In search of improved approaches to antibiotic stewardship:

Can we explain variations in physician practice patterns related to outpatient infection management?

by

RACHEL MARGARET MCKAY

B.A., The University of British Columbia, 2003
M.Sc., Simon Fraser University, 2008

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Abstract

The discovery of antibiotics was one of the most significant advances in modern medicine; however, our reliance on antibiotics is threatened by the spread of resistance. Antibiotic resistance is a natural phenomenon that is exacerbated by selection pressure from antibiotic use. Where prescriptions are required for antibiotics, understanding prescribing behaviour is paramount. Guidelines recommend antibiotics for respiratory tract infections (RTIs) only when pneumonia or other serious complications are suspected. Urine cultures are recommended for complicated, but not uncomplicated, urinary tract infections (UTIs). The objectives of this thesis were to identify factors related to patients, physicians, and geographic regions associated with antibiotic use for RTIs, and urine culturing for UTI; and to explore the extent of variations in these practices across physicians.

A systematic review of the literature was conducted to assess factors that have previously been empirically associated with antibiotic prescribing. Then, using linked administrative datasets, factors associated with antibiotic prescriptions for paediatric respiratory tract infection were analyzed. Urine culture data was subsequently linked in, to explore urine culturing practices.

These analyses demonstrated that observed physician characteristics had a stronger influence on practice patterns that did differences in patient characteristics. In particular, physicians who had been in practice for longer tended to be more likely to prescribe antibiotics, and to order urine cultures. Physicians trained outside of Canada were more likely to prescribe, but less likely to order a urine culture. Female physicians were less likely to prescribe antibiotics, and more likely to order urine cultures. The variation between physicians that remained after accounting for observed characteristics was substantial.

This research demonstrates some common features of physicians that are associated with antibiotic prescribing and urine culture use. However, the variation between physicians in practice styles is greater than the effects of these characteristics. These findings have implications for the design and implementation of antibiotic stewardship efforts to improve antibiotic use. For example, audit and feedback interventions and academic detailing have shown some promise, and may be particularly effective if targeted to physicians with higher prescribing or culturing practices. This thesis demonstrates the utility of administrative datasets in identifying such physicians.

Lay Summary

Antibiotic resistance is an important public health issue. The use of antibiotics encourages antibiotic resistance by killing susceptible bacteria and allowing resistant bacteria to multiply and spread. Appropriate use of antibiotics includes limiting unnecessary use, as well as choosing the right drug, dose, and duration, when their use is warranted. The overarching goal of this thesis is to contribute research evidence that may guide approaches to improving appropriate antibiotic use. I studied factors that may contribute to antibiotic prescribing and urine culture ordering, and assessed differences in physician practice patterns. I found that physician characteristics, such as number of years of clinical experience, medical training outside of Canada, and physician sex, were stronger predictors of use than were patient characteristics, and that there are large differences in individual practice patterns. These findings should help guide the development of antibiotic stewardship interventions.

Preface

A version of chapter 2 has been published [McKay R, Mah A, Law M, McGrail K, Patrick DM. Systematic Review of Factors Associated with Antibiotic Prescribing for Respiratory Tract Infections. *Antimicrobial Agents and Chemotherapy*; 2016;60(7):4106–18]. I was the lead investigator, responsible for conception of the study, and development and registration of the protocol. Law M, McGrail K, and Patrick DM were involved in the early stages of concept formation. Mah A contributed to the search strategy, and we were both equally involved in conducting the review: searching for studies, identifying eligible papers, extracting data, and analysing and interpreting the results. I wrote the manuscript, and Mah A contributed manuscript edits. Law M, McGrail K, and Patrick DM provided additional interpretation and edits to the manuscript.

A version of chapter 3 is being prepared for publication. I was the lead investigator. I conceived the study based on past work on variations in primary health care by McGrail K. I designed the study, under the supervision of my supervisors and committee member, and acquired the data. I conducted all of the statistical coding, with assistance on some variables from Cheng L and Peterson S. I completed the analyses, and wrote the manuscript. Mooney D helped to create Figure 2. McGrail K, Patrick DM, and Law M added important contributions to the presentation and interpretation of the results. Law M was the supervisory author on this analysis.

A version of chapter 4 is being prepared for publication. I conceived the study, after extensive discussions with my supervisors, committee member, and Balshaw R. I acquired the data, conducted all coding and analyses, and wrote the manuscript. Balshaw R provided statistical advice and input. All co-authors contributed to the interpretation and presentation of results. Patrick DM was the supervisory author on this analysis.

Ethics approval was not required for Chapter 2, given that it was a systematic review of published studies. The work presented in chapters 3 and 4 was covered under the University of British Columbia's Behavioural Research Ethics Board certificate H13-00878. Note that all inferences, opinions, and conclusions drawn in this dissertation, arising from use of administrative data, are those of the authors, and do not reflect the opinions or policies of the Data Stewards.

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I have benefitted from the knowledge and momentum in antimicrobial stewardship demonstrated by the Do Bugs Need Drugs? team at the BC Centre for Disease Control. I thank them for their assistance, their interest, and for leading the way. Dr. Allison Mah was an excellent co-reviewer for the systematic review conducted for this thesis. Her dedication and intelligence helped tremendously to move the project along. Dr. Robert Balshaw was generous with his time, and I enjoyed getting to learn from him. I would also like to thank Dr. Romina Reyes for her insight into the urine culture data.

Finally, this dissertation would not have come together without the incredible, patient, and uplifting support of my wonderful network of family and friends. So many people have shown interest in my path, and have provided encouragement in various ways over the years. In particular, I want to thank my parents, Reta and Ian – for your love, pride, and endless practical support. My sister, Emma – for your presence and support. Leon – for your patience, for being my motivation through the last stretch, and for those hugs! And Gareth, my partner in everything – thank you for your unwavering belief in me, and for your love.

Chapter 1: Introduction

Antibiotic resistance is a global public health problem

The discovery of antibiotics was one of the most significant advances in modern medicine (1,2). Antibiotics are used to treat bacterial infections such as pneumonia and syphilis – illnesses that before the antibiotic era commonly caused severe debilitating effects or death. The availability of antibiotics has also increased the success of surgeries, chemotherapy, and organ transplantation, among many other uses (3). Compared to most other drugs, antibiotics are particularly noteworthy for their ability to cure illness, rather than to simply alleviate symptoms (4). Estimates suggest that in excess of several hundred thousand tons of antibiotics are used in humans and animals globally per year (5). In Canada, an estimated 22.8 million antimicrobial prescriptions were dispensed through pharmacies, and over $675 million was estimated to have been spent on antimicrobials, in 2013 (6). Globally, over 73.5 billion units of antibiotics were estimated to have been consumed in 2010 (7).

Worryingly, our reliance on antibiotics is threatened by the spread of resistance. Antibiotic resistance is a rapidly growing global problem, with new bacterial strains emerging that are resistant to increasing numbers of classes of antibiotics (8,9). This leads to greater treatment complexity and in some cases, to a lack of effective treatment options. In 2016, a patient died in the United States from septic shock due to a carbapenem-resistant Enterobacteriaceae (CRE) that was resistant to all available antibiotics (10). A recent study estimated the risk of a pan-drug-resistant bacteria emerging, persisting, and spreading in the UK to be 19% (95% credible interval 7% - 37%) (11), which would cause significant challenges to the health care system.

Additionally, prophylactic uses of antibiotics for surgeries and cancer chemotherapy have shown signs of being impacted by antibiotic resistance (12). The complete cost of antimicrobial resistance extends beyond the comparative costs of treating a resistant vs. a susceptible bacterial strain, and includes the impact on the entire health system – from cancer treatments, caesarean sections, to hip replacements – of reduced effectiveness of antibiotic therapies (13), as well as the macroeconomic impacts of associated morbidity and mortality (14).

Antibiotic use causes selection pressure for resistance

Bacteria have been around for millennia. The capacity for bacteria to demonstrate resistance to antibiotics was noted concurrently with the discovery and development of antibiotics for public use (15). In his Nobel lecture, following his receipt of the award in December, 1945 for his role in the discovery of penicillin, Sir

Alexander Fleming warned of the real possibility for, and consequences of, antibiotic resistance due to inappropriate use (16): "But I would like to sound one note of warning... It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body." Despite this warning, antibiotics have been used inappropriately, exposing bacteria all over the world to concentrations inadequate to kill off certain bacteria, but sufficient to allow resistance mechanisms to propagate. Estimates suggest that 30% of all outpatient antibiotic use is likely unnecessary (17).

Resistance is a natural phenomenon. Resistant mechanisms have developed and persisted among bacteria to combat the action of antibiotics, many of which are derived from naturally occurring compounds. Genetic material that confers antibiotic resistance has been found in permafrost samples dating 30,000 years BCE (18). Although resistance genes may predate the use of antibiotics in medicine, agriculture, and aquaculture, the use of antibiotics increases selective pressure for resistance. Ecological studies have demonstrated the correlation between higher rates of antibiotic use and higher prevalence of antibiotic resistance (19,20). Systematic reviews have confirmed the association at the individual level (21,22).

Antibiotic stewardship

The discovery of new antibiotic compounds has stalled, resulting in few novel therapeutic options to tackle the problem of resistance (23). Antimicrobial stewardship strategies aim to guide the rational and prudent use of antibiotics (24). This involves both curtailing unnecessary use, as well as targeting the selection of antibiotic agent, dose, and duration carefully to the infecting bacteria.

Responding to the significant and global nature of the problem, the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), and the World Organization for Animal Health (OIE) established a tripartite agreement, supported a UN General Assembly resolution, and developed action plans and strategies to address antibiotic resistance (25-28). The consensus from these reports is that this is a multifaceted and complex problem, requiring commitment and action from a number of system levels.

In health systems where prescriptions are required for antibiotics, physicians tend to be the gatekeepers for these medicines. Therefore, understanding decision-making behaviour in relation to prescribing is a necessary component for efforts to shift behaviour in a desired direction (29,30).

Interventions to improve antibiotic prescribing

Several reviews have assessed the impact of interventions to improve prescribing. A 2008 systematic review found that active clinician education (such as educational outreach or interactive workshops) was more effective than passive education in reducing antibiotic prescribing rates (31). A Cochrane Collaboration review, specific to the use of antibiotics in ambulatory care, found that the use of simple audit and feedback or printed education materials alone was generally not effective – concluding that drawing attention to the prescriber's behaviour, in isolation, may not be enough (32). The effects of educational outreach (academic detailing) showed mixed results (32). A more general review of interventions to improve prescribing (not restricted to antibiotics) found that audit and feedback, as well as educational outreach, was modestly effective in improving prescribing when combined with other interventions (33). A review of interventions specifically targeting physicians concluded that interventions with more than one element were more frequently effective than single-element interventions (34). In a review of interventions to influence consulting and antibiotic use for acute respiratory infections among children, delayed prescribing (where a prescription is written, with instructions not to fill unless the patient shows no improvement over a couple of days) showed promise as an intervention to reduce use (35). Finally, a more recent systematic review of antimicrobial stewardship in outpatient settings concluded that each of the various types of interventions was successful in terms of antimicrobial prescribing improvements in some circumstances, but that the multifaceted nature of most interventions made it difficult to isolate the effect of individual components (36).

Studies published since those reviews have continued to demonstrate mixed results. A multifaceted intervention aimed at Dutch family practitioners found some reduction in RTI-related antibiotic prescribing rates among patients over 12 years of age, but not under (37). An intervention aiming to improve first-line antibiotic prescribing for urinary tract infections succeeded, but also documented an unintended effect of an overall increase in antibiotic use for UTI (38). A recent evaluation of three behaviourally-based interventions found that the two interventions with a social component (sending monthly emails to physicians identifying them as either a 'top-performer' or 'not a top-performer'; and requiring a free-text justification for every antibiotic prescribed, that would be visible in the patient's medical record) were successful in reducing rates of inappropriate antibiotic prescribing for acute respiratory tract infections, whereas the intervention that involved automatic alternative suggestions (without any social accountability) showed no improvement (39). A randomized, controlled trial found that web-based training focusing on enhanced communication skills in one study-arm, and the use of C-reactive protein (a laboratory marker of systemic inflammation that is moderately specific for differentiating bacterial from viral infections) testing in another were both effective in reducing antibiotic prescribing rates for acute respiratory tract infections in several countries in Europe (40). A province-wide, mostly web-based, educational campaign launched in Quebec was shown to have favourable impacts on overall antibiotic prescribing (41). Another study documented a reduction in practice-level antibiotic prescribing following a multifaceted online learning intervention, with no differences in hospitalizations (42).

While multifaceted interventions have generally shown the largest effects, enabling their scale up and sustainability can be complex and costly. From this perspective, the effectiveness of a simple audit and feedback intervention targeting the highest antibiotic prescribing practices is particularly appealing (43). However, the long-term sustainability of these interventions has not been well established.

Thus, a variety of intervention types have demonstrated modest improvements in antibiotic use. Multifaceted interventions have tended to be most successful, and interventions based on behavioural tenets show promise. However, intervention-attributable reductions in antibiotic prescribing have generally been limited to around 10%, which may not be substantial enough (31,44). The overuse of antibiotics remains high (17,45).

In order to focus efforts on the most relevant targets, more information is needed about the factors that influence prescribing, as well as about variations in management practices between practitioners. Some writers have suggested that observed variations in medical practice result from differences in the underlying case-mix of patients (46); in order to effectively understand the reasons for any observed variations, we need rigorous analysis that explicitly accounts for patient case-mix, in addition to other factors. Together, this knowledge will inform approaches to improving the effectiveness of antibiotic stewardship programs, which is a key appeal from The World Health Organization's Global Action Plan on Antimicrobial Resistance (25).

This thesis takes a broad view that clinical decision-making is a behaviour that, like any behaviour, is shaped and impacted by multiple forces (30). Different scholarly traditions have proposed various theories or frameworks for understanding clinician behaviour, and, subsequently, the effectiveness of interventions to change behaviour (47). The work presented in this thesis has been implicitly informed by socio-ecological frameworks of behaviour (48), health promotion models (49), and a health services research approach to understanding variations in care (50).

General objective

The overarching goal of this thesis is to contribute research evidence that may guide approaches to antibiotic stewardship programs by identifying targets for interventions. With a focus on physicians as gatekeepers to antibiotics, the aim was to explore the role of patient-, physician-, and area-level factors in understanding physician practice patterns. Respiratory tract and urinary tract infections (RTIs and UTIs) are the most common foci for outpatient antimicrobial stewardship initiatives because they comprise the predominant reasons for antibiotic prescriptions in the community (17,51). The interest in RTIs focuses on the decision to prescribe or not, given that most RTIs are viral and/or self-limiting. The interest in UTIs focuses on the selection of antibiotic agent, dose, and duration of treatment. Urine culturing decisions are very relevant here, as they help guide antibiotic treatment in many cases. Additionally, the results from urine culturing decisions form the basis of our understanding of the distribution of uropathogens in a community setting, and antibiotic resistance thereof.

Specific objectives

1. To identify factors at the levels of patients, physicians, and geographic regions that are associated with:
    a. antibiotic use for RTIs; and,
    b. urine culture ordering for UTI
2. To explore the extent of variations in these practices between physicians

This thesis thus addresses a gap in our understanding about physician practice patterns in the management of community-based infections. It begins with a systematic review of factors that have been reported in the empirical literature to be associated with antibiotic prescribing for respiratory tract infections – a set of syndromes for which antibiotics are widely overused. A population-level analysis of variations in, and drivers of, antibiotic use for respiratory tract infections in children is then described. The focus then moves to urinary tract infections, where antibiotics are largely warranted, but where the selection of agent becomes important. I describe a study that aimed to measure variations in the practice of ordering cultures for urinary tract infection visits. I then conclude by summarizing the findings across studies, exploring the use of a new health behaviour change model, and considering the implications for antibiotic stewardship interventions.

Chapter 2: Systematic Review

Introduction

The rapid and ongoing spread of antimicrobial resistant organisms threatens our ability to successfully treat a growing number of infectious diseases (3,52). It is well established that antibiotic use is a significant, and modifiable, driver of antibiotic resistance (21,53,54), and that antibiotics are often misused (55). In settings where a prescription is required to access antibiotics, the prescriber-patient encounter is a logical target for improving appropriate use.

A narrative review of factors influencing antibiotic prescribing highlighted the multiple sources of influence affecting a potential prescribing encounter, including factors related to the prescribing physician (e.g. fear of failure, diagnostic uncertainty, or inadequate training), the patient (e.g. a high-risk or vulnerable patient history), and the environment (e.g. regulation of pharmaceutical prescribing and dispensing and lack of resources for etiological diagnosis) (56). Another study systematically reviewed reasons for inappropriate antibiotic prescriptions, for any indication, from quantitative studies up to 2008. Of note, half of the studies in this review used data based on simulated case scenarios in which the physician was asked how he/she would respond clinically (57). The main focus of that review was attitudes of prescribers; it found that a desire to fulfill the expectations of the patient/parent and fear of possible complications in the patient were most consistently associated with inappropriate prescribing of antibiotics. The presence of one or more symptoms or signs (e.g. fever, pathological murmur, or productive cough) was associated with antibiotic prescription in most studies assessed. The review also explored characteristics of patients, prescribers, and health care organization in relation to prescribing, but the included studies were either too small in number or too heterogeneous in approach to offer insights in these areas (57). The authors also highlighted the limitations of simulated case scenarios in understanding prescribing behaviour, and called for further studies based on real prescription data. Despite the importance of the topic, there is no existing systematic review to identify drivers of antibiotic prescribing from real prescription data.

