0.00025	2.57	0.0120	0.000144	0.001143	66	6.62	0.0124	0.0937	0.0795	0.0387
_cons	-0.18445	0.16422	-1.12	0.2660	-0.51252	0.143617						
not recommended agent												
month	-9.5E-05	0.000157	-0.61	0.5460	-0.00041	0.000218	66	0.37	0.5463	0.0057	-0.0098	0.02427
_cons	0.135809	0.102974	1.32	0.1920	-0.06991	0.341523						
non-first-line agent												
month	0.001969	0.000325	6.05	0.0000	0.00132	0.002619	66	36.65	0.0000	0.3642	0.3542	0.05034
_cons	-0.6228	0.213636	-2.92	0.0050	-1.04959	-0.19601						
repeat(s) issued on script												
month	-0.0012	0.000185	-6.47	0.0000	-0.00157	-0.00083	66	41.85	0.0000	0.3954	0.3859	0.02867
_cons	1.212897	0.121681	9.97	0.0000	0.969811	1.455984						
private script												
month	-0.00057	7.24E-05	-7.93	0.0000	-0.00072	-0.00043	66	62.87	0.0000	0.4955	0.4877	0.01121
_cons	0.409914	0.047566	8.62	0.0000	0.314889	0.504939						
urine dipstick requested & performed												
month	0.000344	3.98E-05	8.64	0.0000	0.000264	0.000423	66	74.74	0.0000	0.5387	0.5315	0.00616
_cons	0.739175	0.026128	28.29	0.0000	0.686979	0.791371						
temperature recorded during consult												
month	0.001759	0.000117	15.06	0.0000	0.001525	0.001992	66	226.85	0.0000	0.78	0.7765	0.01807
_cons	-1.03954	0.07669	-13.56	0.0000	-1.19275	-0.88634						

Table F-4: Summary of multiple, bivariable linear regression models / Chi-squared linear test for trend for children with initial presentations of urinary tract infection

Linear Regression Model for:	Coef.	Std. Err.	t	P>t	[95% Conf.	Interval]	Num. obs.	F(1, 64)	Prob > F	R-squared	Adj R-squared	Root MSE
antibiotic prescribing rate												
month	0.000506	0.000137	3.68	0.0000	0.000231	0.00078	66	13.57	0.0005	0.175	0.1621	0.02124
_cons	0.410088	0.090142	4.55	0.0000	0.230008	0.590168						
first-line agent												
month	0.000546	0.000142	3.84	0.0000	0.000262	0.00083	66	14.73	0.0003	0.1871	0.1744	0.02202
_cons	-0.18466	0.093466	-1.98	0.0530	-0.37138	0.00206						
second-line agent												
month	0.000975	0.00012	8.16	0.0000	0.000737	0.001214	66	66.63	0.0000	0.5101	0.5024	0.01849
_cons	-0.08013	0.07847	-1.0200	0.311	-0.2369	0.076627						
third-line agent												
month	-0.00027	0.000184	-1.44	0.1540	-0.00063	0.000102	66	2.08	0.1541	0.0315	0.0163	0.0285
_cons	0.334094	0.120941	2.76	0.0070	0.092487	0.575701						
not recommended agent												
month	-0.00126	0.000154	-8.16	0.0000	-0.00156	-0.00095	66	66.58	0.0000	0.5099	0.5022	0.02382
_cons	0.930701	0.101076	9.21	0.0000	0.728778	1.132624						
non-first-line agent												
month	-0.00055	0.000142	-3.84	0.0000	-0.00083	-0.00026	66	14.73	0.0003	0.1871	0.1744	0.02202
_cons	1.184661	0.093466	12.67	0.0000	0.997941	1.371381						
repeat(s) issued on script												
month	-0.00055	0.000209	-2.64	0.0100	-0.00097	-0.00013	66	6.98	0.0104	0.0983	0.0842	0.03232
_cons	0.708788	0.137154	5.17	0.0000	0.434792	0.982783						
private script												
month	-0.00074	9.14E-05	-8.08	0.0000	-0.00092	-0.00056	66	65.32	0.0000	0.5051	0.4974	0.01414
_cons	0.502395	0.060014	8.37	0.0000	0.382504	0.622286						
urine dipstick requested & performed												
month	0.000305	5.61E-05	5.43	0.0000	0.000193	0.000416	66	29.5	0.0000	0.3155	0.3048	0.00867
_cons	0.769744	0.036812	20.91	0.0000	0.696203	0.843285						
temperature recorded during consult												
month	0.002833	0.000276	10.28	0.0000	0.002282	0.003383	66	105.67	0.0000	0.6228	0.6169	0.04265
_cons	-1.61954	0.180989	-8.95	0.0000	-1.98111	-1.25797						

Table F-5: Frequency table of mean prescribing rates for individual antibiotics prescribed for initial presentations of urinary tract infection, January 2012 to June 2017 inclusive, by patient group

Antibiotic Agent	Women	Men	Children < 16yrs
amoxicillin	0.03	0.03	0.08
amoxicillin with clavulanate	0.06	0.12	0.16
azithromycin	0.00	0.00	0.00
benzathine penicillin	0.00	0.01	0.00
cefaclor	0.00	0.00	0.01
cefalexin	0.39	0.36	0.56
ceftriaxone	0.00	0.00	0.00
cefuroxime	0.00	0.00	0.00
ciprofloxacin	0.00	0.01	0.00
clarithromycin	0.00	0.00	0.00
clindamycin	0.00	0.00	0.00
dicloxacillin	0.00	0.00	0.00
doxycyline	0.00	0.00	0.00
erythromycin	0.00	0.00	0.00
flucloxacillin	0.00	0.00	0.00
gentamycin	0.00	0.00	0.00
minocycline	0.00	0.00	0.00
moxifloxacin	0.00	0.00	0.00
nitrofurantoin	0.04	0.04	0.01
norfloxacin	0.02	0.08	0.00
phenoxymethylpenicillin	0.00	0.00	0.00
roxithromycin	0.00	0.00	0.00
sodium fusidate	0.00	0.00	0.00
trimethoprim	0.44	0.33	0.09
trimethoprim with sulfamethoxazole	0.01	0.02	0.08

Table F-6: Frequency table of counts of antibiotic prescriptions for initial presentations of urinary tract infection per half-year, by patient group

Half-year	Women	Men	Children <16	Total
2012h1	232	21	21	274
2012h2	272	26	39	337
2013h1	242	26	31	299
2013h2	220	30	43	293
2014h1	230	33	36	299
2014h2	269	32	44	345
2015h1	303	42	33	378
2015h2	252	38	41	331
2016h1	304	33	41	378
2016h2	325	43	45	413
2017h1	401	57	46	504
total	13636	1631	2087	3851

Table F-7: Frequency table of antibiotic prescribing rates per half-yearly period, by patient group

	2012h1	2012h2	2013h1	2013h2	2014h1	2014h2	2015h1	2015h2	2016h1	2016h2	2017h1
Women											
Prescribing Rate	0.85	0.85	0.85	0.85	0.85	0.87	0.89	0.89	0.88	0.88	0.88
First-line Prescribing Rate	0.48	0.47	0.45	0.43	0.44	0.44	0.42	0.42	0.44	0.42	0.40
Second-line Prescribing Rate	0.33	0.35	0.36	0.37	0.38	0.38	0.42	0.42	0.40	0.42	0.44
Third-line Prescribing Rate	0.07	0.07	0.09	0.12	0.11	0.10	0.09	0.08	0.08	0.07	0.07
Not Recommended Prescribing Rate	0.11	0.11	0.10	0.09	0.08	0.08	0.08	0.08	0.08	0.09	0.09
Non-first-line Prescribing Rate	0.52	0.53	0.55	0.57	0.56	0.56	0.58	0.58	0.56	0.58	0.60
Men											
Prescribing Rate	0.73	0.76	0.75	0.75	0.79	0.78	0.79	0.80	0.78	0.79	0.81
First-line Prescribing Rate	0.35	0.37	0.45	0.40	0.30	0.27	0.27	0.33	0.35	0.28	0.25
Second-line Prescribing Rate	0.34	0.35	0.32	0.31	0.33	0.35	0.40	0.39	0.35	0.40	0.42
Third-line Prescribing Rate	0.20	0.19	0.19	0.24	0.30	0.31	0.25	0.23	0.23	0.23	0.24
Not Recommended Prescribing Rate	0.12	0.09	0.04	0.05	0.07	0.07	0.08	0.05	0.06	0.09	0.09
Non-first-line Prescribing Rate	0.65	0.63	0.55	0.60	0.70	0.73	0.73	0.67	0.65	0.72	0.75
Children											
Prescribing Rate	0.70	0.71	0.75	0.76	0.74	0.74	0.75	0.77	0.77	0.75	0.72
First-line Prescribing Rate	0.13	0.17	0.18	0.17	0.20	0.17	0.15	0.18	0.20	0.20	0.16
Second-line Prescribing Rate	0.54	0.53	0.55	0.53	0.53	0.58	0.58	0.59	0.58	0.56	0.60
Third-line Prescribing Rate	0.16	0.14	0.14	0.20	0.19	0.18	0.18	0.13	0.13	0.17	0.14
Not Recommended Prescribing Rate	0.17	0.16	0.13	0.10	0.08	0.07	0.09	0.10	0.08	0.08	0.10
Non-first-line Prescribing Rate	0.87	0.83	0.82	0.83	0.80	0.83	0.85	0.82	0.80	0.80	0.84

F.2 Additional time series plots

F.2.1 All patients with initial presentations of urinary tract infection

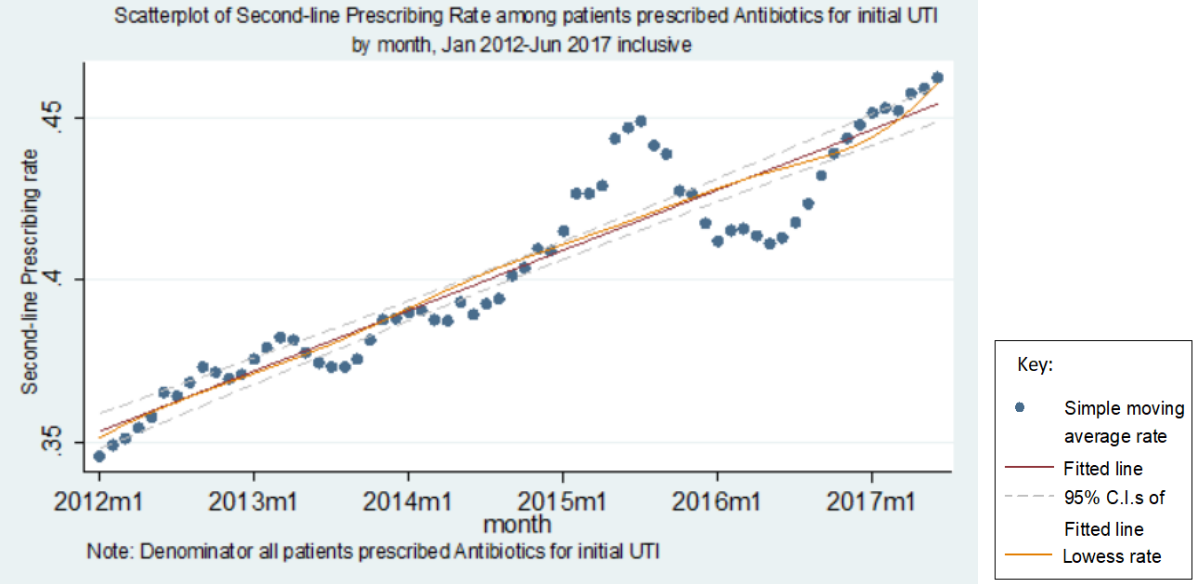


Figure F-1: Time series plot of second-line antibiotic prescribing for all patients with initial presentations of urinary tract infection over time, by month