Physician visits for respiratory tract infections (RTIs) commonly result in an antibiotic prescription (58-60), despite the fact that most upper RTI syndromes are viral in nature. In these cases, antibiotics provide no benefit, and thus guidelines limit their recommended use to certain situations where the etiology is likely bacterial (61-63). Given the common nature of both these conditions and potentially inappropriate prescribing practices around them, RTIs were chosen as the focus for this review. Factors associated with any antibiotic prescribing for RTI were assessed, with the understanding that a significant proportion of this prescribing is unnecessary and would therefore be considered inappropriate.

A comprehensive summary of relevant factors implicated in potentially unnecessary antibiotic use will support physicians to reflect critically on their own practice, and will provide an evidence-based resource for intervention and policy design. Therefore, this systematic review of factors associated with outpatient antibiotic prescribing for acute respiratory tract infections from the quantitative literature was conducted. The purpose of this review was two-fold: first, to identify characteristics of patients, physicians, and the environment that have been associated with antibiotic use; and second, to describe the strengths of associations reported.

Methods

The protocol used for this review is registered with PROSPERO, and can be accessed at http://www.crd.york.ac.uk/PROSPERO (ID=CRD42014010097).

The formal review was restricted to quantitative studies, as the aim was to focus on the strengths of association reported in retrieved studies. This report follows the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (64).

Search strategy

Medline, Embase, and International Pharmaceutical Abstracts were searched. Search terms were determined by specifying the broader concepts we sought to assess (“antibiotic”, “outpatient”, “appropriateness”, “prescribing”, “factors”), and by identifying relevant terms within these concepts. Keywords and MeSH terms were compared from known, relevant studies, as well as similar reviews. In addition, the author of a relevant article (33) provided a list of search terms used in that review, which served as an additional reference. Our list was then further refined through discussion with a librarian, and consensus among the study authors (the final list of search terms is available in Appendix A).

Study selection

Peer-reviewed studies conducted using data from the Organization for Economic Co-operation and Development (OECD) countries were eligible for consideration. This restriction was used to limit the review to factors that could operate in similar health care system contexts and patient populations. In addition, included studies were required to have (1) used actual (not self-reported or intended) prescribing, dispensing, or sales data; (2) investigated the prescription of outpatient antibiotics by physicians, i.e. not over-the-counter purchasing; (3) been observational or experimental in design; (4) been written in English language; (5) described factors at one or more of the levels of interest and assessed the association with the primary outcome of whether or not an antibiotic was prescribed at an individual encounter; and (6) performed multivariable analysis of the associations. These criteria were refined from those presented in the published protocol, based on the initial stages of the review. We omitted 11 studies that included patients with pneumonia, where results were not reported separately for the subgroup of patients without pneumonia.

After performing the full search, titles retrieved from each database were combined and duplicates were removed. Two authors (RM and AM) screened each record for potential relevance. The full-texts of these studies were then assessed for inclusion eligibility, independently by the same two authors. Reference lists of included articles were hand-searched for additional studies. The final search was conducted on October 14, 2015.

Data extraction and quality assessment

A customized data extraction form was developed for this study. All studies that met inclusion criteria were then assessed for quality using a form developed for this review, as there is no single recommended tool for assessing the quality of observational studies. Our tool was based on the SIGN 50 (Scottish Intercollegiate Guidelines Network) for cohort and case-control studies, as recommended by a review of quality assessment tools (65), as well as incorporating elements of the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Institute of Health's National Heart, Lung, and Blood Institute (66). Two authors (RM and AM) independently performed data abstraction and study appraisal. Abstractions and appraisals were compared for each study, and any discrepancies or disagreements were resolved by discussion and consensus. Both reviewers extracted all the information from each study. There were no major discrepancies between reviewers.

The primary outcome of interest was an antibiotic prescription. Because antibiotic prescribing is a decision made at the level of the prescriber, but recorded at the level of the patient, there is a natural clustering of patients within prescribers when multiple patients are included per prescriber. We noted whether and how analysts accounted for this clustering.

Data synthesis

Adjusted odds ratios (aOR) were extracted for each factor-antibiotic prescription association. Meta-analysis was not pursued, as significant heterogeneity among studies was expected. All factors identified were extracted. Selected forest plots are presented in Figures 2-9. An alpha of 0.05 was used in all studies for constructing confidence intervals, and was the basis of our interpretation of statistically significant and non-significant findings.

Results

Description of included studies

Our initial search identified 3435 records, of which 2848 non-duplicate titles were screened for inclusion (Figure 1). Our initial search included non-English articles; however, of the few non-English abstracts retrieved and reviewed, none met the criteria for inclusion. Forty-four articles were considered relevant. Of these, 16 were determined to be of insufficient quality or to have insufficient details to allow further inclusion. The 28 included articles were considered to be of good or high quality (59,67-93) (Table 1). Two studies reported results as risk ratios (81,84), which precluded us from directly comparing them to the odds ratios reported in the other studies given that antibiotic prescription is a relatively common occurrence. Consequently, results from these studies are included in the tables, but not in the forest plots.

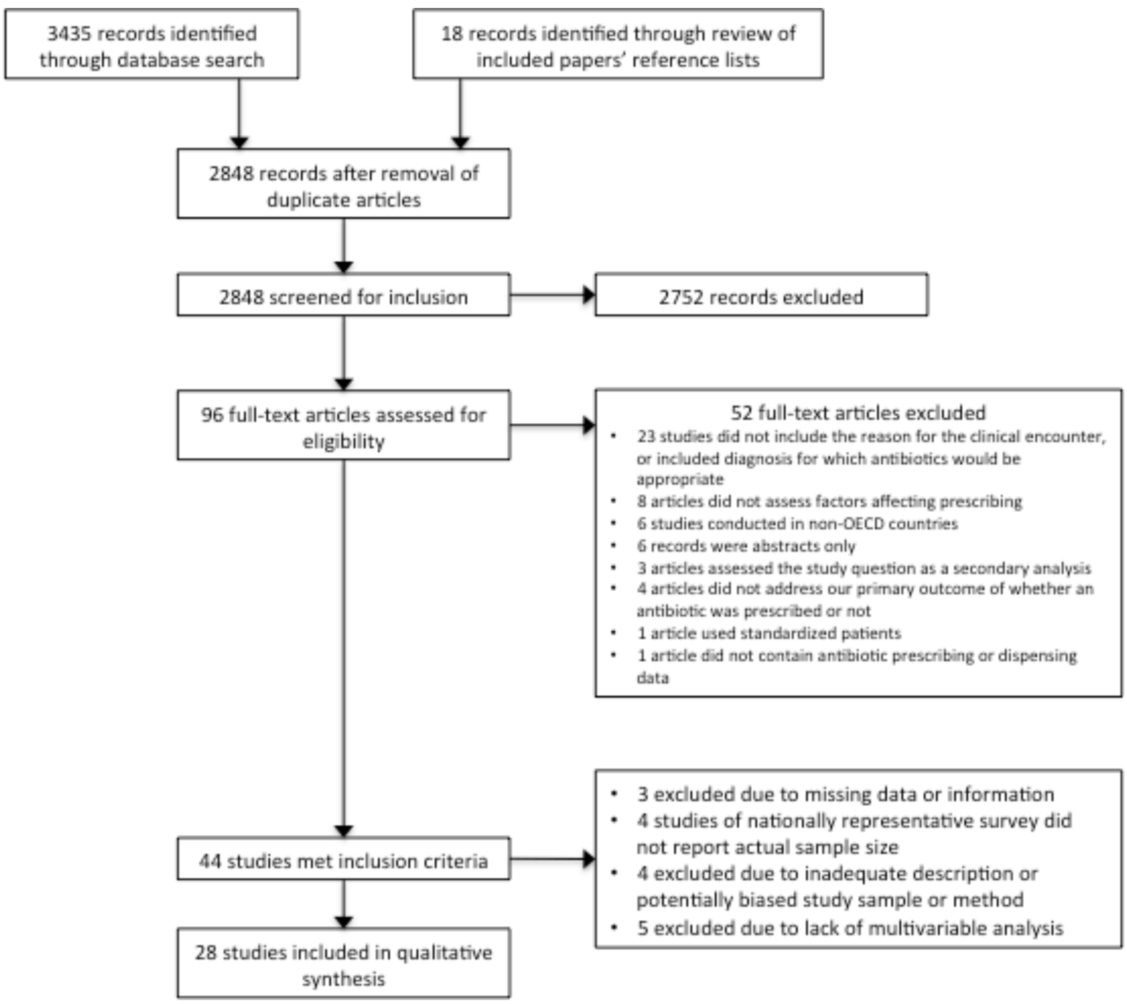


Figure 1: Flow chart for study inclusion

Just over half of the included studies were from the United States (US) (n= 15) (59,67,68,71,73,75,77,78,80,85-87,92-94), with the remainder from Canada (n= 3) (81,84,90), The Netherlands (n= 2) (76,82), Germany (n= 2) (70,89), Italy (n= 1) (74), UK (n=1) (72), Belgium (n=1) (69), and a network of 13 European countries (n=3) (83,88,91). Eight of the US studies used the NAMCS (National Ambulatory Medical Care Survey) or NHAMCS (National Hospital Ambulatory Medical Care Survey) datasets for their analyses. (59,75,78,80,85-87,93) Analyses included paediatric populations only in 5 studies (67,74,75,85,90); adult populations only in 10 studies (59,70-72,86-89,93,94) while the rest either included all ages, or did not specifically describe the patient population.

One study explored prescribing of both physicians and Nurse Practitioners (80). We only report the results from the physicians to allow comparison with the other studies.

Table 1: Description of included studies

Study author and reference	Study Description	Participants	Factors Examined*	Authors Conclusions and Summary of Key Findings
Ahmed, M. N., et al. (2010). "Antibiotic prescription pattern for viral respiratory illness in emergency room and ambulatory care settings." Clinical pediatrics 49(6): 542-547.	Retrospective cross-sectional study of pediatric patients presenting to primary care provider's offices, convenient care clinics and emergency departments for URTI, pharyngitis or bronchitis.	904 children aged 0-18 years old.	dx, sp, age, sex, ins, st, fv, cmb, co, cng	Emergency department physicians and family practice physicians were more likely to prescribe antibiotics for acute respiratory illnesses compared to pediatricians.
Akkerman A.E., et al. (2005a) "Analysis of under- and overprescribing of antibiotics in acute otitis media in general practice." Journal of Antimicrobial Chemotherapy 56(5):569-574.	Prospective cross-sectional study of factors associated with antibiotic prescribing for acute otitis media.	458 patients aged 0-87 years old with a median age of 4 years old.	age, sv, pppe	Patients who should not have been prescribed an antibiotic according to guidelines were younger than 24 months, more severely ill according to GP and their GP assumed their parents expected an antibiotic.
Akkerman, A. E., et al. (2005b). "Determinants of antibiotic overprescribing in respiratory tract infections in general practice." Journal of Antimicrobial Chemotherapy 56(5): 930-936.	Prospective cross-sectional study of patients with sinusitis, tonsillitis or bronchitis assessing patients' expectations of antibiotics for their illness and factors affecting inappropriate prescribing.	1490 patients aged 0-98 years old.	ins, co, sv, pppe, inflam, whz, age	Patients who received an antibiotic prescription that was not in accordance with the Dutch national guidelines, had more inflammation signs such as fever, were more severely ill according to their GP and their GP more often assumed that they expected an antibiotic, compared with those who did not receive an antibiotic prescription.
Altiner, A., et al. (2010). "Fluoroquinolones to treat uncomplicated acute cough in primary care: Predictors for unjustified prescribing of antibiotics." Journal of Antimicrobial Chemotherapy 65(7):1521-1525.	Prospective cross-sectional study of patients presenting with acute cough, examining factors associated with antibiotic prescription.	2745 patients aged 16-96 years old.	sv, fv, sm, dos, age, n pt fv, sv pt pr	The more severely ill a patient was rated by their physician, the more likely they were to receive antibiotics, especially if the rest of the patients in that physicians practice were relatively healthy.

Table 1: Description of included studies

Study author and reference	Study Description	Participants	Factors Examined*	Authors Conclusions and Summary of Key Findings
Aspinall, S. L., et al. (2009). "Antibiotic prescribing for presumed nonbacterial acute respiratory tract infections." American Journal of Emergency Medicine 27(5): 544-551.	Prospective cross-sectional study of patients presenting with acute respiratory illness to Veterans Affairs emergency departments.	667 patients with a mean age of 55 years.	cmb, fv, spm, sob, abs, dx, age, sp	Antibiotic use was high and varied substantially for URIs and acute bronchitis. Specific signs and symptoms, a diagnosis of acute bronchitis, and provider age and specialty were associated with antibiotic prescribing.
Brown, D.W., et al. (2003) "Antibiotic prescriptions associated with outpatient visits for acute upper respiratory tract infections among adult medicaid recipients in North Carolina." NC Med J 64:4.	Retrospective cross-sectional database review to assess factors related to antibiotic prescription for acute upper respiratory tract infections.	2413 patients aged 18-64 years old.	dx, age, sex, race, urb	63% of people received antibiotics for a nonbacterial respiratory tract infection.
Butler, C. C., et al. (2011). "Antibiotic prescribing for discoloured sputum in acute cough/lower respiratory tract infection." European Respiratory Journal 38(1): 119-125.	Data obtained from a prospective cohort of primary care networks from 13 European countries, looking at antibiotic prescription for acute cough as well as patient symptom resolution over time.	2419 patients aged 35-60 years old.	spm	Adults presenting in primary care with an acute cough, who produced discoloured sputum were more likely to be prescribed antibiotics.
Cadieux, G., et al. (2007). "Predictors of inappropriate antibiotic prescribing among primary care physicians." CMAJ Canadian Medical Association Journal 177(8): 877-883.	Retrospective cross-sectional data obtained from a historical cohort and administrative databases, assessing factors associated with inappropriate antibiotic prescriptions for acute respiratory illness.	104230 patient encounters over 9 years.	mcq, img, yr in p, vol	Physicians who had been in practice longer, who were international medical graduates and who had high-volume practices were more likely to prescribe antibiotics inappropriately.

Table 1: Description of included studies

Study author and reference	Study Description	Participants	Factors Examined*	Authors Conclusions and Summary of Key Findings
Cadieux, G., et al. (2011). "Are physicians with better clinical skills on licensing examinations less likely to prescribe antibiotics for viral respiratory infections in ambulatory care settings?" Medical care 49(2): 156-165.	Retrospective cross-sectional data from historical cohort and administrative database assessing physician clinical skills on licensing exams in relation to inappropriate antibiotic prescibing.	129592 patient encounters over 15 years.	loc, dx, sex, age, urb, pt edu, pt inc, cmb, p clin sc, vol, img, sp	Better clinical and communication skills on licensing exams reduced the risk of antibiotic prescription for viral respiratory infections amongst female physicians but not male physicians. Younger, more well-educated patients were less likely to be prescribed an antibiotic. Patients with more comorbidities were more likely to receive antibiotics.
Coenen, S., et al. (2006) "Antibiotic prescribing for acute cough: the effect of perceived patient demand." British Journal of General Practice.	Prospective cross-sectional data collection to assess factors affecting antibiotic prescription for acute cough.	1448 patients presenting to GPs office with acute cough.	age, cmb, sm, sv, pppe, dos, spm, fv, ha, mya, whz, sob, cp, ano, fat, hr, abs, pd, re, fu, gpt, fee, geo, spiro, p age, p load, hm v	Physician perceived patient demand for antibiotics is associated with prescription of antibiotics.
Coenen, S., et al. (2013). "Are Patient Views about Antibiotics Related to Clinician Perceptions, Management and Outcome? A Multi-Country Study in Outpatients with Acute Cough." PLoS ONE 8 (10)	Cross-sectional data from a prospective cohort from 13 European countries assessing the association of patient expectations with physician prescribing practices.	2690 patiens with a median age of 48 years old.	pt exp, pt hp, pt ask, pppe	Patient expectations, hopes or asking for antibiotics were not associated with symptom severity at presentation or symptom resolution during the subsequent 28 days regardless of whether an antibiotic was prescribed. Patient expectations and physician perception of patient views were strongly associated with antibiotic prescribing.

Table 1: Description of included studies

Study author and reference	Study Description	Participants	Factors Examined*	Authors Conclusions and Summary of Key Findings
Dosh, S. A., et al. (2000). "Predictors of antibiotic prescribing for nonspecific upper respiratory infections, acute bronchitis, and acute sinusitis. An UPRNet study. Upper Peninsula Research Network." Journal of Family Practice 49(5): 407-414.	Cross-sectional study of factors associated with prescription of antibiotics for acute respiratory infections in outpatient family practice.	482 patients over the age of 4 years old.	rhin, pnd, pur nd, abs, sin tn	Presence of rales, rhonchi, sinus tenderness, postnasal drainage, purulent nasal discharge and clinicians perceptions of clinical course of the illness affected the likelihood of antibiotic prescription.
Fischer, T. (2005) "Influence of patient symptoms and physical findings on general practitioners' treatment of respiratory tract infections: a direct observation study." BMC Family Practice.	Prospective cross-sectional study using medical student observation to assess factors associated with antibiotic prescription for respiratory tract infections.	273 patients aged 14-88 years old.	ab ph, tm abn, la, abs, sin tn, fat, whz, fv, spm	Antibiotic prescribing was associated with specific patient symptoms and physical exam results.
Gaur, A. H., et al. (2005). "Provider and practice characteristics associated with antibiotic use in children with presumed viral respiratory tract infections." Pediatrics 115(3): 635-641.	Retrospective cross-sectional examination of NHAMCS data to determine factors associated with antibiotic prescription to viral respiratory tract infections.	1952 patients aged 0-18 years old.	age, sex, race, geo, ins, dx, hous st, nontch, bf gl	Staff physicians are more likely to prescribe antibiotics for viral respiratory tract illness compared to trainees, and staff at non-teaching hospitals are more likely to prescribe antibiotics than staff at teaching hospitals.
Gonzales, R., et al. (1997) "Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians." JAMA 278(11):901-904.	Retrospective cross-sectional database review to assess factors related to antibiotic prescription for acute upper respiratory tract infections.	548 patients aged greater than 18 years old.	age, sex, race, geo, ins, sp	Only rural practice was an independent risk for antibiotic therapy for URIs.

Table 1: Description of included studies

Study author and reference	Study Description	Participants	Factors Examined*	Authors Conclusions and Summary of Key Findings
Gonzales, R., et al. (1999). "The relation between purulent manifestations and antibiotic treatment of upper respiratory tract infections." Journal of General Internal Medicine 14(3): 151-156.	Retrospective cross-sectional data from an insurance database was used to assess the factors associated with antibiotic prescription in acute upper respiratory tract infection.	322 patients above the age of 18 years old.	sm, pur nd, spm, ab ph, tm abn, sin tn, la, fv, cmb, mis wk	33% of patients with URI were prescribed antibiotics, often in the setting of purulent manifestations with purulent nasal discharge, green phlegm production, tonsillar exudate and current tobacco use predicting antibiotic prescription for URIs.
Holmes, W. F., et al. (2001). "Symptoms, signs, and prescribing for acute lower respiratory tract illness." British Journal of General Practice 51(464): 177-181.	Cross-sectional survey of physicians assessing factors associated with antibiotic prescribing for acute respiratory illness.	391 patients above the age of 16 years.	sex, age, spm, abs	Although the minority of patients had abnormal signs on physical exam, when present, discoloured sputum and abnormal chest findings increased the chances of antibiotic prescription.
Kozyrskyj, A. L., et al. (2004) "Evidence-based prescribing of antibiotics for children: role of socioeconomic status and physician characteristics." CMAJ 171(2).	Retrospective cross-sectional study of population based database to assess factors associated with antibiotic prescription.	4870 patients with a mean age of 8.5 years.	p age, img, sp, year, sea, age, sex, pt inc	Almost half of physician visits for VRTIs resulted in an antibiotic prescription and second line antibiotics were prescribed in 20% of visits for common childhood infections.
Ladd, E. (2005). "The use of antibiotics for viral upper respiratory tract infections: an analysis of nurse practitioner and physician prescribing practices in ambulatory care, 1997-2001." Journal of the American Academy of Nurse Practitioners 17(10): 416-424.	Study utilizing retrospective cross-sectional data from NHAMCS and NAMCS databases to assess the prescribing practices of nurse practitioners as compared to physicians, and the factors that influence antibiotic prescribing in each group.	14198 patient encounters over 5 years.	loc, dx, year, sex, age, geo, race, ins, sup med	NPs have similar prescribing practices for viral upper respiratory tract infection as MDs. Patient race and insurance type influenced NP antibiotic prescribing.

Table 1: Description of included studies

Study author and reference	Study Description	Participants	Factors Examined*	Authors Conclusions and Summary of Key Findings
Linder, J. A., and D. E. Singer. (2003a) "Desire for antibiotics and antibioitic prescribing for adults with upper respiratory tract infections." J Gen Intern Med 18: 795-801.	Prospective survey at the time of patient encounter to assess influence of patient desire for antibiotics on physician prescribing practices.	310 patients with a mean age of 34 years.	pt exp, abs, ab ph,	39% of patients wanted antibiotics. Wanting antibiotics was associated with an antibiotic prescription.
Linder, J. A. and R. S. Stafford (2001). "Antibiotic treatment of adults with sore throat by community primary care physicians: a national survey, 1989-1999." JAMA 286(10): 1181-1186.	Retrospective cross-sectional study using NAMCS database to examine antibiotic prescriptions for sore throat.	1852 patients above the age of 18 with a mean age of 38.	year, age, sex, race, ins, sp, geo, urb	Predictors of antibiotic use for sore throat were younger patient age and physician specialty being general practice.
Mangione-Smith, R., et al. (1999). "The relationship between perceived parental expectations and pediatrician antimicrobial prescribing behavior." Pediatrics 103(4 Pt 1): 711-718.	Prospective nested cohort study of factors associated with inappropriate antimicrobial prescribing and parental satisfaction with the visit.	306 parents of pediatric patients were assessed.	race, pt inc, prev abx, otal, st, co, cmb, rhin, tm abn, pt exp, pppe, p att	Physicians were significantly more likely to inappropriately prescribe antibiotics if they believed a parent desired antimicrobials.
Moro, M. L., et al. (2009). "Why do paediatricians prescribe antibiotics? Results of an Italian regional project." BMC Pediatrics 9(pp 69)	Prospective cross-sectional survey of patients presenting to pediatricians with respiratory tract infections.	4352 patient encounters.	age, imi, day care, pppe, ab ph, sin tn, otal, periorb, diar, tm abn, la, otor, fv, rhin, cmb, p age	No difference in the probability of antibiotic prescription was found between ambulatory practices and hospital emergency service paediatricians. The presence of an interviewer in the ambulatory was negatively associated with antibiotic prescription.
Nyquist, A. C., et al. (1998). "Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis." JAMA 279(11): 875-877.	Retrospective cross-sectional data from NAMCS database was used to look at factors affecting prescribing for children with acute respiratory illness.	531 patients aged 0-18.	age, sex, race, geo, urb, ins, sp	Colds, URIs, and bronchitis accounted for over 20% of all antibiotic prescriptions provided by US ambulatory physicians to children (<18 years) in 1992.

Table 1: Description of included studies

Study author and reference	Study Description	Participants	Factors Examined*	Authors Conclusions and Summary of Key Findings
Roumie, C.L., et al. (2006) 'Differences in antibiotic prescribing among physicians, residents and nonphysician clinicians." The American Journal of Medicine 118:641-648	Retrospective cross-sectional study using NAMCS and NHAMCS data to assess factors associated with antibiotic prescription patterns.	1504 patients presenting to outpatient or emergency department with acute respiratory illness.	loc, sp, hous st	The odds of receiving an antibiotic were greater in a visit to a nonphysician clinician for respiratory diagnosis where antibiotics are rarely indicated. Resident physicians prescribe fewer antibiotics for respiratory diagnoses where antibiotics are rarely indicated than physicians or nonphysician clinicians.
Rutschmann, O. T. and M. E. Domino (2004). "Antibiotics for upper respiratory tract infections in ambulatory practice in the United States, 1997-1999: does physician specialty matter?" Journal of the American Board of Family Practice 17(3): 196-200.	Retrospective cross-sectional review of NAMCS data to assess relationship between physician specialty and antibiotic prescribing for URI.	956 patients over the age of 18 years old.	age, sex, race, geo, urb, ins, sp, pcp, time, cxr, year	Antibiotics were still prescribed for more than 40% of the URIs seen in adult ambulatory practice between 1997 and 1999 in the United States.
Smith, S. S., et al. (2013). "Variations in antibiotic prescribing of acute rhinosinusitis in United States ambulatory settings." Otolaryngology - Head & Neck Surgery 148(5): 852-859.	Retrospective cross-sectional assessment of NAMCS and NHAMCS data to assess factors affecting antibiotic prescription for acute rhinosinusitis.	881 patients with a mean age of 46.2 years.	sp, age, cmb	First, antibiotics continue to be widely prescribed to treat ARS. Second, when physicians prescribe antibiotics for ARS visits, they choose broad-spectrum antibiotics in the majority of cases. Third, there are significant variations in antibiotic prescribing for ARS by physician specialties and patient age.

Table 1: Description of included studies

Study author and reference	Study Description	Participants	Factors Examined*	Authors Conclusions and Summary of Key Findings
Stanton, N., et al. (2010). "Are smokers with acute cough in primary care prescribed antibiotics more often, and to what benefit? An observational study in 13 European countries." European Respiratory Journal 35(4): 761-767.	Prospective survey assessing relationship between smoking status and antibiotic prescription for acute cough.	2549 patients above the age of 18 years old.	age, cmb, sm, dos	Primary care clinicians prescribed antibiotics more frequently to smokers than nonsmokers. This suggests that, despite differences in training and practice setting, clinicians may have similar attitudes towards prescribing antibiotics for smokers.

* Legend for Factors

Patient Level Factors: Ab ph = abnormal pharynx, Abs = altered breath sounds, Age = patient age, Ano = anorexia, Chil = chills, Cmb = patient comorbidity, Cng = congestion, Co = cough, Cp = chest pain, Cxr = cxr performed, Day care = child attendance at day care, Diar = diarrhea, Dos = duration of symptoms, Dx = diagnosis, Dx test = diagnostic tests ordered, Fat = fatigue, Fv = fever, Gen = general symptoms, Ha = headache, Hr = high risk patient as determined by physician, Htn = hypertension, Hypox = hypoxia, Imi = parents born abroad, Inflam = signs of inflammation, Ins = patient medical insurance type, La = lymphadenopathy, Meds = other concurrent medications, Mis wk = patient missed work, Mya = myalgias, Otor = otorhea/otalgia, Pain = moderate to severe pain, P att = patient attitude toward antibiotic prescribing, P clin sc = physician clinical skills exam score, Pd = percussion dullness, Periorb = periorbital edema, Pnd = postnasal discharge, Ppc = perceived parental concern about child's illness, Prev abx = previous antibiotics for similar illness, Pt ask = patient asked physician for antibiotic, Pt edu = patient level of education, Pt exp = patient expectation for antibiotic, Pt hp = patient hope for antibiotic, Pt inc = patient income, Pur nd = purulent nasal discharge, Race = patient race, Rhin = rhinorrhea, Rr = elevated respiratory rate, Se = patient concern about side effects of antibiotics, Sex = patient sex, Sin tn = sinus tenderness, Sm = patient is a smoker, Sob = shortness of breath, Spm = sputum, St = sore throat, Sup med = patient on supportive (non-antibiotic) medication, Sv = severity of illness, Tach = tachycardia, Time = time spent with patient, Tm abn = tympanic membrane abnormality, Viral = viral diagnosis noted by physician, Wait = patient waited >2 hours to see physician, Whz = wheeze

Provider Level Factors: Bact = physician belief that acute bronchitis and URI caused by bacteria, Br spc = tendency of physician to use broad spectrum antibiotics, Fee = fee structure and billing, Fu = follow up with physician, Gpt = GP special training, High rx = physician high prescriber, Hm v = mean number of physician home visits, Hous st = housestaff compared to staff physicians, Img = international medical graduate, Loc = physician practice location, Mcq = physician score on Infectious diseases component of licencing exam, Non phy = patient seen by provider other than medical doctor, Nontch = physicians at non-teaching hospitals compared to staff at teaching hospitals, N pt fv =number of patients in the physician's practice with fever, Own = physician owns medical practice, P age = physician age, Ph sex = physician sex, Phy blf = physician belief about antibiotics for treatment of colds, P load = physician patient load, Pppe = physician perception of patient expectations, p/t = physician works part-time, Re = patient referral, solo = physician in solo practice, Sp = physician specialty, Spiro = availability of spirometry in physician office, Sv pt pr = severity of other patients illness within physician's practice, Vol = physician practice volume, Vol uri = volume of URI diagnosis in physician practice, Yr In p = physician years in practice

Environment Level Factors: Bf gl = prior to guideline update compared to after, Geo = geographic location, New = new patient, Pcp = physician is patients primary care provider, Sea = season, Urb = urban vs rural, Year = year of visit

Methodological quality of studies

The reasons for a study to receive an overall quality rating of poor were the lack of appropriate control (or description of control) for confounders (n= 5), inadequate presentation of results (lack of confidence intervals (n=2), lack of clear presentation of results in tables (n=1)), or using nationally representative survey data but failing to provide the study sample size (i.e. reporting only the extrapolated population estimates; n=4), and potentially biased study samples or methods (n= 4).

Despite most studies discussing both patient-level and physician-level factors, many of these did not adequately account for the clustering of patients within physicians, or did not adequately describe the methods for doing so. Failing to account for this clustering will tend to underestimate the variation in a statistical model (95), thus underestimating the width of the confidence interval and giving a false impression of precision.

Appropriateness of prescribing

While all studies focused on acute respiratory tract infections, they differed with regards to which diagnoses were specifically included and excluded. All studies were focused on over-prescription of antibiotics (the use of antibiotics in cases where they are never or rarely indicated). Some additionally reported under-prescription (lack of prescription in cases where guidelines suggest they should be used), or other aspects of appropriate antibiotic use, such as selection of the optimal drug in cases where antibiotic use is considered necessary. Where these aspects of appropriateness were differentiated, we only extracted information on over-prescribing.

Factors associated with antibiotic prescription for respiratory tract infections

Eighty factors were discussed in one or more studies, while 29 were addressed in three or more studies (Table 2; table of all factors identified included as Appendix B). Results presented here focus on those factors addressed in at least three or more studies. We are not able to address every factor, so have selected some to discuss in more depth. The presentation of factors here is grouped into those at the patient level (e.g. diagnosis of acute bronchitis, patient expectation of antibiotics, and factors associated with the illness presentation – presence of fever, purulent sputum or nasal discharge, tonsillar exudate, abnormal tympanic membrane); and those at the physician level (e.g. specialty of the physician, and whether the physician perceives that the patient expects an antibiotic prescription).

Table 2: Factors associated with antibiotic prescribing for RTI: direction of results by number of studies reporting each factor, for factors investigated by 3 or more studies

Factor	No. studies with positive association	No. studies with negative association	No. studies without significant association	Total number of studies
Patient level factors				
Patient age*	6	--	13	19
Patient male sex	1	--	9	10
Comorbidity	2	--	7	9
Patient medical insurance type*	1	--	7	8
Ethnicity*	1	--	6	7
Black vs. white race	--	1	5	6
Fever	5	--	1	6
Bronchitis	5	--	--	5
Purulent sputum	5	--	--	5
Respiratory physical exam findings	5	--	--	5
Patient desire for antibiotics	3	--	1	4
Smoker	3	--	1	4
Cough	1	--	2	3

Table 2: Factors associated with antibiotic prescribing for RTI: direction of results by number of studies reporting each factor, for factors investigated by 3 or more studies

Factor	No. studies with positive association	No. studies with negative association	No. studies without significant association	Total number of studies
Duration of illness	1	--	2	3
Household income	--	1	2	3
Pharyngitis	3	--	--	3
Rhinorrhea	--	2	1	3
Sinus pain on exam	3	--	--	3
Tonsillar exudate	3	--	--	3
Tympanic membrane abnormality	3	--	--	3
Physician level factors				
Physician specialty*	6	--	2	8
Physician perception of desire for antibiotics	6	--	--	6
Severity of illness	4	--	--	4
High volume practice	1	--	2	3
International medical graduate	2	1	--	3
Area-level factors				

Table 2: Factors associated with antibiotic prescribing for RTI: direction of results by number of studies reporting each factor, for factors investigated by 3 or more studies

Factor	No. studies with positive association	No. studies with negative association	No. studies without significant association	Total number of studies
Geographic location*	1	--	6	7
Rural vs. urban	3	--	4	7
Year of visit	--	--	4	4
Visit location (office, ED, hospital clinic)*	1	--	2	3

* denotes categorical variable with different possible reference groups, and therefore the direction of effect is not always comparable. We have categorized any study that found a statistically significant association in one direction as a positive association for illustrative purposes.