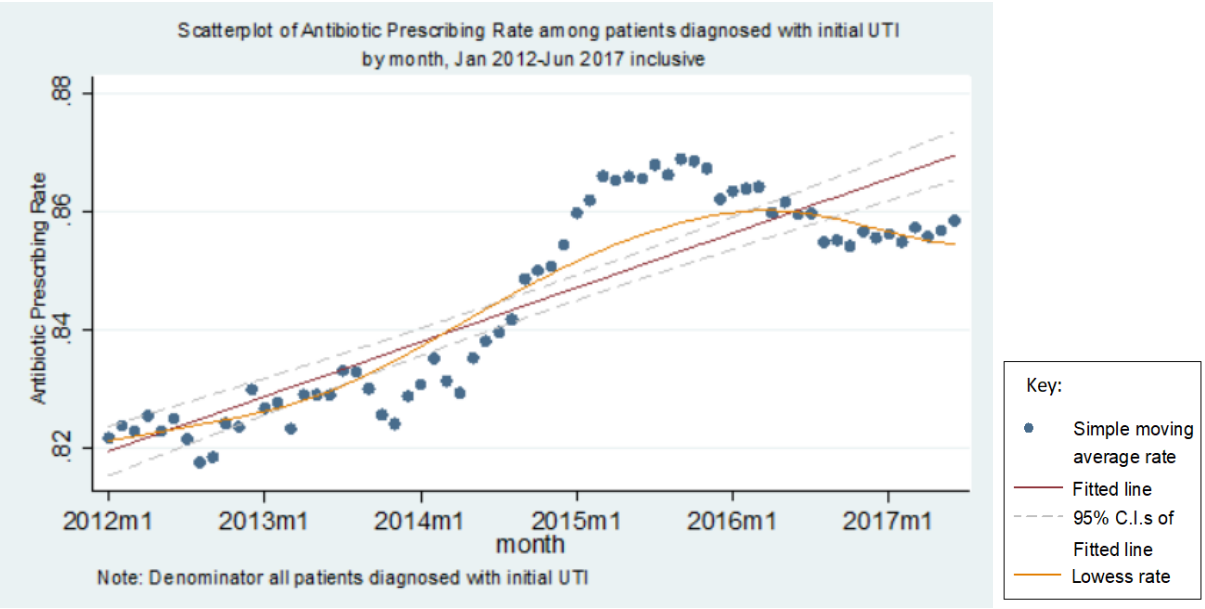


Figure F-2: Time series plot of antibiotic prescribing for all patients with initial presentations of urinary tract infection over time, by month

F.2.2 Women sixteen years and over with initial presentations of urinary tract infection

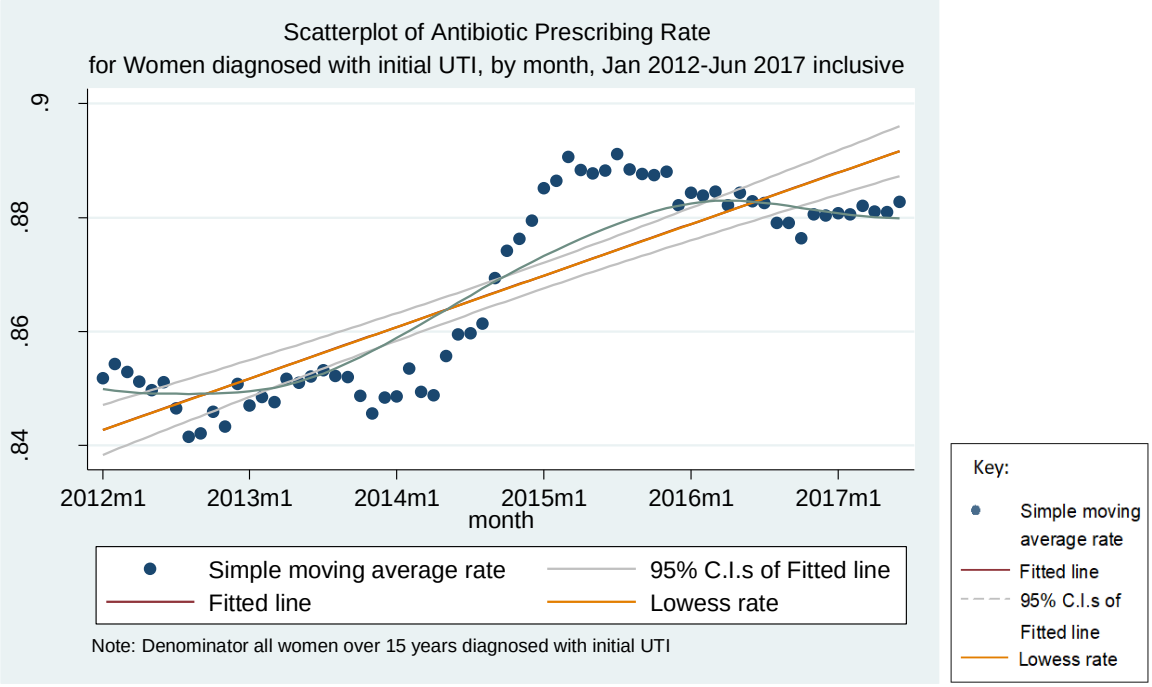


Figure F-3: Time series plot of second-line antibiotic prescribing for women of sixteen years and over with initial presentation of urinary tract infection over time, by month

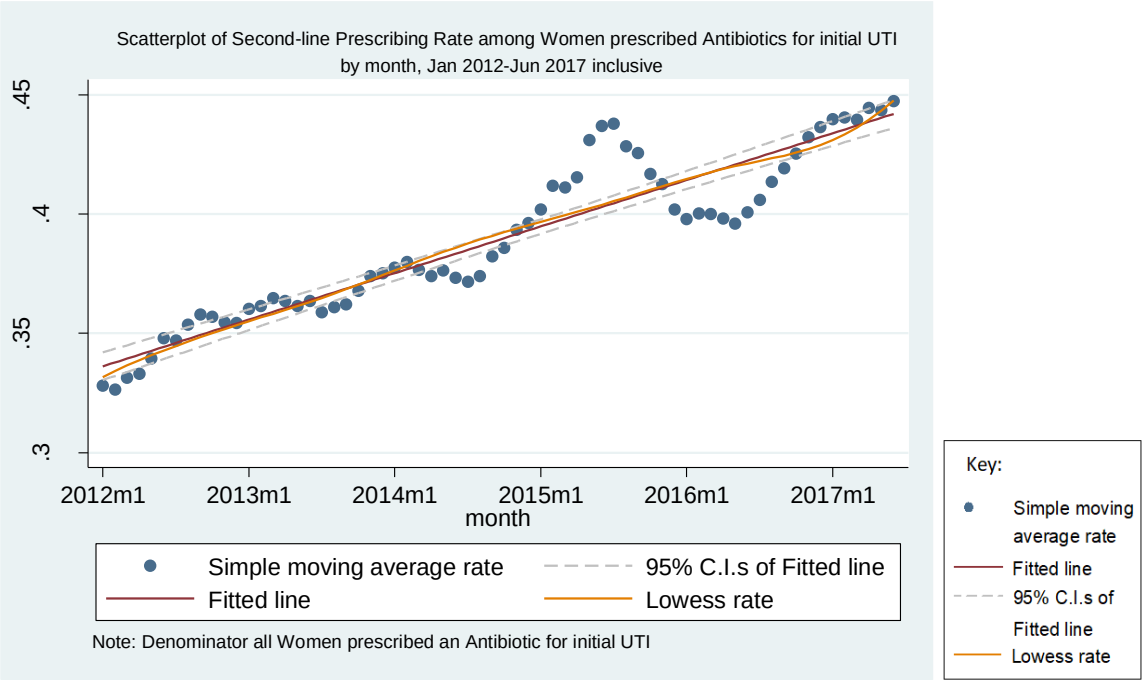


Figure F-4: Time series plot of second-line antibiotic prescribing for women of sixteen years and over with initial presentations of urinary tract infection over time, by month

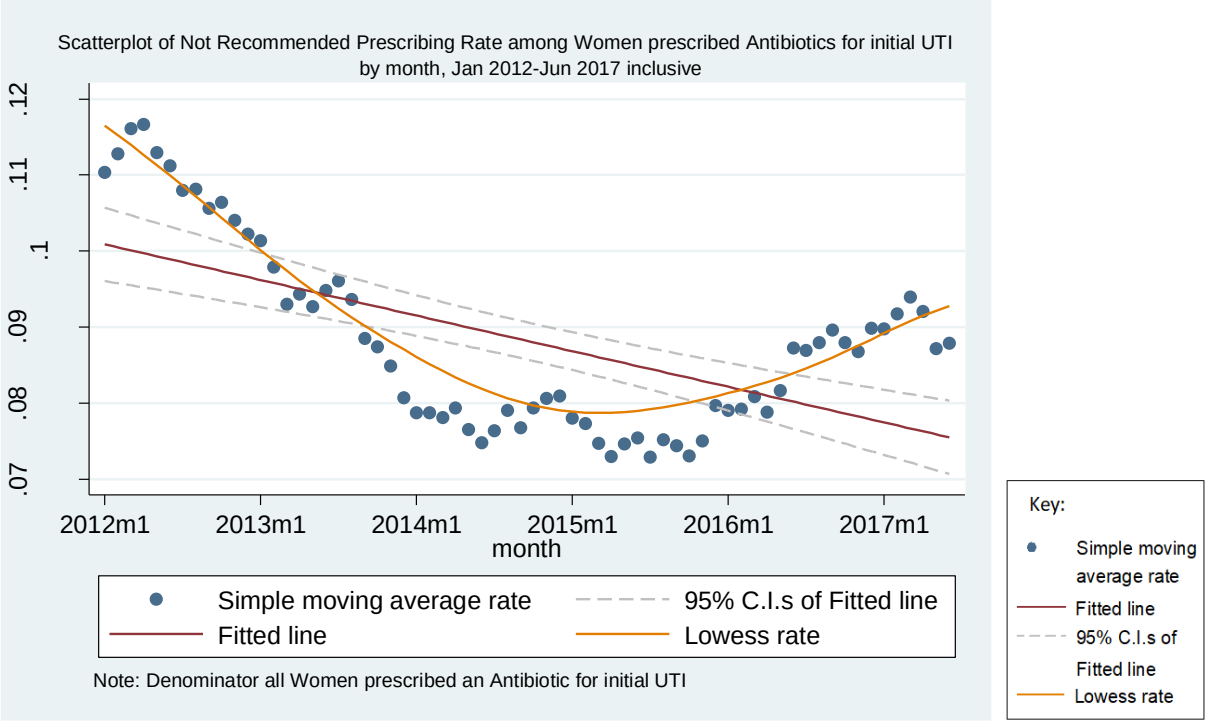


Figure F-5: Time series plot of prescribing for antibiotic agents not recommended in the guidelines for women of sixteen years and over with initial presentations of urinary tract infection over time, by month

F.2.3 Men sixteen years and over with initial presentations of urinary tract infection

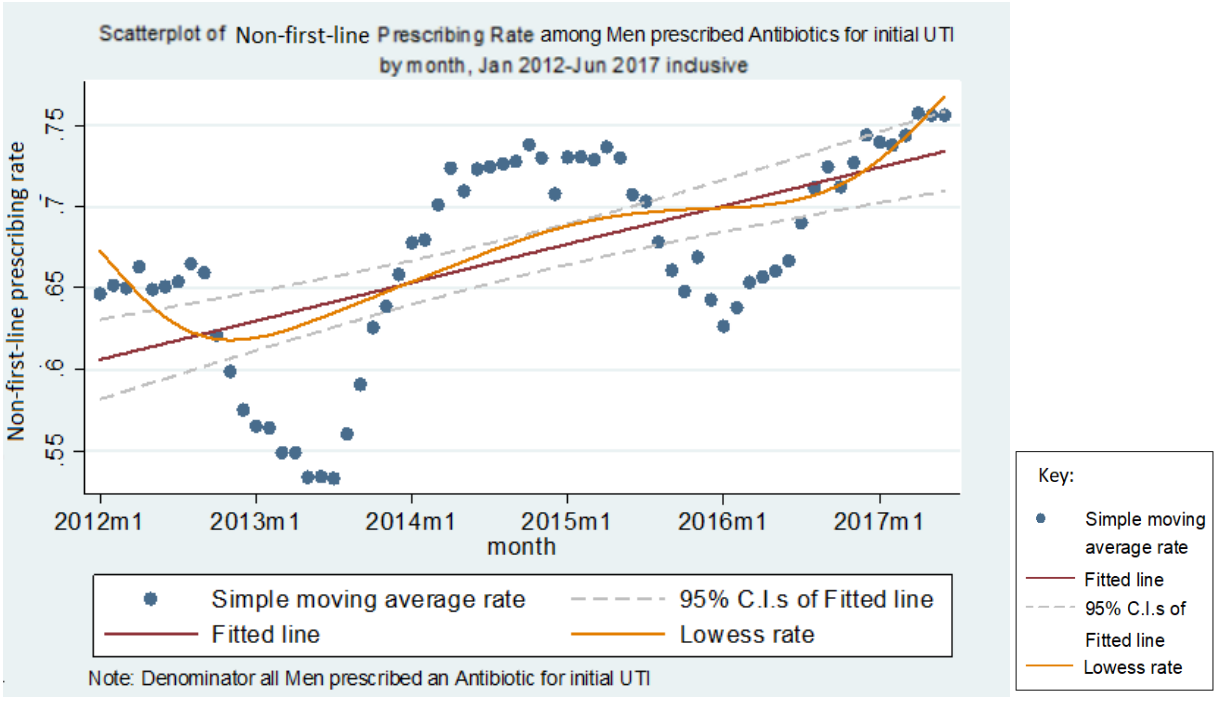


Figure F-6: Time series plot of non-first-line antibiotic prescribing for all men of sixteen years and over with initial presentation of urinary tract infection over time, by month