Patient-level factors

Patient age and sex were the most commonly studied factors. Of the 10 studies that explored sex (59,67,72,75,77,80,84,85,87,90), just one found a statistically significant association between male sex and higher odds of antibiotic prescription (90). Nineteen studies explored age as a factor (59,67-69,72,74-77,80,82,84-90,93); of all of the comparisons made, 18 aORs were non-significant, 10 suggested that older people had higher odds/risk of a prescription than younger people, and 3 suggested that younger people had higher odds. Generally, among studies focusing on children, older children had higher odds of prescription than younger children; although one study found that toddlers had lower odds of overprescribing than babies for aOM (76). One study found that patients over 65 had lower odds than young and middle-aged adults (93), while another found that adults over 30 had higher odds than adults under 30 (68). Two studies found increasing age to be associated with higher odds of prescription (88,90), while one found the opposite (86). As the age groupings and reference categories differed across all studies, it is difficult to draw firm conclusions from these studies regarding age. Nine studies assessed medical comorbidities as a factor associated with prescribing (67-69,71,73,74,84,88,93); in seven of those, no association was found, while in two studies the presence of comorbidities was associated with prescribing. The types of comorbidities, and the ways they were captured, varied by study.

Diagnosis of bronchitis

Six studies assessed the association of a diagnosis of bronchitis with an antibiotic prescription (67,68,77,80,84,85); all found statistically significant positive associations (aORs ranging from 2.9 to 15.9), although only two reported the number of unique physicians in the sample and accounted for clustering (Figure 2a).

Factors related to physical exam findings

The results of physical exam findings (fever, purulent sputum or nasal discharge, abnormal respiratory exam, physical exam findings of tonsillar exudate, physical exam findings of abnormal tympanic membrane) were heterogenous, but tended towards higher odds of prescription with these findings (Figures 2b-2f). Across the six studies that assessed abnormal respiratory exam (68-70,72,92,94) (Figure 2d), for instance, all showed a statistically significant positive association with antibiotic prescription in adjusted analyses, with aORs ranging from 3.0 to 19.9. Five of the seven studies assessing the association between purulent sputum or nasal discharge and antibiotic prescription described a statistically significant positive relationship (68,69,71,72,92) (Figure 2c), while one found no relationship (83), and one had a 95% confidence interval very close to 1 (70).

Two of the studies that addressed fever were of children (67,74), while the rest were of adults (69,70,94) (Figure 2b). The fever associations point estimates for aORs were all relatively low (ranging from just over 1, to less than 3), compared with some of the other factors identified. Each study developed a multivariable model with differing variables: all controlled for some set of physical symptoms; five of the six studies also controlled for comorbid conditions (in varying ways) (67-69,74,94).

The confidence intervals for three of the four studies that assessed the finding of an abnormal tympanic membrane were quite wide (70,73,94) (Figure 2f) , reflecting relatively small sample sizes and potentially few events, although the number of events was not reported.

Patient expectations

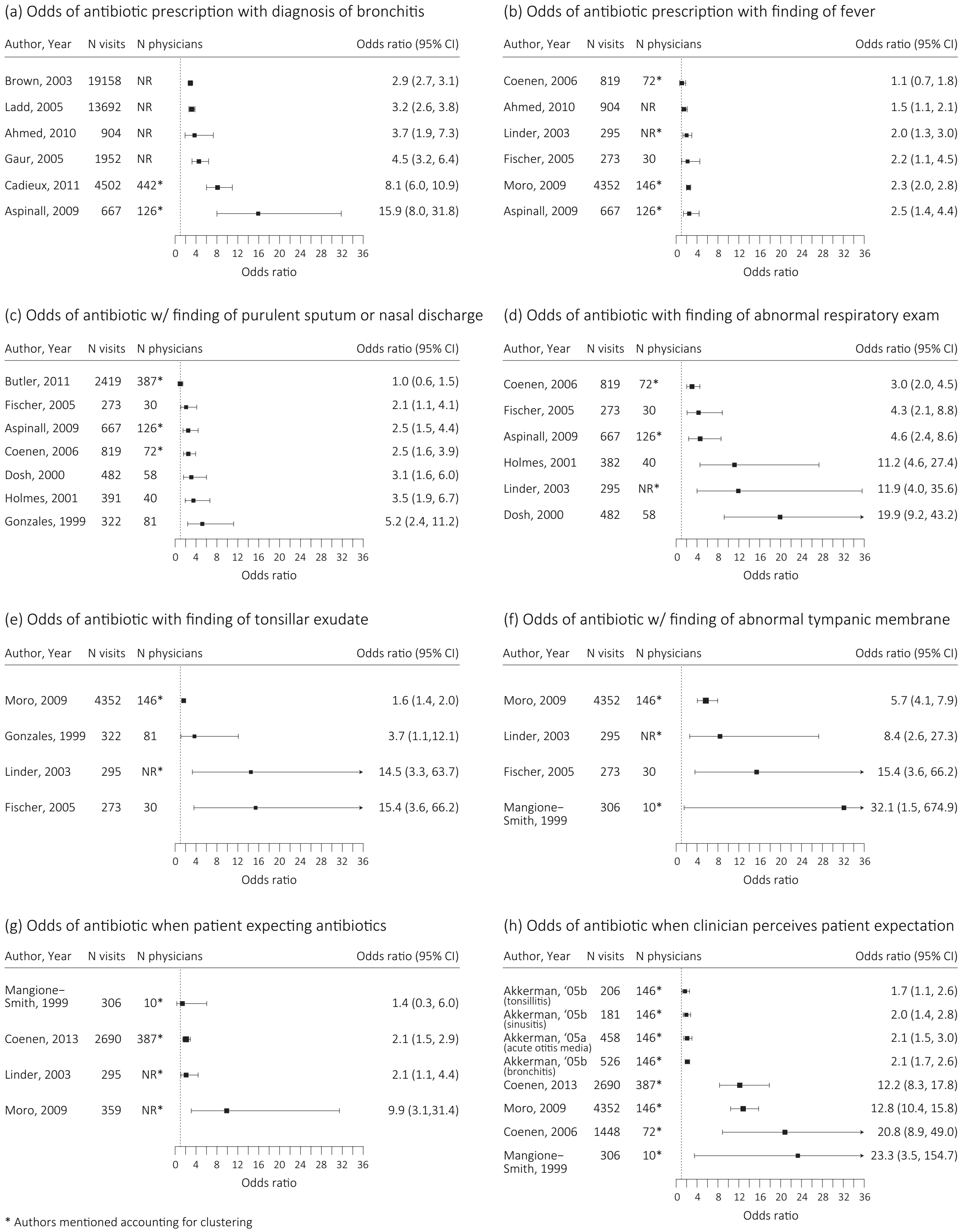
Of the four studies that addressed an association of prescribing with patient expectation of antibiotics, one (74) found a strong association (aOR 9.9; 95% CI 3.1 – 31.4), while the other three found weaker or no associations (Figure 2g).

Prescriber-level factors

The specialization of the prescriber was the most commonly assessed factor in this category; however, designated reference groups differed across studies, making them difficult to compare.

Of the eight studies that assessed prescriber specialty, three were performed in exclusively pediatric populations and five in adult populations. In the pediatric studies, pediatricians were consistently less likely to prescribe an antibiotic than the referent group, which included emergency department physicians, general practitioners and non-pediatric specialists, respectively. The aOR for pediatrician prescribing compared to non-pediatrician specialties ranged from 0.1-0.6 (67,75,90). Of the studies in adults, one study found no association of prescriber specialty and antibiotic prescription (59), one study assessed other prescribers as compared to otolaryngology as the referent group and found other groups to prescribe significantly more than otolaryngologists (range of aOR 3.9-7.9) (93). Of the remaining three, two studies found internists prescribed less than general practitioners and emergency room providers (aORs 0.4-0.8) (68,87) and one found no difference between internist and family practitioner prescribing (aOR 0.9 CI 0.7-1.2) (86).

Five studies (in six reports) looked at the association between a clinician's perception that a patient expected an antibiotic, and prescribing an antibiotic (Figure 2h) (69,73,74,76,82,96). All found statistically significant positive associations, ranging from aOR 1.7 to 23.3. All of these studies both reported the number of physicians in the sample, and mentioned the use of a statistical technique to account for clustering.



* Authors mentioned accounting for clustering
NR: Not reported

Figure 2: Forest plots of results for selected factors

Note: the size of the point is proportional to the number of visits analyzed in each study, with larger points representing larger samples.

Area-level factors

Geographic region was reported in 7 studies (59,69,75,80,85-87). Six of the 7 studies used the NAMCS or NHAMCS data out of the United States, which record geographic regions as South, Northeast, Midwest, and West (59,75,80,85-87). Only one of these studies found any statistically significant differences, with lower odds of prescription in the south and west regions as compared to the northeast (85). The final study was from Belgium; the odds of an antibiotic prescription were statistically significantly higher in West Flanders (aOR 3.95, 95% CI 4.9-176.7) and Brussels (aOR 29.2, 95% CI 1.6-9.8), as compared to Antwerp (69).

Discussion

This review compiles research on factors associated with antibiotic prescribing for RTI, and found good evidence that factors beyond a clear bacterial diagnosis are associated with prescription decisions for RTIs. This is important because the majority of RTIs are viral, and therefore do not improve with use of an antibiotic. A substantial proportion of antibiotic use for RTIs is, therefore, inappropriate, and unnecessarily contributes to risk of adverse reactions as well as antibiotic resistance. By identifying factors that are associated with prescribing, antibiotic stewardship programs and interventions may be better able to target their activities.

Diagnosis and physical exam findings

A diagnosis of bronchitis was consistently associated with increased odds of antibiotic prescription, although most of the studies reporting this association did not account for clustering of patients among physicians. This practice may be indicative of a suspicion of underlying bacterial illness, in particular, pneumonia (63). However, guidelines and reviews commonly recommend against this method of management as studies have shown that antibiotic prescription for acute bronchitis is minimally effective, resulting in a half day reduction in cough but no reduction in functional impairment compared to placebo, and resulting in increased adverse events (61,97,98).

Several physical exam findings were associated with antibiotic prescription. The probable explanation for this association is the physician's belief that these findings are more indicative of a bacterial etiology for the patients' symptoms. Recent guidelines have addressed issues of presumptive distinctions between viral and bacterial URIs (99). Some symptoms are suggestive of a possible bacterial diagnosis, and should therefore lead to investigation of bacterial etiology; for instance, fever and patchy tonsillopharyngeal exudates are associated with bacterial Group A Streptococcal (GAS) pharyngitis (100). Suspicion of GAS pharyngitis, however, should initiate a throat swab to guide appropriate treatment, as the majority of pharyngitis remains viral in origin (101). Similarly, abnormal findings on chest auscultation may lead to suspicion of pneumonia; however, confirmation of the diagnosis with a follow-up chest x-ray should be performed prior to the administration of antibiotics (102).

Ultimately, differentiating definitively between bacterial and viral causes of RTIs based on signs and symptoms alone is seldom possible, and this imprecision and concern about missed bacterial diagnosis likely drives over-prescription of antibiotics. Use of point-of-care tests and improved organism-prediction algorithms may be useful in a number of circumstances. While additional diagnostic tools may add some effort, and cost, the price of continuing to use antibiotics for RTI as a safeguard, rather than a directed therapy, is likely greater.

Physician specialty

In general, we found that pediatricians tended to have better prescribing practices with lower rates of antibiotic prescription for RTIs. A lower rate of antibiotic prescribing was also seen amongst internal medicine specialists, although not to the same extent. Conversely, front line providers such as emergency department physicians, general practitioners and family physicians generally had higher rates of antibiotic prescribing for RTIs. Reasons for higher prescribing rates may relate to physician training, but more likely reflect the practice environment in which these providers see patients. Emergency departments and outpatient family medicine clinics are busy, high volume environments and may not provide the opportunity for patient follow-up. This environment may tend to increase physician diagnostic uncertainty and concern about missing a diagnosis for which antibiotics are warranted – factors previously described as influencing prescriber treatment decisions (56).

Patient expectations

Physician perception of patient (or parent, in the case of paediatric patients) expectation for antibiotics was a more consistent predictor of antibiotic prescription than actual patient expectation of antibiotics. It should be noted that, among the studies assessing physician perception of patient/parent desire for antibiotics, while all of the studies reported positive associations, the set of analyses by Akkerman and colleagues (76,82) reported lower point estimates and tighter confidence intervals. Due to the conversion from log scale, higher point estimates will necessarily have wider confidence intervals. In fact, when expressed in logit, the width of the confidence intervals from the Coenen (91) and Moro (74) studies are not appreciably different from the Akkerman studies.

The observed variability in point estimates between the Akkerman study and the others could be due to differences in settings. The Akkerman study was conducted in the Netherlands, where antibiotic use is the lowest in Europe (103). A culture of judicious use may moderate to some extent the effect of perceived pressure on physicians. This variability in point estimates suggests that we should not put too much emphasis on the magnitude of the association *per se*, but rather the positive nature of the observed associations.

A qualitative study of physicians' strategies for managing perceived patient expectations for antibiotics noted that the physicians in the study were often reluctant to explicitly determine patients' expectations, as this could lead to direct confrontation if those expectations were not aligned with the physician's therapeutic recommendation (104). Instead, physicians preferred to assess perceived expectations and manage those. However, perceptions are not always accurately aligned with patient expectations (74,92). Interestingly, in the study by Coenen et al., if patients explicitly asked for antibiotics (as reported by the patient), this did not have a significant effect on prescribing and there was a trend towards reduced prescribing, in contrast to the physician perceiving that a patient was expecting an antibiotic, which was associated with prescribing (91). This may suggest that by asking, the patient addresses directly the issue at hand, allowing for a discussion regarding the need for antibiotics to ensue. While these two variables (a patient expecting antibiotics and a physician perceiving that a patient expects antibiotics) may not be completely independent, the possible distinction is worth consideration.

Communication strategies of both patients and clinicians may shape clinicians' assumptions or perceptions regarding patient expectation for antibiotics (105,106). In a systematic review of qualitative studies about how communication affects prescription decisions, Cabral discusses the opportunity for miscommunication that can arise when a patient/parent endeavours to justify the need for consultation, which can be perceived as an expectation of antibiotics by the clinician. Additionally, the clinician's use of minimizing and normalizing statements – which may be part of the clinical approach of reassurance and intended to pave the way for not prescribing antibiotics – may be interpreted by the parent/patient as questioning the need for consultation (105).

Some physicians have indicated that they prescribe antibiotics under likely unnecessary circumstances because it provides a quick resolution to the clinic visit, and improves satisfaction of patients (107,108). However, the amount of time spent with a patient has not been independently associated with antibiotic prescriptions (109,110). Additionally, there is some evidence that patient satisfaction with a physician encounter is not dependent on having received antibiotics (111). This is important to note in the context of physicians prescribing based on perceived patient expectation, as presumably this phenomenon is intended to improve patient satisfaction. One study found that the odds of a patient reporting satisfaction with a physician visit for acute RTI were higher when the patient received information or reassurance than when they received an antibiotic (112). If, however, the patient was expecting antibiotics, the odds of satisfaction were similar among those who received information and those who received an antibiotic (112).

Limitations

The patient populations included in the studies in this review are diverse. While the benefit is that the factors identified stem from varied populations and as such are more representative, the consequence is that we were not able to identify factors associated with particular age groups or illnesses.

We decided to extract and report on adjusted effect estimates as unadjusted estimates are too potentially confounded to be meaningful, and this is in line with recommendations from the Cochrane Handbook on Systematic Reviews of Interventions (113). However, this creates a challenge for interpretation, as each study controls for a different set of variables, and adjusted estimates are sometimes only presented for those variables that remain in the final model. Our findings are thus potentially biased towards statistically significant associations. For instance, one study found that patient expectation was associated with antibiotic prescription on bivariable, but not multivariable analysis controlling for a number of potential confounders, and the numeric value of the non-significant result was not reported (92). Similarly, a general publication bias would operate in the same direction.

Additionally, the definitions used to denote each factor were not standardized across studies. For instance, fever was specified dichotomously as >99º F, or not (68); dichotomously as > 38º C, or not (69,74); per ºC > 37 (94), or not defined/patient reported (67,70).

In studies where adequate description of clustering techniques was not provided, the precision of point estimates should be interpreted with due caution; in particular, point estimates that appear to be statistically significant, but whose confidence limits are close to the null, should be evaluated with care.

While we set out to identify factors at the levels of the patient, the prescriber, and the environment, our review ultimately focused mostly on those at the patient level, with just a few factors appearing at the physician level. At the environment level, geographic region, outpatient encounter setting, year of encounter and urban vs. rural location were the only factors identified with most studies failing to demonstrate an association of these factors with prescribing practices. Additional studies that addressed factors at the level of the environment were excluded for not assessing individual level prescriptions, but rather area-level rates of prescribing. These studies are still important, and are casting necessary light on higher-level influences on prescribing, but were not possible to include here.

Most RTIs are viral, and antibiotics do not shorten the duration of illness or have other positive effects on viral infections. However, there are some situations where an antibiotic could be considered an appropriate treatment for an RTI. Our review does not distinguish between appropriate and inappropriate prescribing for RTI, and instead assumes that most prescribing would be considered inappropriate. This was done because the assumption made by many of the studies included was that any antibiotic prescribing for RTI was inappropriate; however, few attempted to assess appropriateness in a systematic way.