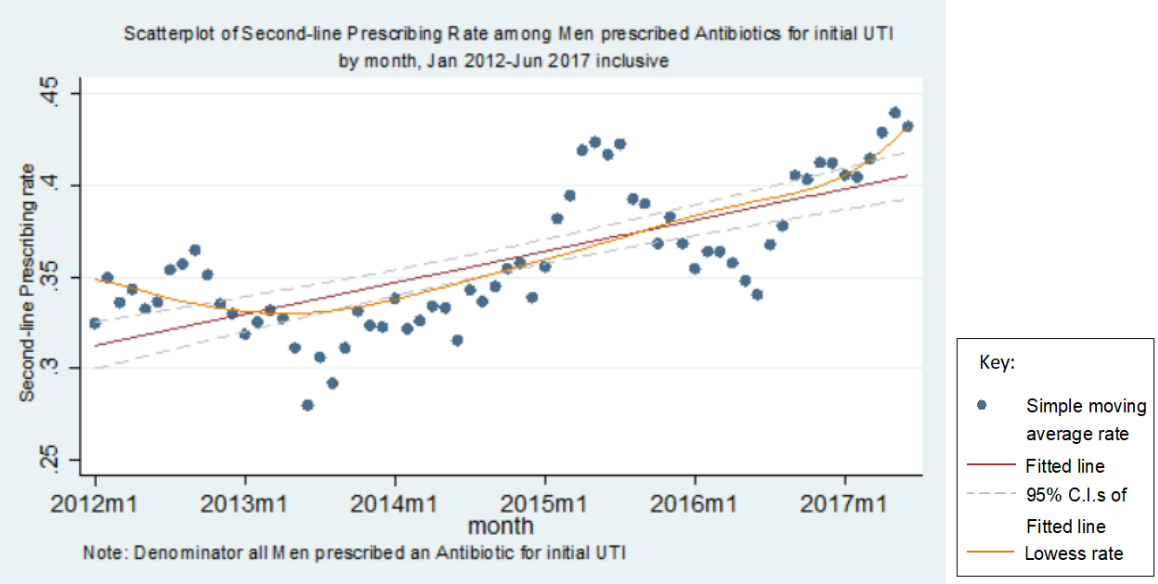


Figure F-7: Time series plot of second-line antibiotic prescribing for all men of sixteen years and over with initial presentations of urinary tract infection over time, by month

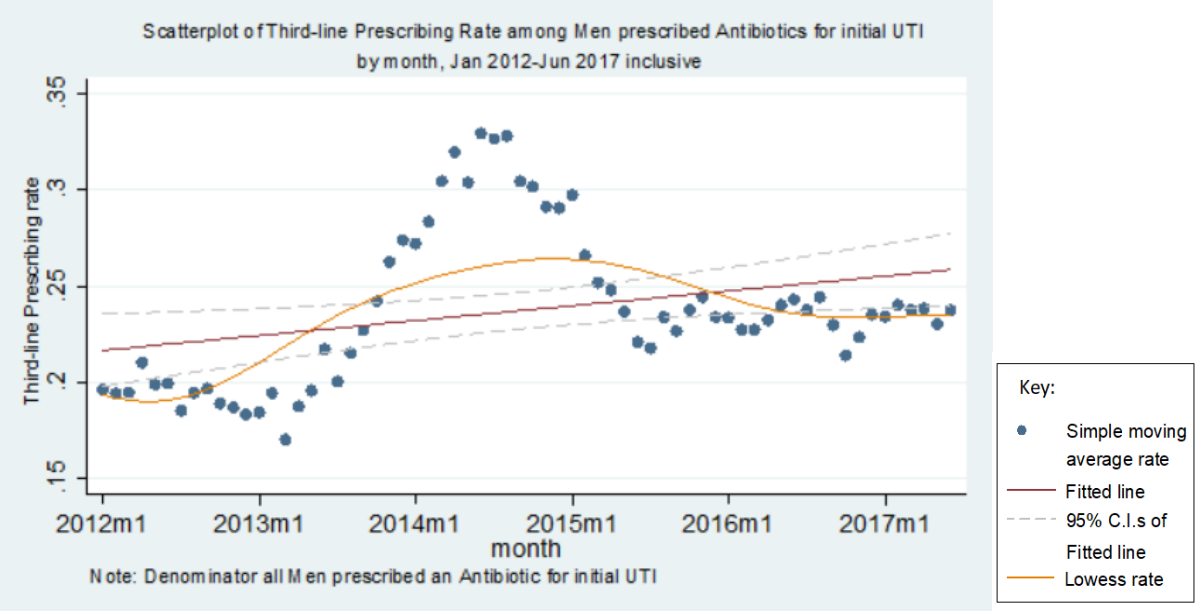


Figure F-8: Time series plot of third-line (and last resort) prescribing for all men of sixteen years and over with initial presentations of urinary tract infection over time, by month

F.2.4 Children under sixteen years of age with initial presentations of urinary tract infection

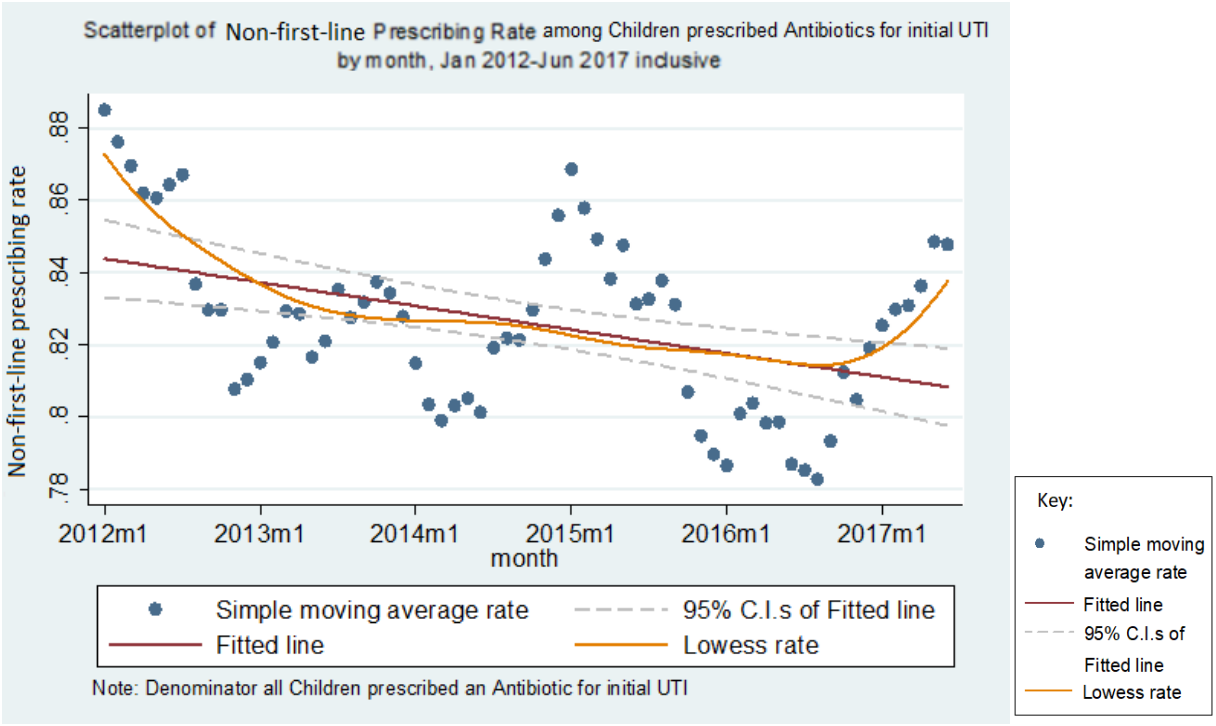


Figure F-9: Time series plot of non-first-line antibiotic prescribing for children under sixteen years over time, by month

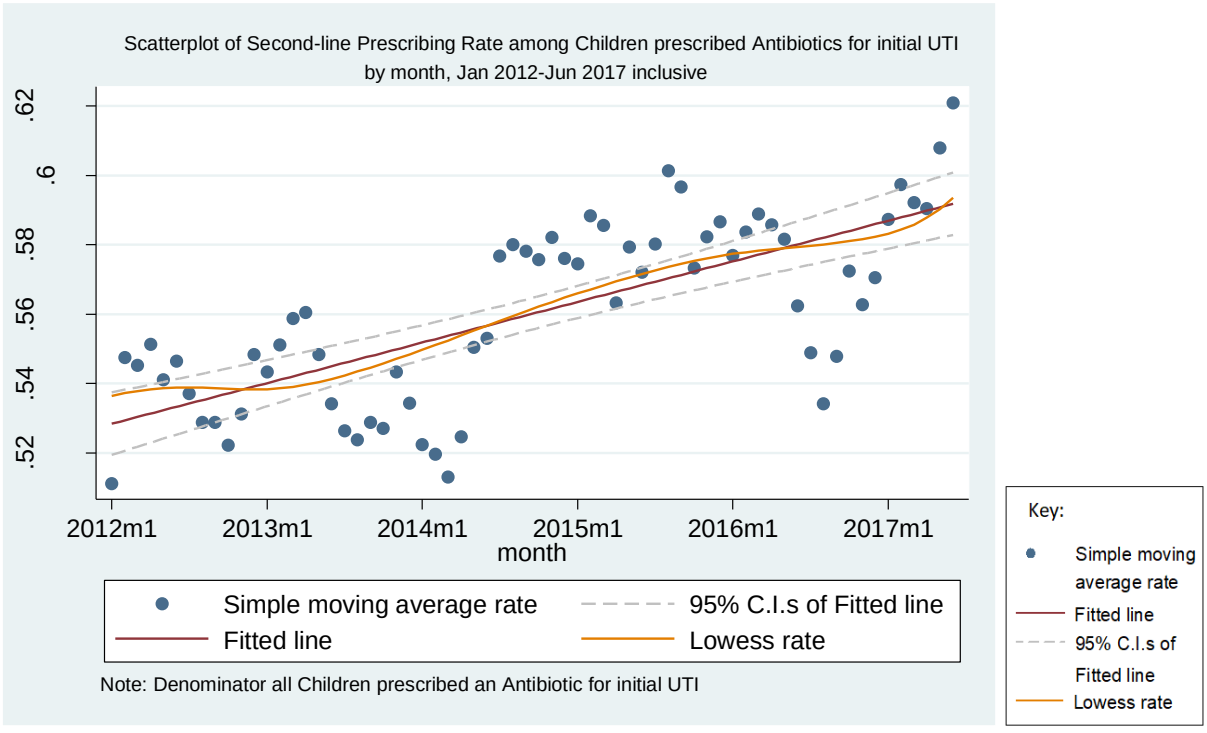


Figure F-10: Time series plot of second-line antibiotic prescribing for children under sixteen years of age over time, by month

APPENDIX G – APPENDIX TO THE DISCUSSION (CHAPTER 8): COMPARISON WITH QUALITY INDICATORS

G.1 Comparison with quality indicators for upper respiratory tract infection

The antibiotic prescribing in this dataset for initial presentations of URTI were compared against ESAC prescribing indicators and WHO AWaRe program targets (6,11). Antibiotic prescribing rates were 31%, 74%, 58% and 12% for acute rhinosinusitis, acute pharyngitis/tonsillitis, AOM and influenza/ILI, respectively. Of conditions excluding influenza/ILI, non-first-line prescribing occurred 68% of the time for rhinosinusitis, 47% of the time for pharyngitis/tonsillitis and 53% for AOM.

As detailed in **Table G-1**, for the strong majority of ESAC indicators published in 2011 (6), the proportions of patients treated with antibiotics for each and all condition(s) were higher than recommended. Non-first-line prescribing was substantially higher than recommended for all URTI conditions (6). Quinolone use was, however, consistently within the recommended low range (6).

These results suggest that there is room for improvement with respect to decisions whether to treat with antibiotics, and substantial room for improvement regarding the choice of antibiotic agent when prescribing. Performance on indicators regarding the use of recommended agents was poor, with the exception of quinolone use (6).

As seen in **Figure G-1**, 84% of antibiotic prescriptions for URTI in this dataset were on the 2019 WHO Access list, in excess of the 60% level (11). By URTI condition, this ranged from 65% for influenza/ILI to 90% for AOM. There were no instances of use for any antibiotics classified by WHO as ‘Reserve’ (11).