Despite the typical drawbacks to this kind of review, we identified several main findings. First, we conclude that physicians can reflect on their own perceptions about patient expectation of antibiotics. Prescribers should feel justified to deflect perceived pressure from patients. Valuing the patient's experience, appreciating their time in coming in to seek advice about their symptoms, and providing clear information about how long symptoms might be expected to last and about what symptomatic treatment is recommended, may help in reducing unnecessary use of antibiotics. Second, a number of physical exam findings were independently associated with antibiotic prescribing, despite the lack of evidence that these signs and symptoms are indicative of bacterial infection. Third, there was limited data addressing potential associations between area-level factors and antibiotic prescribing at the individual level. This may be a fruitful area for further research.

Policy implications

Our findings suggest several possible policy directions. Continued education – primarily via audit and feedback, or academic detailing – is warranted to highlight the viral etiology of most RTIs, in particular of acute bronchitis, and associated lack of benefit of antimicrobial treatment in these cases. Similarly, continued education should focus on signs and symptoms that are and are not associated with an increased risk of bacterial infection. Guidelines have been useful in reducing volume of antibiotic use (36). While a number of guidelines pertaining to respiratory tract infections exist, it may be beneficial to enhance them with clear descriptions both of signs and symptoms that are, and are not, likely to be associated with bacterial infection. Improved access to point-of-care diagnostic aids for bacterial pneumonia may help relieve uncertainty about the diagnosis, and therefore reduce the practice of prescribing antibiotics due to this uncertainty. Given the strong influence of physician perception of patient desire for antibiotics on prescribing practices, greater focus on communication strategies physicians can use in negotiating the clinical encounter with a patient may also be useful. It should be noted that as passive education has not generally proven to be effective, the dissemination of basic brochures to doctors' offices containing information about appropriate antibiotic prescribing – for instance – would not be expected to have a significant impact. Efforts should be reserved for and channelled towards those activities with the greatest impact potential, as discussed above.

There has been documented success with public policies to reduce antibiotic consumption, which are often educational campaigns aimed at the public and general practitioners (114). A systematic review of interventions aimed at public knowledge and awareness of antibiotic use and resistance found that these campaigns were generally associated with reductions in antibiotic prescribing in the short term (115). Further emphasis on knowledge levels among the general public should be a priority, in an effort to reduce both actual and perceived patient demand for antibiotics. This public awareness effort could be expanded to encourage patients to engage in a dialogue with their physicians about the need or lack of need for antibiotics, such that the clinical encounter involves appropriate discussion and counselling, and avoids practices based on unclear communication and perceptions.

Systematic reviews conclude that antibiotic stewardship programs show promise for optimizing antibiotic therapy both in hospital (116) and community settings (31-33). The components of these programs differ across implementations, and specific behavioural outcomes vary (e.g. decision to treat with antibiotics or not; choice of antibiotic when deemed appropriate; route, dose, and duration of antibiotic therapy), but in general these initiatives have been associated with improvements in the use of antibiotics. Further development and expansion, with thorough evaluation, of antibiotic stewardship programs for the outpatient setting could include individualized feedback on physician prescribing practices in relation to those of their peers (117), as well as increased regulatory control of pharmaceutical availability, with the hopes of improving guideline compliance and reducing unnecessary antimicrobial use.

Conclusion

While it is difficult to distil the clinical encounter into discrete factors, this review highlights broad areas that can be integrated into future efforts to promote judicious use of antibiotics. Reinforcement of signs and symptoms of viral respiratory illnesses, as well as supporting clear communication between physicians and patients, may be useful areas of focus.

Chapter 3: Variations in Antibiotic Use

Introduction

Antibiotic use in humans and animals is one of the most important drivers of resistance (8). A particular area of concern has been the inappropriate use of antibiotics for respiratory tract infections (RTIs). For example, seventy percent of paediatric outpatient antibiotic prescriptions are for RTIs (58). The majority of these infections are either caused by viruses, for which antibiotics are not effective, or resolve spontaneously with very little added benefit from antibiotic therapy (63,97,118). The National Institute for Health and Care Excellence in the United Kingdom has a guideline which suggests that patients with acute otitis media, acute sore throat, common cold, acute rhinosinusitis, and acute cough do not generally require antibiotic treatment; antibiotics are indicated for those at risk of complications, such as pneumonia (119). In British Columbia, the Bugs and Drugs guidelines (61) have been adapted for use by the provincial academic detailing service, as well as provincial stewardship programs. Recent estimates suggest that up to 50% of antibiotic use for RTIs in both children (120) and adults (17) is likely unnecessary or inappropriate. Therefore, decreasing antibiotic prescribing for paediatric RTIs is an obvious target for study and intervention.

Despite this need, clinically significant and sustained behaviour change has remained difficult to achieve (121). Prescribing decisions are complex, and there are documented variations in antibiotic prescribing both across medical practice networks (122) and individual physicians (123,124) that cannot be fully explained by the patient's clinical presentation. Patient (125), physician (87,126,127), and geographic (128-130) characteristics have been previously associated with antibiotic prescribing – for RTIs and more generally. However, the investigation of these factors using appropriate multilevel frameworks that simultaneously account for factors at different levels is sparse (123,124), as are studies specifically of children.

Therefore, this study used population data to study variations in antibiotic prescribing for children with RTIs to assess which observable physician characteristics are associated with prescribing after controlling for relevant patient and regional variables. Several recent qualitative studies have highlighted the role of physician deliberations in prescribing decisions (108,131,132). In particular, this study sought to identify characteristics from population-based data that would help inform the design of future interventions.

Methods

Data sources

This analysis used administrative data for all residents of the province of British Columbia (BC) (population approximately 4.7 million), excluding populations that are federally insured, from 2002 to 2012 (133). The vast majority of primary care services in BC are billed on a fee-for-service basis under the universal Medical Services Plan (MSP); these administrative claims data contain patient and practitioner identification variables, an ICD-9 code assigned at the visit, as well as other variables pertaining to the type of service provided (134). Prescription drug information is available through the provincial PharmaNet database, which contains a record for every prescription medication dispensed at a community pharmacy in the province, excluding antiretroviral medications (135). It is important to note that these data represent the moment of dispensing a drug at a pharmacy, not a prescription written in a physician's office specifically. It is therefore likely that these data underestimate true prescriptions. These data also contain patient and prescriber identification variables. Physician demographics were obtained from the BC College of Physicians and Surgeons (136). Hospitalization data were obtained from the Discharge Abstract Database (137), which contains information about every hospitalization – including diagnoses assigned, length of stay, and discharge disposition.

Study cohort

All patient visits for RTIs between 2005 and 2011 were identified using existing methods (138). This cohort was then subsetted to those less likely to require an antibiotic prescription: acute nasopharyngitis, acute sinusitis, acute pharyngitis, acute tonsillitis, acute laryngitis and tracheitis, acute upper respiratory infections of multiple or unspecified site, acute bronchitis or bronchiolitis, viral pneumonia, or influenza (ICD-9 codes 460-466, 480, or 487) (61). The cohort was then limited to the stable cohort of individuals registered with MSP for 275 or more days in a given year (on a per year basis) (139). Clinicians were additionally limited to those with at least one antibiotic prescription written, for any condition, during our study time period, to ensure a population of practitioners "eligible" to prescribe.

Measurements

Outcome

To determine whether an encounter resulted in prescribing, each visit was linked to the closest prescription for an antibiotic (ATC code J01.xx) filled within five days, matching on both patient and prescriber identification. The five-day time frame was selected to allow for prescriptions that are not filled immediately, and to be comparable with previous studies from the same jurisdiction (140).

Factors

Patient level

A number of factors at the patient level were considered. Patient demographics included age, sex, and neighbourhood income quintile as an indicator of socioeconomic status. The number of different GPs seen in the past 3 years for each individual was counted as a proxy for patient attachment with a general practitioner (GP). The Usual Provider Continuity index was calculated as the proportion of visits in the previous three years that were with the same physician as the RTI visit (141). The index is usually calculated within a time frame of one year; however, it was extended to three years to account for individuals who may not see a physician every year, given that RTIs are acute infection episodes that commonly affects generally well individuals in addition to those who are chronically ill. This variable was subsequently dichotomized above and below the median proportion of 0.1. A recent antibiotic use variable was constructed for each patient visit by assessing whether any antibiotic prescription (again, J01.xx) was dispensed in the community in the 6 months prior to the RTI visit. Follow up visits were defined as any visit for an RTI within 14 days of another RTI visit.

Two measures of clinical condition were included. First, the Johns Hopkins Adjusted Clinical Groups® (ACG®) System version 10.0.1 was used to assess expected health service need, as a proxy for health status (142). This categorization system groups an individual's diagnosis codes over one year into 32 clusters, or Aggregated Diagnostic Groups (ADGs), based on duration of the condition (acute, recurrent, or chronic), severity of the condition, diagnostic certainty, etiology of the condition, and the involvement of specialty care (143). An individual can be assigned multiple ADGs, as the clusters are not mutually exclusive. Each ADG is a group of diagnoses that is expected to be similar in terms of severity and persistence of the condition. The number of ADGs assigned to each individual, each year, was used as a general indicator of comorbidity.

Second, nine high-risk conditions were selected: diabetes, chronic obstructed pulmonary disease, chronic kidney disease, asthma, cystic fibrosis, immunosuppression, chronic liver disease, congestive heart failure, and ischemic heart disease. A diagnosis was considered to be relevant if an individual had at least two physician visits for that condition, or one hospitalization for the condition, within a two-year period. If the patient had ever met the criteria for a condition of interest, after 2002 and before the date of the RTI visit, they were considered to have the condition.

Physician level

Measures of physician claim volume and frequency of respiratory tract infection management were derived by counting the total number of claims billed on the day of the RTI visit (daily volume), and the proportion of visits in the past 30 days with a diagnosis of RTI, per physician. Claim volume was then categorized into quartiles. The rate of RTI consultations in the past 30 days was divided into categories based on the distribution of the data. As the number of eligible visits per physician was heterogeneous, a variable was included based on the quartile distribution of the number of RTI visits in the past year to control for this.

Physician demographic variables included year of birth, sex, place and year of medical school graduation, and specialty. The number of years between medical school graduation and the RTI visit was calculated as years of clinical experience. International medical graduates were identified as physicians who graduated medical school outside of Canada, as indicated in the College of Physicians and Surgeons of BC records.

Regional level

There are 89 local health areas (LHA) nested within five geographic Health Authorities (HA) in BC. Annual measures of LHA population demographics (median age, proportion of the population under 15 years of age, and proportion of the population over 65 years of age), were included to assess whether population distribution, at a regional level, may impact antibiotic prescribing decisions (for instance, if physicians working in areas with more elderly populations may be more likely, in general, to use antibiotics). Data on meteorological temperature readings assigned to each LHA (144) were used to calculate a 28-day moving average for each visit day. Calendar year and quarter (for seasonal effects) were also included in the models.

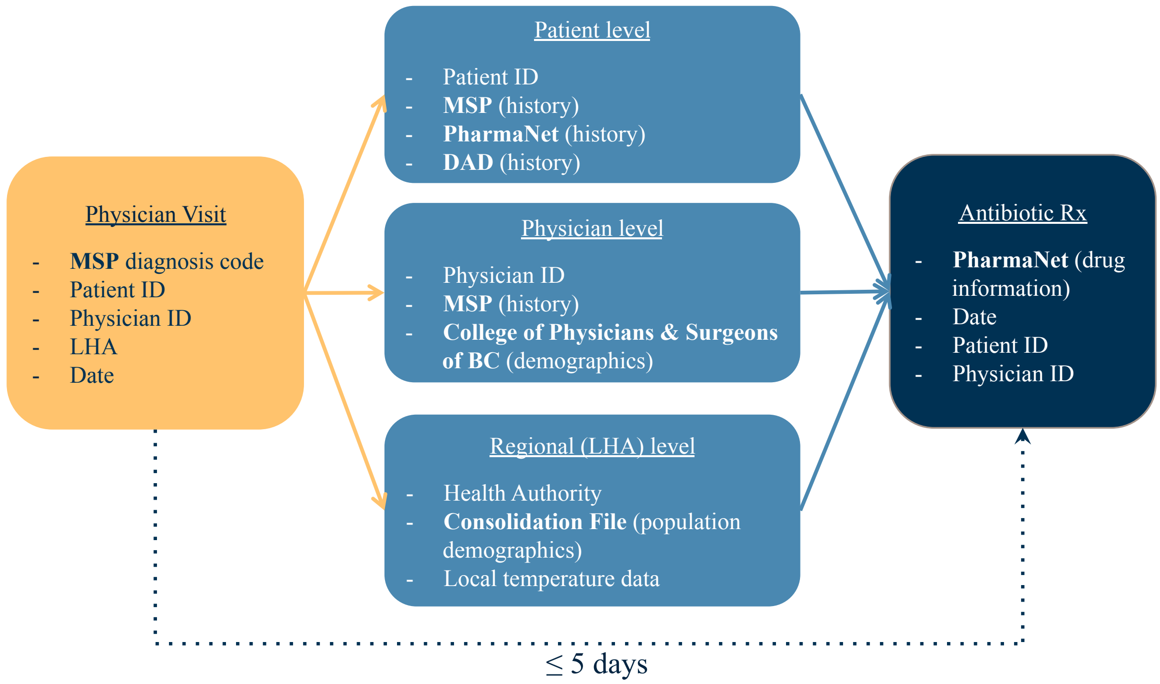


Figure 3: Overview of linkage design for RTI study

Statistical analysis

Generalized Linear Mixed Models (GLMMs) with a binary distribution and logit link were fit to estimate variance parameters for the physician clustering level (the random effect), and log-odds parameters for the covariates (the fixed effects). Complete cases were used for analysis. As twenty-eight percent of patients had only one visit in the dataset, this caused difficulty in modeling patient-level variation. One visit per person was therefore randomly selected for modeling (124).

The analysis was conducted by first running an empty random intercept model, accounting only for the physician random effect. A series of successive models was then estimated by adding blocks of variables in the following order: year and quarter of the visit to address seasonality; patient-level variables to assess how physician-level effects resulted from differences in patient composition (145); physician-level variables; and finally regional-level variables. All variables were retained in the models, regardless of statistical significance. While there are different strategies for model-building, this analysis took the approach of retaining all variables in the models regardless of statistical significance for the following reasons: first, it may allow better comparison with other studies as coefficients are documented for all variables explored; second, as one of the study's goals was to explore how the variation changed across models, it was desirable to nest the models; and third, given the large size of the data, the impact on the degrees of freedom that these insignificant variables may impose was not a primary concern.

The variation is described in several ways. First, the intra-class correlation (ICC) was calculated according to the latent variable method[1] (146). The median odds ratio (MOR) is also reported, which can be interpreted as the median of the distribution of odds ratios that could theoretically be obtained by comparing two randomly chosen patients (with the same covariate values) from two different physicians (145,148,149). The MOR provides a measure of the variation between physicians; if it is close to 1, there is no variation between physicians. R^2_{GLMM} measures are reported for each model as the proportion of variance in the outcome explained by the model (marginal R^2 describes the proportion of the total variance explained by the fixed effects in the model, and conditional R^2 describes the proportion of the total variance explained by the fixed and random effects) (150). The proportion change in the variance (PCV) is also reported. The PCV indicates the relative change in the physician-level variance parameter between different models. It is calculated as the ratio of variances, subtracted from one.

Results

Between 2005 and 2011, just under 3 million paediatric RTI visits were identified. Randomly selecting one visit per person left 671,342 observations, of which 28% were associated with an antibiotic dispensing (Table 3).

Table 3 shows descriptive statistics for both the complete dataset and analytic subset. Half of the visits in the complete dataset were with female patients (47.5%), and the median patient age was 4 (interquartile range 2-9). Figure 4 shows overall monthly trends in RTI visits.