The WHO AWaRe program (current 2019) provides targets for at least 60% systemic antibacterials to be from their Access list (11). Performance against this indicator was well above the target for all conditions apart from influenza/ILI (11). The results compared against the WHO AWaRe program appear promising, however, they should be interpreted with a degree of caution (11). Note the WHO AWaRe program sets the same targets for use in countries with little pharmaceutical or medical legislation, regulation and oversight (11).

Table G-1: Compilation of indicators including the European Surveillance of Antibiotic Consumption indicators by Adriaenssens et al. (6) and relating to respiratory tract infection (6)

Prescribing Quality Measure / Indicator	Recommendation	Condition				
		Acute URTI (excluding influenza/ILI & AOM)	Acute Rhinosinusitis	Acute Pharyngitis / Tonsillitis	Acute Otitis Media (AOM)	Influenza/ ILI
prescribing rate (%)		31%	31%	71%	58%	12%
non-first-line antibiotic prescriptions (%)		68%	68%	47%	53%	n/a*
ESAC indicator 2b: Percentage of patients older than 1 year with acute upper respiratory infection (ICPC-2-R: R74) prescribed antibacterials for systemic use (ATC: J01) (R74_J01_%)	0-30%	33%	33%	71%	59%	12%
ESAC indicator 2b: =2a receiving the recommended antibacterials (ATC: J01CE) (R74_RECOM_%)	80-100%	32%	32%	53%	47%	n/a*
ESAC Indicator 2c: 2c. =2a receiving quinolones (ATC: J01M) (R74_J01M_%)	0-5%	<<1%	<<1%	<<1%	1%	<1%
ESAC Indicator 4a: Percentage of patients older than 1 year with acute tonsillitis (ICPC-2-R: R76) prescribed antibacterials for systemic use (ATC: J01)	0-20%			71%		
ESAC Indicator 4b: =4a receiving the recommended antibacterials (ATC: J01CE) (R76_RECOM_%)	80-100%			53%		
ESAC Indicator 4c:=4a receiving quinolones (ATC: J01M)	0-5%			<<1%		
ESAC Indicator 5a: 5a. Percentage of patients older than 18 years with acute/chronic sinusitis (ICPC-2-R: R75) prescribed antibacterials for systemic use (ATC: J01)+	0-20%		33%			
ESAC Indicator 5b: .=5a receiving the recommended antibacterials (ATC: J01CA or J01CE)+	80-100%		32%			
ESAC Indicator 5c: =5a receiving quinolones (ATC: J01M) (R75_J01M_%) +	0-5%		<<1%			
ESAC Indicator 6a: Percentage of patients older than 2 years with acute otitis media/myringitis (ICPC-2-R: H71) prescribed antibacterials for systemic use (ATC: J01)&	0-20%				59%	
ESAC Indicator 6b:=6a receiving the recommended antibacterials (ATC: J01CA or J01CE)&	80-100%				56%	
ESAC Indicator 6c: =6a receiving quinolones (ATC: J01M)&	0-5%				<1%	
prescriptions on WHO AWaRe Access list (%)	>=60%	82%	76%	87%	90%	65%

Note: + chronic sinusitis excluded from this dataset such that comparison must keep the difference in diagnostic criteria in mind.

Note: & myringitis excluded from acute otitis media diagnostic group .

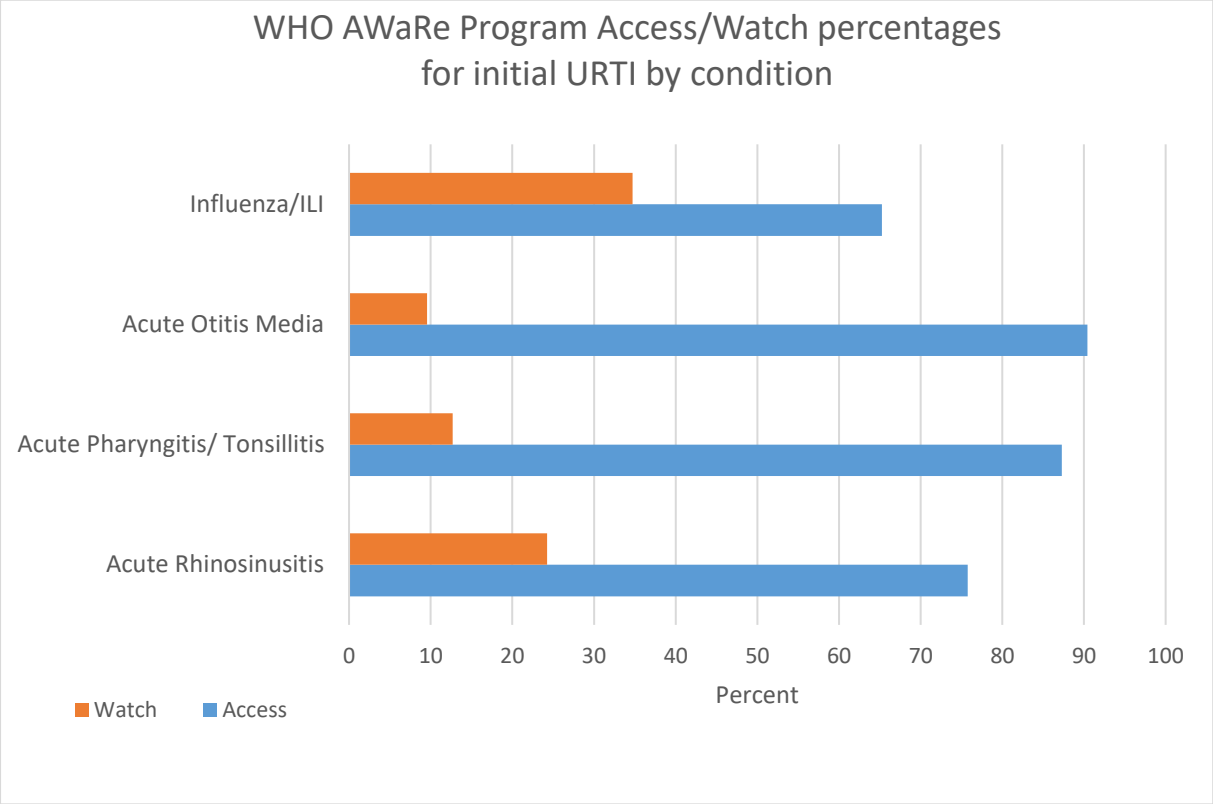


Figure G-1: Comparison of the antibiotic prescribing for upper respiratory tract infection conditions in this dataset with the World Health Organization's 2019 Access, Watch and Reserve classifications (11)

G.2 Comparisons with quality indicators for urinary tract infection

The prescribing rate was 85% for all patients, with prescribing rates of 87% for women, and 78% for men and 75% for children, respectively. 57% of women, 68% men and 82% children under sixteen received antibiotic prescriptions other than first-line. The prescribing rate was 87% for women at least 16 years of age and the same for women at least 18 years of age. ESAC-net indicators presented by Adriaenssens et al. (6) recommend 80-100% for women at least 18 years with acute cystitis. However, as seen in **Table G-2** below, only 43% of women in this dataset (aged either sixteen years and over or eighteen years and over) received the recommended (first-line) antibiotic, whereas 80-100% is also the recommended range for ESAC (6). Quinolone use among women with acute cystitis was within ESAC range of under five percent, coming in at 2% for women of at least sixteen or eighteen years of age in this dataset (6).

Table G-2: Compilation of indicators including the European Surveillance of Antibiotic Consumption indicators published by Adriaenssens et al. (6) relating to acute cystitis

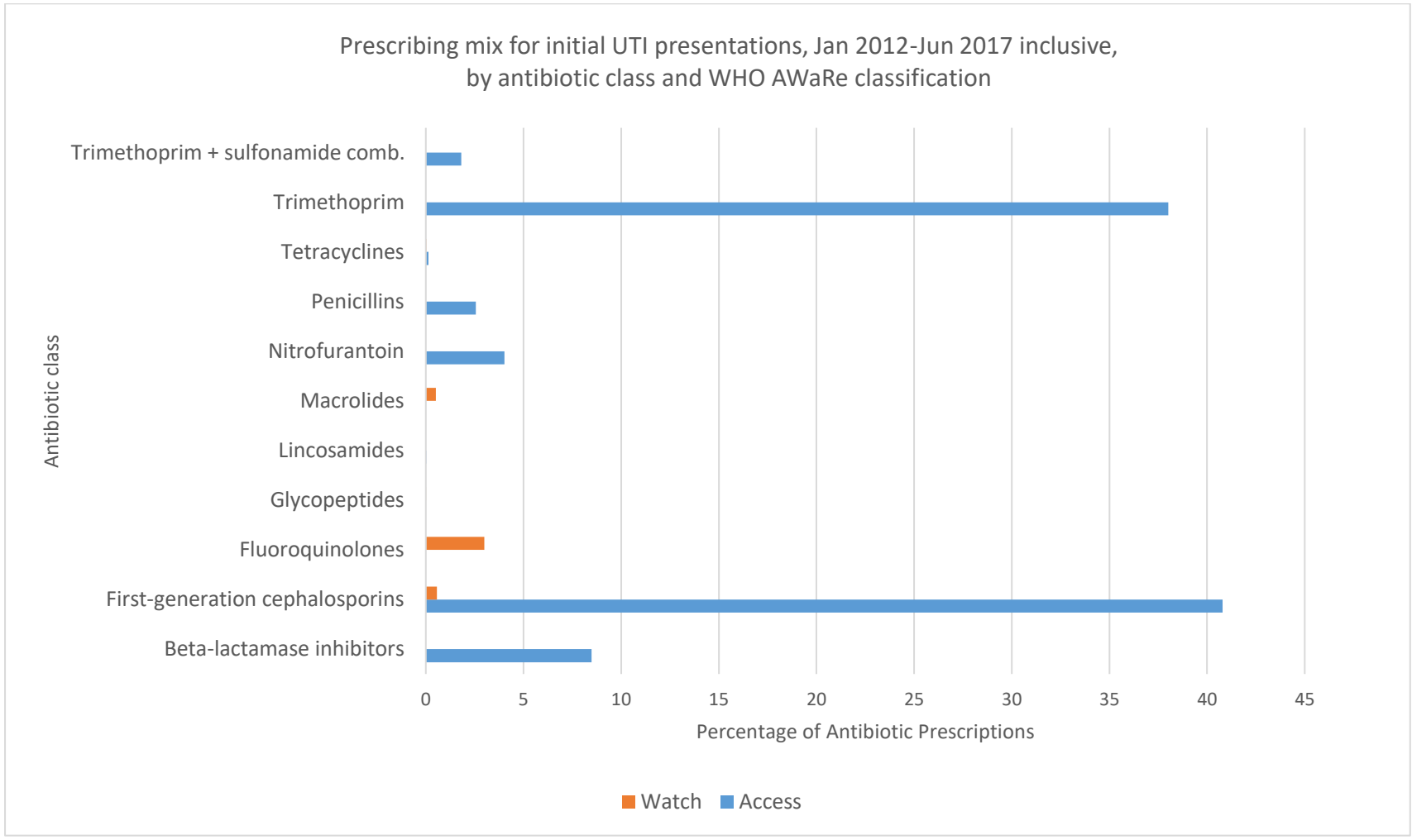
Measure	Recommendation	Findings *
prescribing rate all patients (%)	n/a	85%
non-first-line antibiotic prescriptions all patients (%)	n/a	60%
Percentage of female patients older than 18 years with cystitis/ other urinary infection (ICPC-2-R: U71) prescribed antibacterials for systemic use (ATC: J01)	80-100%	87%
=3a. receiving the recommended antibacterials (ATC: J01XE or J01EA or J01XX)	80-100%	43%
=3a receiving quinolones (ATC: J01M)	0-5%	2%
prescriptions on WHO AWaRe Access list (%)	>=60%	97%

Note * same result confirmed regardless of age cut-off- for women 16 years and over and over 18 years.

UTI performed reasonably well against 2019-released WHO AWaRe program (11). Only 2% antibiotics prescribed were on the Watchlist (11). However, these are all antibiotics that are Not Recommended in Australian guidelines at the time. So in another sense, improvements can also be made.

These result from comparing quality indicators suggest that there is substantial room for improvement with respect to the choice of antibiotic when prescribing, but that the decision to prescribe is generally good. The data indicates reasonable quinolone prescribing within the range of ESAC indicator 3c (6). Furthermore, WHO AWaRe program (11) (as at 2019 and closest to the study period) provides targets of at least 60% systemic antibacterials prescribed to be from WHO's Access list, for which these WA-based GPs adhered to 97% of the time (11). There were no instances of prescriptions from WHO's (2019) Reserve list (11).

Figure G-2: Comparison of the antibiotic prescribing for urinary tract infection in this dataset with the World Health Organization's 2019 Access, Watch and Reserve classifications (11)



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