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[1] In the logistic case, the ICC is not simply the sum of the variances at each level, as the lowest level variance is on the logistic scale, while the higher-level variances are on the probability scale. Several methods have been proposed to accommodate this (146). The most straightforward and widely used is the latent variable method, which converts the individual-level variation to the logistic scale by assuming that an underlying, unobserved, continuous variable (say, z_i) measures the propensity to observe the outcome (i.e. to prescribe an antibiotic), y_i. Following this formulation, $y_i = 1$ when $z_i > 0$ and, $y_i = 0$ when $z_i < 0$. This latent variable follows a logistic probability distribution, with individual variance = $\frac{\pi^2}{3} = 3.29$ (146). The total variance is then the sum of the higher-level variance, plus 3.29, and the ICC can be measured using this total variance as the denominator (145-147)

Table 3: Distribution of variables by antibiotic prescription for respiratory tract infections visits in children

	Full dataset			Sample of one visit per person		
	Proportion of all visits (N=2,996,186)	Within category associated with an antibiotic prescription (N=834,673)	Within category not associated with an antibiotic (N=2,161,513)	All visits (N=671,342)	Associated with an antibiotic prescription (N=183,118)	Not associated with antibiotic (N=488,224)
Overall	**100**	**27.9**	**72.1**	**100**	**27.3**	**72.7**
Year, %						
2005	11.3	30.3	69.7	13.2	31.6	68.4
2006	15.4	29.4	70.6	16.2	30.6	69.4
2007	14.7	28.5	71.6	13.7	28.9	71.1
2008	14.1	28.8	71.2	12.6	28.4	71.6
2009	16.9	22.9	77.2	16.1	21.2	78.9
2010	13.1	28.0	72	12.2	25.8	74.3
2011	14.6	28.6	71.5	16.1	25.4	74.6
Patient Sex, %						
Female	47.5	27.9	72.1	48.9	27.3	72.7
Male	52.5	27.82	72.2	51.2	27.3	72.7
Missing (n)	2			1		
Median patient age (IQR)	4 (2-9)	6 (3-10)	4 (1-8)	6 (2-11)	8 (4-12)	5 (1-10)
Missing (n)	2			2		
Follow up RTI, %	14.0	24.6	75.5	7.9	24.3	75.8
Quintile of Annual Income Per Person Equivalent (QAIPPE), %						
QAIPPE 1	22.2	28.6	71.4	20.4	27.6	72.4

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QAIPPE 2	22.7	28.7	71.3	20.9	27.8	72.2
QAIPPE 3	20.0	27.6	72.4	20.5	27.3	72.7
QAIPPE 4	18.2	26.9	73.1	20	26.9	73.1
QAIPPE 5	15.7	27.1	72.9	18.2	26.7	73.3
Missing (n)	38,224			9,157		
Diabetes, %	0.2	33.1	66.9	0.2	33.3	66.7
Asthma, %	12.4	31.5	68.5	8.1	31.1	68.9
Cystic fibrosis, %	0.2	18.6	81.4	0.1	17.7	82.3
Immune deficiency, %	0.2	30.2	69.8	0.2	28.7	71.3
Chronic liver disease, %	0.04	27.8	72.2	0	26.4	73.6
Congestive heart failure, %	0.04	27.2	72.8	0	22.9	77.1
COPD, %	0.5	31.5	68.5	0.3	31.4	68.7
Chronic kidney disease, %	0.1	28.7	71.4	0.1	28.5	71.6
Recent antibiotic use, %	9.12	24.5	75.5	9.4	24.1	75.9
Median ADG sum (IQR)	4 (2-5)	4 (2-5)	4 (2-5)	3 (2-5)	3 (2-4)	3 (2-5)
Missing (n)	9			2		

Table 3: Distribution of variables by antibiotic prescription for respiratory tract infections visits in children

		Full dataset			Sample of one visit per person		
		Proportion of all visits (N=2,996,186)	Within category associated with an antibiotic prescription (N=834,673)	Within category not associated with an antibiotic (N=2,161,513)	All visits (N=671,342)	Associated with an antibiotic prescription (N=183,118)	Not associated with antibiotic (N=488,224)
Proportion of visits in past 3 years with this provider, %							
	No visits	36.6	28.6	71.4	46.8	28.7	71.3
	Less than or 30% (more than none)	30.2	28.6	71.4	25.5	27.9	72.1
	More than 30%	33.2	26.3	73.7	27.8	24.4	75.6
Median number of different GPs seen in past 3 years (IQR)		5 (3-7)	5 (3-8)	5 (3-7)	4 (2-6)	4 (2-6)	4 (2-6)
Season, %							
	Mar-May	24.2	29.1	70.9	24.5	29.0	71.0
	Jun-Aug	15.0	29.5	70.5	14.5	29.7	70.3
	Sep-Nov	29.3	25.4	74.6	28.8	24.0	76.0
	Dec-Feb	31.5	28.4	71.6	32.3	27.8	72.3
Physicians (N)		6404			6148		
Physician sex, %							
	Female	27.7	23.5	76.6	28.3	23.0	77.0
	Male	72.3	29.5	70.5	71.7	28.9	71.1
	Missing (n)	10,398			1,910		
Physician specialty, %							
	ER	0.6	25.1	74.9	0.7	25.2	74.8
	Pediatrics	2.9	11.2	88.8	2.4	12.8	87.2

Table 3: Distribution of variables by antibiotic prescription for respiratory tract infections visits in children

	Full dataset			Sample of one visit per person		
	Proportion of all visits (N=2,996,186)	Within category associated with an antibiotic prescription (N=834,673)	Within category not associated with an antibiotic (N=2,161,513)	All visits (N=671,342)	Associated with an antibiotic prescription (N=183,118)	Not associated with antibiotic (N=488,224)
Other	0.8	41.8	58.2	0.7	40.7	59.3
GP	95.7	28.3	71.7	96.2	27.6	72.5
Proportion of visits for RTIs in past 30 days, %						
None	0.6	20.4	79.6	0.7	21	79
0-2.5%	5.7	21.7	78.3	6.9	22.1	77.9
2.5-5%	14.7	24.4	75.6	16.8	24.7	75.3
5-7.5%	16.5	26	74	17.8	26.2	73.8
7.5-10%	14.8	27.9	72.2	14.8	27.4	72.6
10-15%	22.1	29.9	70.1	20.6	29.3	70.7
15-20%	14	31.9	68.1	12.2	30.9	69.1
More than 20%	11.7	29.4	70.6	10.2	28.7	71.3
Medical school graduation location, %						
Canada	62.1	24.3	75.8	64.1	23.8	76.2
International	37.9	33.8	66.2	36	33.4	66.6
Missing (n)	70,648			15,683		
Daily patient volume, %						
1st quartile (<28 visits)	22.8	23.2	76.9	25.3	23.3	76.7
2nd quartile (28-37 visits)	24.9	26.4	73.6	26.6	26.2	73.8
3rd quartile (38-48 visits)	26.0	28.9	71.1	25.7	28.7	71.3
4th quartile (>48 visits)	26.3	32.3	67.7	22.4	31.4	68.6

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Years experience, %						
0-5	4.6	21.8	78.2	5.2	20.8	79.3
6-10	9.3	22.1	77.9	9.8	22.4	77.6
11-15	13.0	24.0	76.0	13.4	24.3	75.7
16-20	18.5	26.9	73.1	18.2	27.0	73.1
21-25	16.8	28.7	71.3	16.5	27.7	72.3
26-30	13.9	30.0	70.0	13.7	29.3	70.7
31-35	11.9	30.7	69.3	11.6	29.7	70.3
36-40	7.4	30.7	69.3	7.2	29.7	70.3
40+ years	4.7	39.1	60.9	4.5	37.9	62.1
Missing (n)	4,032			1,050		
Number of RTIs seen in the current year, %						
1st quartile (<248)	20.4	20.8	79.2	24.8	21.5	78.5
2nd quartile (248-490)	22.2	25.6	74.5	25.1	25.9	74.1
3rd quartile (490-972)	25.2	28.2	71.8	25	28.5	71.5
4th quartile (>972)	32.2	33.7	66.4	25	33.2	66.8
Median proportion of LHA population over age 65 (IQR)	0.13 (0.10-10.15)	0.13 (0.10-0.15)	0.13 (0.11-0.15)	0.13 (0.11-0.16)	0.13 (0.10-0.16)	0.13 (0.11-0.16)
Median proportion of LHA population under age 15 (IQR)	0.18 (0.16-0.21)	0.19 (0.17-0.22)	0.18 (0.16-0.21)	0.18 (0.16-0.21)	0.19 (0.16-0.21)	0.18 (0.16-0.21)
Median of median age of LHA population (IQR)	39 (36-41)	38 (35-41)	39 (37-41)	39 (37-42)	39 (37-41)	39 (37-42)

Table 3: Distribution of variables by antibiotic prescription for respiratory tract infections visits in children

	Full dataset			Sample of one visit per person		
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Health Authority, %						
Interior	11.8	27.8	72.2	14.5	28.0	72.1
Fraser	46.3	29.6	70.4	41.3	28.5	71.5
Vancouver	23.2	22.4	77.6	22.3	21.9	78.1
Vancouver Island	12.2	26.4	73.6	14.3	26.5	73.5
Northern	6.5	37.5	62.5	7.5	36.6	63.4
Missing (n)	4,689			1,251		
Median 28-day moving average apparent temperature (IQR)	4.73 (0.57-11.76)	4.62 (0.33-12.14)	4.77 (0.66-11.57)	4.49 (0.36-11.50)	4.42 (0.17-12.14)	4.52 (0.43-11.24)

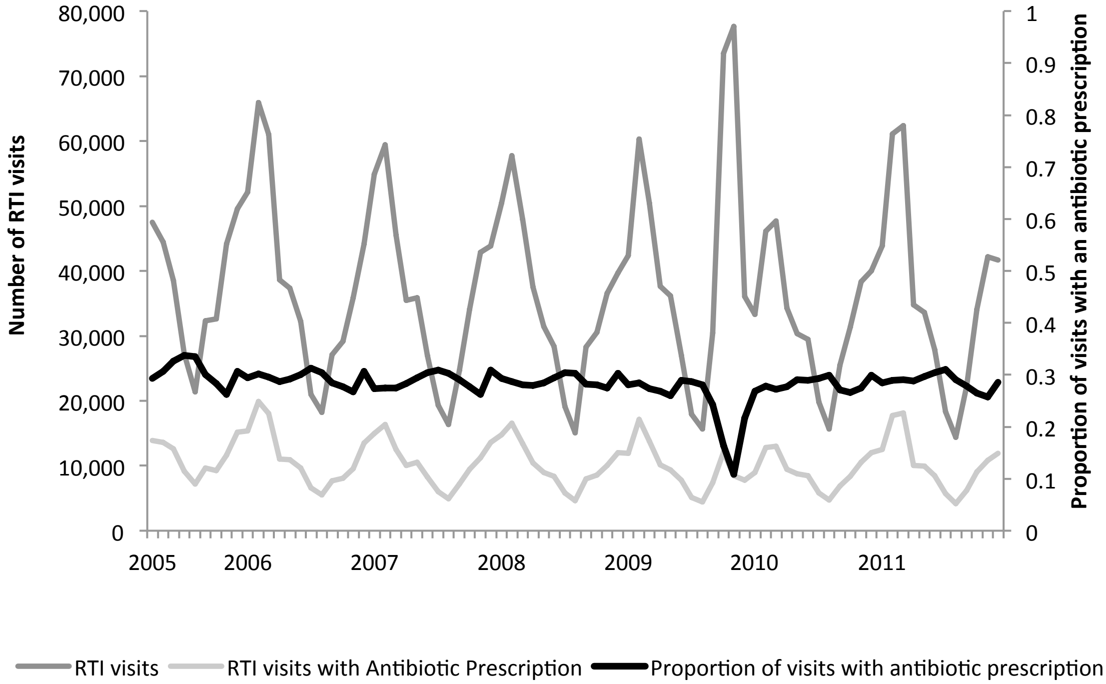

Figure 4: Monthly number of respiratory tract infection visits overall, visits with antibiotic prescriptions, and monthly proportions of visits with antibiotic prescriptions, from 2005 to 2011 in British Columbia, Canada[2].

These visits were conducted by 6,404 unique physicians; these were female physicians in 27.7% of visits, mostly GPs (95.7% of visits), with an average of 22.5 years of experience, across visits. Just over 8% of practitioners in the complete dataset (527/6404) never prescribed antibiotics. These practitioners had fewer visits overall (median 3, IQR 1-8). Figure 5 shows the wide variation in prescribing rates by physician; the median proportion of visits associated with a prescription was 19.2% (IQR 10.0 – 33.1).

[2] The spike in visits for RTI at the end of 2009 is likely attributable to the H1N1 influenza pandemic. The decrease in proportion of visits treated with an antibiotic is most likely a function of the higher number of visits as well as greater awareness about the viral illness circulating – public health advice at the time focused on the appropriate use of antiviral medication.

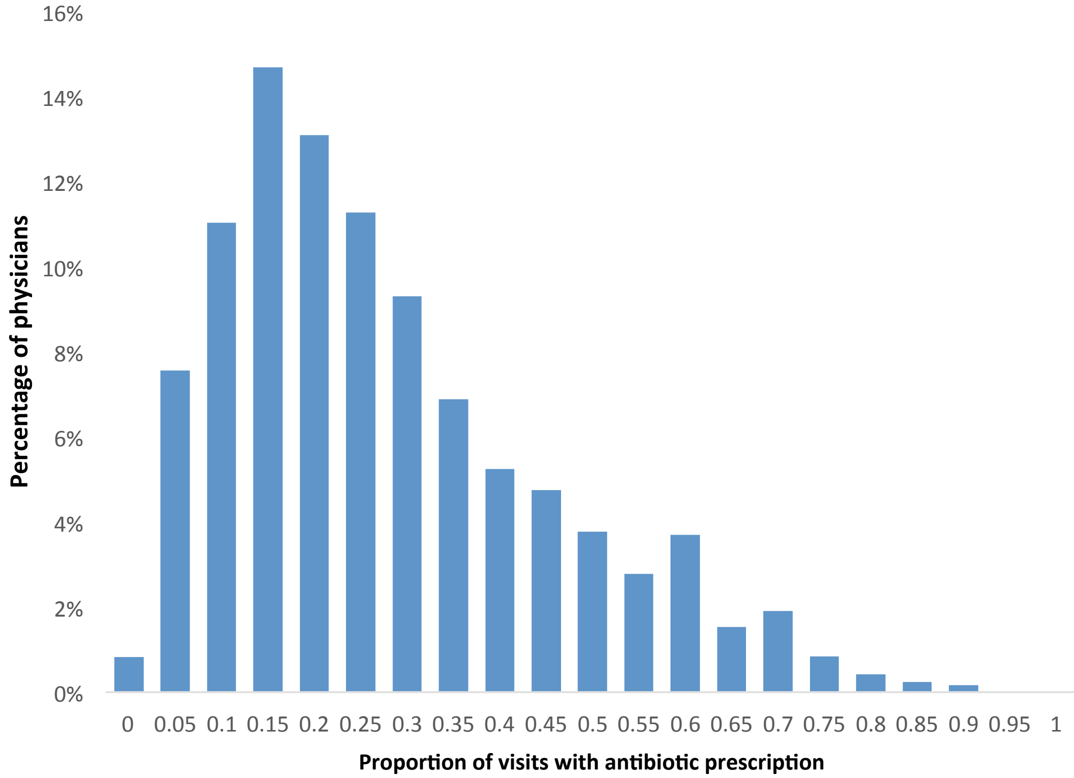

Figure 5: Histogram of proportion of pediatric respiratory tract infection (RTI) visits associated with an antibiotic prescription, per physician, between 2005 and 2011*.

* Frequencies are weighted by the total number of RTI visits.

Model results

Results of the series of models are presented in Table 4. The final model, with all covariates, was based on 645,094 observations due to missing data (96%).

Table 4: Generalized linear mixed model results of antibiotic prescription for paediatric respiratory tract infections

		Empty model		Basic model with year only		With Patient Covariates		With Patient & Physician Covariates		With Patient, Physician, and LHA Covariates	
Random effect		**Variance**	**SE**	**Variance**	**SE**	**Variance**	**SE**	**Variance**	**SE**	**Variance**	**SE**
Physician		0.96	0.023	0.95	0.022	0.91	0.011	0.78	0.019	0.76	0.019
Fixed effects		**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**OR**	**95% CI**	**OR**
Constant term		0.27	0.26 - 0.27	0.35	0.34 - 0.36	0.18	0.17 - 0.18	0.10	0.09 - 0.11	0.10	0.08 - 0.12
Year (reference: 2005)	**2006**			0.93	0.91 - 0.95	0.94	0.92 - 0.96	0.91	0.88 - 0.93	0.90	0.88 - 0.92
	2007			0.89	0.87 - 0.91	0.93	0.91 - 0.95	0.88	0.86 - 0.90	0.87	0.85 - 0.89
	2008			0.85	0.83 - 0.87	0.92	0.9 - 0.94	0.87	0.85 - 0.89	0.86	0.84 - 0.88
	2009			0.58	0.57 - 0.6	0.61	0.6 - 0.63	0.58	0.56 - 0.59	0.57	0.56 - 0.59
	2010			0.76	0.74 - 0.78	0.92	0.9 - 0.94	0.83	0.81 - 0.86	0.83	0.81 - 0.85
	2011			0.75	0.73 - 0.77	0.94	0.92 - 0.96	0.86	0.83 - 0.88	0.85	0.82 - 0.87
Season (reference: Jun-Aug)	**Mar-May**			0.98	0.97 - 1.00	0.99	0.97 - 1.00	1.05	1.03 - 1.07	0.99	0.97 - 1.02
	Sep-Nov			0.80	0.79 - 0.82	0.80	0.79 - 0.82	0.86	0.85 - 0.88	0.80	0.77 - 0.82
	Dec-Feb			0.99	0.97 - 1.00	0.96	0.94 - 0.98	1.06	1.04 - 1.09	0.95	0.92 - 0.98
Patient gender (reference: Male)	**Female**					0.97	0.96 - 0.98	0.97	0.96 - 0.98	0.97	0.96 - 0.98
Patient age (per year increase)						1.08	1.08 - 1.08	1.08	1.08 - 1.08	1.08	1.08 - 1.08

Table 4: Generalized linear mixed model results of antibiotic prescription for paediatric respiratory tract infections

		Empty model		Basic model with year only		With Patient Covariates		With Patient & Physician Covariates		With Patient, Physician, and LHA Covariates	
Follow up RTI						0.98	0.96 - 1.01	0.97	0.95 - 1.00	0.97	0.95 - 1.00
QAIPPE quintile (neighbourhood SES) (reference: QAIPPE 1, lowest)	**QAIPPE 2**					1.00	0.98 - 1.02	1.00	0.98 - 1.02	1.00	0.98 - 1.02
	QAIPPE 3					1.01	0.99 - 1.03	1.01	0.99 - 1.03	1.01	0.99 - 1.03
	QAIPPE 4					1.02	1. - 1.04	1.02	1.00 - 1.05	1.02	1.00 - 1.04
	QAIPPE 5					1.03	1.01 - 1.05	1.04	1.02 - 1.06	1.04	1.02 - 1.06
Diabetes						1.08	0.95 - 1.22	1.05	0.93 - 1.19	1.05	0.93 - 1.19
Asthma						1.06	1.04 - 1.08	1.06	1.04 - 1.08	1.06	1.04 - 1.08
Cystic fibrosis						0.96	0.8 - 1.16	0.97	0.80 - 1.18	0.97	0.80 - 1.18
Immune deficiency						0.92	0.8 - 1.07	0.92	0.79 - 1.06	0.92	0.79 - 1.06
Chronic liver disease						1.07	0.74 - 1.56	1.03	0.70 - 1.52	1.00	0.68 - 1.48
Congestive heart failure						1.30	0.88 - 1.92	1.12	0.75 - 1.69	1.12	0.74 - 1.68
COPD						0.87	0.78 - 0.98	1.14	1.02 - 1.29	1.15	1.02 - 1.29
Chronic Kidney Disease						0.90	0.72 - 1.13	1.12	0.89 - 1.40	1.12	0.90 - 1.40
Recent antibiotic use						0.85	0.83 - 0.87	0.86	0.84 - 0.88	0.86	0.84 - 0.88
ADG sum						0.97	0.97 - 0.97	0.97	0.97 - 0.97	0.97	0.97 - 0.97
Percentage of visits in past 3 years with this	**No visits**					1.20	1.18 - 1.22	1.21	1.19 - 1.24	1.21	1.19 - 1.24

Table 4: Generalized linear mixed model results of antibiotic prescription for paediatric respiratory tract infections

		Empty model		Basic model with year only		With Patient Covariates		With Patient & Physician Covariates		With Patient, Physician, and LHA Covariates	
physician (reference: 30% or more)	**Less than 30%**					1.07	1.05 - 1.09	1.07	1.05 - 1.09	1.07	1.05 - 1.09
Number of different GPs seen in past 3 years						1.02	1.02 - 1.02	1.02	1.02 - 1.02	1.02	1.02 - 1.02
Physician gender (reference: male)	**Female**							0.89	0.84 - 0.94	0.91	0.86 - 0.96
Physician specialty (reference: GP)	**ER**							0.79	0.61 - 1.02	0.79	0.62 - 1.02
	Pediatrics							0.47	0.41 - 0.55	0.48	0.42 - 0.56
	Other							0.88	0.72 - 1.06	0.89	0.73 - 1.07
Proportion of physician's visits in the past 30 days which were RTI (reference: more than 20%)	**None**							1.34	1.21 - 1.49	1.36	1.23 - 1.51
	>0 to 2.5%							1.42	1.35 - 1.49	1.45	1.38 - 1.52
	2.5 to 5%							1.40	1.34 - 1.45	1.42	1.36 - 1.48
	5 to 7.5%							1.32	1.27 - 1.37	1.33	1.29 - 1.38
	7.5 to 10%							1.25	1.21 - 1.30	1.26	1.22 - 1.31
	10 to 15%							1.21	1.17 - 1.25	1.22	1.18 - 1.25
	15 to 20%							1.13	1.10 - 1.16	1.13	1.10 - 1.16
Physician's medical school location (reference: Canada)	**International**							1.77	1.68 - 1.88	1.73	1.63 - 1.83
Patient volume the day of the RTI visit (reference:	**2nd quartile**							0.99	0.97 - 1.01	0.99	0.98 - 1.01

Table 4: Generalized linear mixed model results of antibiotic prescription for paediatric respiratory tract infections

		Empty model		Basic model with year only		With Patient Covariates		With Patient & Physician Covariates		With Patient, Physician, and LHA Covariates	
1st quartile)	**3rd quartile**							0.97	0.95 - 0.99	0.97	0.95 - 0.99
	4th quartile							0.94	0.92 - 0.96	0.94	0.92 - 0.97
Years of experience (reference: 0-5)	**6-10**							0.98	0.93 - 1.03	0.99	0.94 - 1.04
	11-15							1.07	1.01 - 1.14	1.08	1.02 - 1.15
	16-20							1.15	1.08 - 1.22	1.16	1.09 - 1.24
	21-25							1.21	1.13 - 1.29	1.23	1.15 - 1.31
	26-30							1.29	1.21 - 1.39	1.32	1.23 - 1.41
	31-35							1.32	1.23 - 1.42	1.35	1.26 - 1.46
	36-40							1.36	1.25 - 1.47	1.39	1.29 - 1.51
	40+ years							1.41	1.28 - 1.56	1.46	1.33 - 1.61
Number of RTIs seen in the current year (reference: 1st quartile <248)	**2nd quartile (248-490)**							1.10	1.07 - 1.13	1.11	1.08 - 1.14
	3rd quartile (490-972)							1.17	1.12 - 1.21	1.19	1.15 - 1.23
	4th quartile (>972)							1.27	1.21 - 1.33	1.31	1.25 - 1.37
Proportion of LHA population over age 65 (per 10%)										0.99	0.98 - 1.00
Proportion of LHA population under age 15 (per 10%)										1.12	1.06 - 1.17

Table 4: Generalized linear mixed model results of antibiotic prescription for paediatric respiratory tract infections

		Empty model	Basic model with year only	With Patient Covariates	With Patient & Physician Covariates	With Patient, Physician, and LHA Covariates	
Median age of LHA population (centred on mean)						1.19	1.11 - 1.27
Health Authority	**Interior**					1.07	1.02 - 1.13
(reference: Vancouver Coastal)	**Fraser**					1.00	0.97 - 1.03
	Vancouver Island					1.03	0.98 - 1.08
	Northern					1.20	1.13 - 1.28
28 day moving average temperature						0.99	0.99 - 0.99
N observations used		671,342	671,342	662,202	645,815		645,094
AIC		616,216.2	692,274.7	666,759.5	648,692.3		647,788.8
ICC (proportion of total variance attributable to between-physician differences)		22.6%	22.4%	21.6%	19.2%		18.8%
MOR		2.55	2.53	2.48	2.33		2.30
PCV (relative to intercept-only model) at level of physician		--	1.49%	5.86%	18.55%		20.82%
PCV (relative to previous model) at level of physician		--	1.49%	4.44%	13.48%		2.78%
R^2_{GLMM} **- Marginal (proportion of total variance in the outcome that is explained by the fixed effects)**		--	0.03%	2.62%	4.23%		4.25%

Table 4: Generalized linear mixed model results of antibiotic prescription for paediatric respiratory tract infections

	Empty model	Basic model with year only	With Patient Covariates	With Patient & Physician Covariates	With Patient, Physician, and LHA Covariates
R^2_{GLMM} - Conditional (proportion of total variance in the outcome that is explained by fixed and random effects in the model)	--	22.39%	23.65%	35.47%	36.00%

*AIC: Akaike Information Criterion; ICC: Intra-class correlation; MOR: Median Odds Ratio; PCV: Percent change in variance

Model variation

Before accounting for other variables, the intra-class correlation (ICC) was 22.6%, indicating that between-physician differences accounted for nearly one-quarter of the total variation in antibiotic prescribing. Patients seen by higher-prescribing physicians had a median 2.6 times higher odds of receiving a prescription compared to peers seen by another physician.

After adjusting for patient, physician, and regional factors, the between-physician differences (ICC) accounted for 18.8% of the total variation. Patients seen by higher-prescribing physicians had a median 2.3 times higher odds of receiving a prescription compared to peers seen by another physician. The largest decrease in between-physician variation was observed when the physician-level characteristics were included in the model. Controlling for characteristics at the physician level explained nearly one-fifth of the variation attributed to physicians (the proportional change in variance (PCV) relative to the empty model is 18.6%), whereas controlling for patient-level characteristics only explained 6%. The inclusion of a few select regional level variables, including gross-level geographical indicators, while statistically significant, did not explain much of the physician-level variation. Overall, this suggests that the vast majority of variation was driven by individual physician practice styles.

Patient-level factors

As shown in the final model, having a recent antibiotic prescription was associated with a lower probability of prescribing at this visit. Older children, and children with asthma or COPD had higher odds of receiving a prescription. A lack of physician familiarity was also associated with more prescribing: patients with fewer than 30% of their medical visits in the past 3 years with the RTI physician had a higher likelihood of prescribing (OR 1.07, 95% CI 1.05-1.09), as did those with no documented visits with any provider in the past 3 years (OR 1.21, 95% CI 1.19-1.24).

Clinician-level factors

Paediatricians had lower odds of prescribing compared with GPs (OR 0.48, 95% CI 0.42 – 0.56). Physicians who graduated medical school outside of Canada had 1.73 times greater odds of prescribing (95% CI 1.63-1.83). The number of US-trained physicians was small, and grouping them with Canadian graduates did not change the results (data not shown). With every 5 years increase in experience (years since finishing medical school), the odds of prescribing an antibiotic increased, from 1.08 (95% CI 1.02-1.15) among those with 11-15 years experience, to 1.46 (95% CI 1.33-1.61) among the most experienced of physicians (those with more than 40 years experience), relative to newly graduated physicians with under 5 years experience. Physicians who had seen relatively fewer RTIs in the past 30 days were more likely to prescribe, compared with those for whom 20% or more of their visits were coded as RTIs. This was generally an inverse step-wise relationship – the effect was largest among physicians with a smaller proportion of RTI visits, and the effect decreased in magnitude as the proportion of RTI visits increased.

Interpretation

In the past 10 years, strong public health messages have promoted reductions in the prescribing of antibiotics for RTIs. The present study found that just under 28% of visits for RTIs between 2005 and 2011 in BC were associated with an antibiotic prescription. As was noted previously, this is an underestimate of actual prescriptions, as it represents dispensing events. Fleming-Dutra (17) estimated from American national survey data that 21.2% of viral upper respiratory tract infections in the in 2010-11 year were associated with an antibiotic prescription, while estimates for bronchitis, sinusitis, and pharyngitis were 55.2%, 84.7%, and 56.2% respectively. In Korea, 58.7% of upper respiratory tract infections were associated with an antibiotic prescription in 2009-2011 (151). In France, 51.4% of acute rhinopharyngitis cases were treated with antibiotics (124). In one region of Spain, 35% of all RTIs were associated with an antibiotic (152). The definition of RTIs used in the present study included acute sinusitis and acute pharyngitis, for which antibiotics are sometimes, but infrequently, indicated. The decisions to include sinusitis and pharyngitis, and to group together RTI codes, rather than analyze them separately, were made for several reasons: first, to accommodate potential 'diagnosis shifting' (whereby a physician may be more likely to record a diagnosis that more appropriately warrants antibiotic treatment, such as sinusitis, when the physician has already decided to provide a prescription) (153); second, the proportion of cases for which antibiotics are indicated is small – 10-20% of acute pharyngitis, and 0.5-2% of acute sinusitis have an underlying bacterial etiology (61); third, as the ICD codes are used for billing, but not diagnostic purposes, their use may not discriminate assumed etiologies in a perfect way. One study in Quebec, Canada, found a positive predictive value (PPV) of 0.93 for all respiratory infections combined, but lower PPVs for individual codes (138). In line with other studies, a declining secular trend in antibiotic prescribing for RTIs over time was observed (154-156).

These results revealed a median 2.3-fold variation between physicians in the odds of prescribing an antibiotic, after accounting for a number of relevant patient, physician, and regional factors. In a cross-country comparison, Cordoba (157) reported MORs ranging from 2.6 for Denmark to 6.8 for Russia, and Mousquès (124) reported an MOR of 2.9 for France, from similar analyses. The evidence of lower variation in our study could be the result of differences in the sets of variables controlled for (unadjusted MORs were 2.9 for France, 2.5 in the present study, and not reported in the text of Cordoba (157), but from the figure appears to be about 2.6 for Denmark to 6.0 for Russia), or from differences in the health care system contexts. The proportion of variance attributable to the physician level in this study (18.8%) was higher than that reported in an earlier analysis of physician prescribing for upper RTI (12.9%) (158). The current study extends these previous findings with a population-based analysis of children across 7 years of data using a multilevel modeling framework. Additionally, measures of healthcare usage and clinician practice characteristics were included, which have not previously been accessible.

Measured physician level factors had the most influence, as observed factors decreased the between-physician variance by 13.5% beyond that addressed by observed patient factors, and 18.6% overall – but, importantly, the rest of the variation remains unaccounted for. This suggests that individual physician practice style may be driving the majority of the variation in antibiotic prescribing for RTIs. In comparison, patient and regional effects were relatively small.

Some patient-level variables showed statistically significant associations, such as asthma, patient age, and recent antibiotic use. However, these effects were relatively small, and overall did not have a large effect on the model.

Physician experience had a clear positive gradient association with prescribing, a finding which is consistent with previous studies of the association between clinical experience and quality of health care (159). This paradoxical result could represent a cohort effect (159), due to the growing awareness and inclusion of antibiotic resistance training in medical curricula in recent years. It is also possible that with more experience, physicians become more set in their routine ways of practicing medicine, and so have not integrated changes in guidelines and recommendations regarding treatment of RTIs as readily as newer practitioners. At least one study found that physicians did not change their prescribing habits much over time (160).

These results suggest that the volume of recent frequency in managing RTIs may have an effect: physicians whose practice in the past month had included a smaller proportion of RTIs were more likely to prescribe an antibiotic in a given case, after controlling for season and all the other variables. The volume-outcome association has been shown most commonly among surgical procedures (161), but also among some medical conditions (162).

The recent RTI volume variable described above, as well as the practitioner experience variable, showed clear step-wise relationships with the outcome. While a linear form was not imposed on these variables, there is an apparent dose-response, which increases confidence in interpreting these results.

Paediatricians and Emergency Room (ER) physicians were less likely to prescribe than GPs. ER physicians who work on a salary, rather than fee-for-service, basis, would not have contributed to the data we used for this analysis. It is therefore possible that RTIs managed by ER physicians are not reliably captured in these data. There has been a concerted effort within the paediatrician community to raise awareness about inappropriate and unnecessary antibiotic prescribing, and our findings lend support to the success of this effort.

Thus, these findings suggest a few novel targets for physician-focused interventions; however, it is also important to note that a substantial amount of variability (18.8%) in antibiotic prescribing between physicians remains unexplained. While further research to elucidate the reasons for and mechanisms behind the reported associations is warranted, the findings presented here would suggest a potential benefit from focusing on physicians who have been in practice longer and internationally trained physicians. Targeting of continuing education and academic detailing efforts, tailoring our foreign-trained licensing requirements, and provision of individualized feedback via prescription database extracts may be relevant approaches in these respects. Further investigation of the lower prescribing rates among paediatricians may provide insight applicable to other community settings.

Roughly one-fifth of the physician-level variations could be explained by the observed characteristics included, while the remainder is unexplained. Previous qualitative studies have highlighted some features that impact the prescribing process, such as confidence in the diagnosis, perceived patient pressure, and clinical autonomy (106,108,163). Without also considering these and other influences, interventions will likely not succeed in reducing physician-level variations on a large scale. Targeted behavioural interventions should not be the only strategy for reducing outpatient paediatric antibiotic use; continued efforts to improve public knowledge and to reduce patient expectation of an antibiotic for most RTI, as well as consideration of the role of policy options, is required (115).

Considering the shape of the distribution of physician-level antibiotic prescribing for RTIs (Figure 5), it might be assumed that focusing efforts on reducing the proportion of visits at which the most frequent prescribers treat with antibiotics would not have much effect on the overall median. Therefore, the median proportion of visits associated with an antibiotic prescription, per physician, should likely not be the main metric used to evaluate the impact of potential interventions.

Limitations

Several limitations are worth bearing in mind as these results are interpreted. The systematic review of factors associated with antibiotic prescribing for RTI, presented in Chapter 2, identified a number of patient clinical and patient-physician communication factors as relevant (164). The present study was unable to include several of these measures, due to the nature of our data. However, many known determinants have been addressed in this model. A number of variables had missing data, as is common with administrative data. Physician demographic variables, in particular, had a high rate of missing values.

A 5-day timeframe was chosen for linkage of physician visits to antibiotic prescriptions, reasoning that this would allow sufficient time to include delayed prescription fills. Additionally, this timeframe has commonly been used in the past (140,165), so its use here is consistent. A study from the Netherlands used four days for linkage of any prescription to any visit (166). However, there is no validated linkage algorithm for associating a dispensing event with a physician visit, so this timeframe is, to a certain extent, arbitrary.

These models only allowed for variation in the intercept – i.e. the underlying probability of antibiotic prescription across clinicians. It is statistically possible to assume variability in each clinician's response across levels of the covariates (by including random slopes for these presumed variables), but these models are computationally even more complex to fit, so for this analysis it is assumed that the effect of each variable is common across physicians.

Geographically, local health areas were the smallest unit. However, with 89 across the >940,000 km^2 of British Columbia, these are still relatively large physical boundaries. Regional effects on antibiotic prescribing could potentially operate within smaller geographic boundaries – for instance clustered around schools, daycares, or other neighbourhood unit – which may be masked by the use of a larger unit. Regional Health Authority (of which there are only five) was included as a dummy variable in the analysis, and this, in particular, may not adequately represent nuanced geographic effects.

Conclusion

This population-level analysis demonstrated that variations are apparent between physicians in the decision to manage paediatric RTIs with antibiotics. Previous studies (described in Chapter 2) have explored determinants of prescriptions, but have not as frequently explicitly considered the variations between physicians in their propensity to prescribe. Those that have (e.g. (123,124)), have not focused on the paediatric population. The present analysis suggests that measured physician-level factors account for more of the physician-level variations in prescribing than do measured patient-level factors. A large proportion of the variations remain unexplained by all of the measured factors included in this study. The design of effective community-oriented programs and policies should focus both on characteristics of physicians shown to be correlates with prescribing, but just as importantly – if not more – should aim to address variations in use of these essential drugs.

Chapter 4: Variations in Urine Culturing

Introduction

Urinary tract infections (UTI) affect approximately 10% of women over the age of 18 every year, and about 60% of women will experience at least one episode in her lifetime (167,168), making UTIs one of the most common types of bacterial infections among outpatients (169-172). While more common in women, UTIs affect men as well (173). UTIs cause considerable discomfort and impact on quality of life (174-176), cost the healthcare system a significant amount (an estimated $2.3 billion in the US in 2010-equivalent dollars) (168,177), and add to the burden of antibiotic exposure which increases individual risk for antibiotic resistant infections as well as population-level spread of resistant bacteria (21,178). Complicated UTI generally refers to infection present in an individual with comorbidities, urological abnormalities, men, and postmenopausal women, while most other cases are considered uncomplicated (169).

An essential partner in both hospital and community-based antibiotic stewardship initiatives is the microbiology laboratory, which performs the clinical function of working up samples to determine the presence of pathogens, and, where indicated, to determine the susceptibility of the pathogen to pharmaceutical compounds. Laboratories also publish aggregate trends in antibiotic resistance, which guide empirical treatment recommendations.

Escherichia coli is the predominant pathogen involved in UTI (179,180). Current guidelines recommend treating most uncomplicated UTIs empirically, with urine culture recommended only for patients with complicated UTI, recurrent UTIs, acute pyelonephritis, or at risk of infection with antibiotic resistant organisms (181-183). Local resistance rates should inform treatment practices (169). Knowledge of local resistance rates derives from urine culture testing results. At best, then, the laboratory-based resistance rate could be considered an overestimate of true community circulation, given that they should be based primarily on complicated UTIs (184). However, practice patterns are largely unknown. Previous studies have suggested poor adherence to UTI diagnosis and management guidelines (185-187), although the primary focus of these studies has been on decisions regarding antibiotic treatment. Understanding current patterns of urine culturing practice will therefore have the potential to inform our approach to community-level antibiotic stewardship.

Prior estimates have found that community UTIs in women cost €44 million in direct costs in France in 2012 (equivalent to approximately $57.8 million in 2012 Canadian dollars), and on average, a urine culture cost €17.55 (equivalent to about $23.05 in 2012 Canadian dollars) (188). Considering an estimated 5.4 million primary care visits for UTI (coded as cystitis, other disorders of bladder, or unspecified site) a year in the US (130), and reports that between 36% and 78% of adult women with UTI had a urine culture ordered (185,186,189), the potential cost associated with urine cultures is significant.

From the laboratory perspective, urine cultures comprise a large proportion of the workload; one estimate suggested that 19-32% of all submitted cultures in a clinical laboratory are urine cultures from the outpatient setting (190). Variations in medical practice have been documented for virtually every condition or procedure studied (191), and it is likely that variations would also be seen among urine culture use (192). However, research is lacking on the extent and potential drivers of variation in urine culture submission.

A better understanding of the use of culture services for UTI and variations in practice will support meaningful discussion around the appropriate and efficient ordering of laboratory services in the current era of increasing resistance. The objective of this study was to assess factors associated with urine culture for acute uncomplicated cystitis, and to examine variations in culture use across physicians. To accomplish this, laboratory microbiological analysis data from urine cultures was linked with physician visit and antibiotic prescribing administrative data. The focus was on patient and physician-level factors, because these were most relevant in the RTI study. Additionally, the outpatient laboratory coverage varies around the province, so any area-level variables would be confounded by coverage probability. This is further described below.

I hypothesized that factors suggesting complicated or recurrent UTIs, or UTIs at higher risk of antibiotic resistance, would be associated with urine cultures. I further hypothesized that we would find marked variations in urine culturing practice between physicians. The focus remained on physician-level variables that were found in the RTI analysis (reported in chapter 3) to be associated with antibiotic prescribing, predicting that they would be relevant to urine culture ordering as well.

Methods

Patient visits

The cohort was constructed as all physician visits with general practitioners (GPs) for cystitis (ICD 9 code 595) in the province of British Columbia, Canada (2011 population was ~4.5 million) between 2005 and 2011 from the universal Medical Services Plan (134), among patients registered with MSP for at least 275 days of a given year (i.e. patients could be eligible for one year, but not another). Urine culture data were obtained from LifeLabs, a private community-based laboratory serving the province (193). When a physician orders an outpatient urine culture, the patient is free to provide that culture in any designated facility. LifeLabs' market share varies around the province, but was approximately 60-62% province-wide, based on publicly available financial statements, during the time frame of this study (194). Visits were linked to antibiotic prescriptions (J01) dispensed within 3 days following the visit, and to urine cultures dated within 4 days following the visit (135). In assigning these timeframes, it was assumed that, due to the nature of physical symptoms of UTI, patients have little incentive to delay prescriptions. The time frame for cultures was selected based on the assumption that patients will typically present on the same or next day for culture, but that an allowance of an extra day or two would maximize linkages.

In 0.45% of visit records, more than one antibiotic was dispensed on the same day. As we were only looking at UTI diagnoses, we could not determine whether multiple antibiotics were intended for the UTI, or for another infection; we therefore excluded these cases.

Measures

Outcome

We identified urine cultures associated with UTI visits as those that occurred within 4 days following the UTI visit, and with matching patient and practitioner identifiers. The primary outcome was whether a urine culture was associated with the UTI visit.

Patient and physician variables

At the patient level, age groups were categorized as under 15, 15-24, 25-39, 40-54, 55-69, 70-84, and 85 or older. Recent antibiotic use was defined as a filled prescription for any antibiotic in the 6 months preceding the UTI visit. Long term care facility residence at the time of the UTI visit was assessed using the Home and Community Care files (195). The visit was considered to be a potential treatment failure follow-up if it occurred within 28 days of a previous visit for UTI that had been associated with an antibiotic, similar to previous definitions (196,197). Using patient hospitalization records (137), patients who had been discharged from hospital in the past 30 days were identified. Patients were considered to have diabetes if at least 2 physician visits within a 2-year period, or one hospitalization, with a diagnosis code of diabetes occurred any time after 2002 and before the UTI visit. As a proxy for patient attachment with their general practitioner (GP), the proportion of visits in the previous three years that were with the same physician as the UTI visit was calculated (141), and dichotomized at the median (0.073).

At the physician level, variables included sex of the practitioner, as well as variables previously shown to be associated with antibiotic prescribing decisions in the same time period (reported in Chapter 3): medical school location (Canada vs. elsewhere), clinical experience (years of practice), and a measure of UTI service within the physician's practice (number of UTI visits billed in the past 3 months).

Costs

Costs were estimated by assigning a fee of $19.57 for every culture identified in our dataset, plus an additional $21.16 ($9.55 for the biochemical identification of the microorganism, and $11.61 for the antibiotic susceptibility test) for each organism identified on culture (up to a maximum of three for urine), according to the current Medical Services Plan fee items. These are the amounts that LifeLabs would be currently reimbursed by the province.

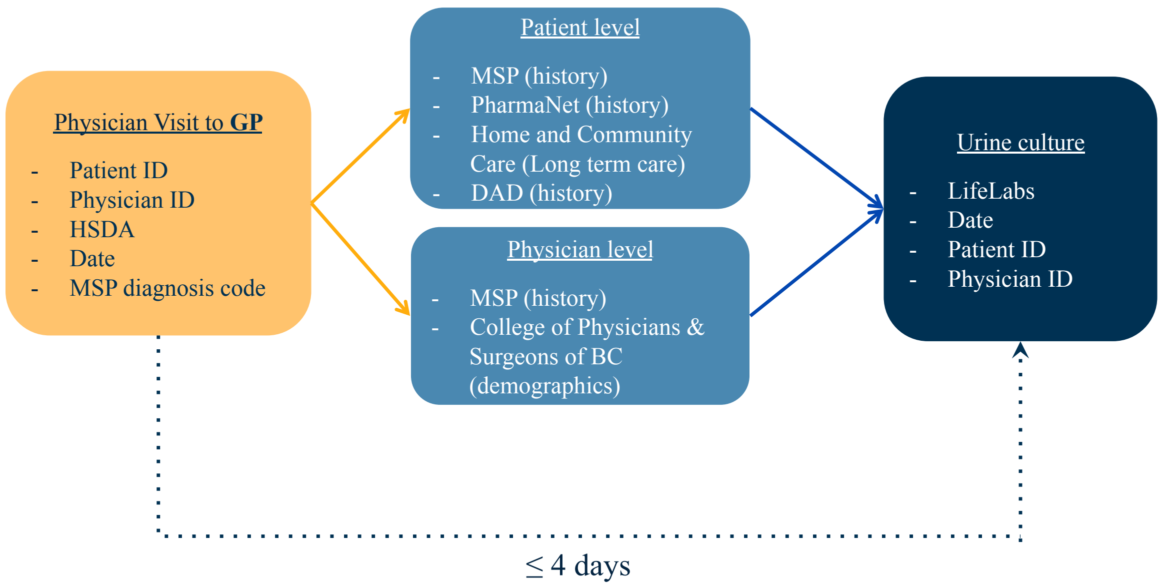

Figure 6: Overview of linkage design for UTI study

Statistical analysis

Analyses were stratified by sex of the patient. Generalized linear mixed models with a logit link to were used to estimate the log odds of a urine culture being associated with a UTI visit. This method allowed for the natural clustering of patient visits within physicians.

The intraclass correlation coefficient (ICC) was calculated by the latent variable method (146). The Median Odds Ratio (MOR) represents the median of the theoretical distribution of odds ratios that could be obtained by comparing two randomly chosen patients, with the same covariate values, from two different physicians (and repeating this for all possible pairs of physicians) (145,148,149).

Several sensitivity analyses were conducted to explore the impact of geographic variation of LifeLabs coverage. First, the same model was estimated, but without the HSDA variable, in order to examine the effect of this variable on parameter estimates. The analysis was subsequently restricted to the Vancouver Coastal and Fraser health authority regions where LifeLabs has the greatest market share.

Results

Between 2005 and 2011, BC's population averaged approximately 4.35 million, meaning this study population includes approximately 30.5 million person-years of study time. During the study period, there were 1,288,696 visits for cystitis, by 595,714 unique patients, seen by 5,825 unique physicians. Male physicians conducted 71% of all visits; two-thirds of visits were conducted by Canadian medical school graduates; just over a quarter (26.1%) of visits were conducted by physicians with 0-15 years of experience, and almost half were conducted by physicians with 16-30 years of experience. Eighty-four percent of these visits were among female patients. Among females, visits were skewed towards younger adults, with 56% of female visits occurring among patients between the ages of 15 and 54. In contrast, 32% of male visits were within these ages. Fifty-nine percent of male visits were among those aged 55 or older, whereas 38% of female visits were. While 42% of visits overall were not associated with an antibiotic prescription, 22% were associated with a prescription for ciprofloxacin, 17% received nitrofurantoin, and 12% received trimethoprim/sulfamethoxazole, respectively; the remainder received a different antibiotic prescription. Overall, 14% of visits were associated with a urine culture (Table 5).

Table 5: Distribution of visits and urine cultures

	Females			Males			Total		
	Total # of visits (N)	% of female visits	% with urine cultures	Total # of visits (N)	% of male visits	% with urine cultures	Total # of visits (N)	% of total visits	% with urine cultures
Overall	1,040,636	83.5	15.7	198,594	16.5	9.1	1,239,230	--	14.6
Calendar year									
2005	131,969	12.7	16.7	25,053	12.6	11.4	157,022	12.7	15.9
2006	137,069	13.2	16.3	26,390	13.3	10.7	163,459	13.2	15.4
2007	143,861	13.8	13.9	27,855	14.0	7.6	171,716	13.9	12.9
2008	148,443	14.3	14.3	28,703	14.5	7.6	177,146	14.3	13.2
2009	152,304	14.6	15.4	29,638	14.9	8.2	181,942	14.7	14.2
2010	161,365	15.5	16.1	29,972	15.1	9.0	191,607	15.5	15.0
2011	165,355	15.9	17.1	30,983	15.6	9.3	196,338	15.8	15.9
Patient age group									
0-14	62,013	6.0	16.1	19,102	9.6	10.9	81,115	6.6	14.9
15-24	141,838	13.6	17.8	9,691	4.9	9.8	151,529	12.2	17.3
25-39	226,468	21.8	17.6	22,747	11.5	9.8	249,215	20.1	16.9
40-54	223,781	21.5	16.7	33,683	17.0	9.8	257,464	20.8	15.8

Table 5: Distribution of visits and urine cultures

	Females			Males			Total		
	Total # of visits (N)	% of female visits	% with urine cultures	Total # of visits (N)	% of male visits	% with urine cultures	Total # of visits (N)	% of total visits	% with urine cultures
55-69	167,187	16.1	15.1	43,887	22.1	9.4	211,074	17.0	13.9
70-84	148,046	14.2	13.0	51,256	25.8	8.1	199,302	16.1	11.7
85+	71,303	6.9	9.1	18,228	9.2	6.6	89,531	7.2	8.6
This visit is a potential treatment failure follow-up (within 28 days of a prescription for UTI)									
No	991,303	95.3	15.6	192,846	97.1	9.0	1,184,179	95.6	14.5
Yes	49,303	4.7	17.4	5,748	2.9	11.4	55,051	4.4	16.7
The patient is a long term care resident at the time of the visit									
No	1,005,774	96.7	16.0	189,971	95.7	9.2	1,195,745	96.5	14.9
Yes	34,862	3.4	7.5	8,623	4.3	5.2	43,485	3.5	7.0
Patient has had an antibiotic prescription in the past 6 months									
No	811,225	78.0	16.0	146,851	74.0	9.3	958,076	77.3	15.0
Yes	229,441	22.1	14.5	51,743	26.1	8.4	281,154	22.7	13.4
Diabetes									

Table 5: Distribution of visits and urine cultures

	Females			Males			Total		
	Total # of visits (N)	% of female visits	% with urine cultures	Total # of visits (N)	% of male visits	% with urine cultures	Total # of visits (N)	% of total visits	% with urine cultures
No	941,523	90.5	16.1	163,634	82.4	9.4	1,105,157	89.2	15.1
Yes	99,113	9.5	12.2	34,960	17.6	7.7	134,073	10.8	11.0
In hospital within 30 days of UTI visit									
No	1,034,191	99.4	15.8	194,163	97.8	9.1	1,228,354	99.1	14.7
Yes	6,445	0.6	7.1	4,431	2.2	5.9	10,876	0.9	6.6
Patient-physician familiarity									
Patient has no visits in past 3 years	34,941	3.4	17.2	7,233	3.6	11.8	42,174	3.4	16.2
<=7.3% (median) of patient's visits in past 3 years were with the UTI physician	521,199	50.1	16.2	76,037	38.3	8.9	597,236	48.2	15.3
>7.3% of patient's visits in past 3 years were with UTI physician	484,496	46.6	15.1	115,324	58.1	9.0	599,820	48.4	13.9
Physician sex									

Table 5: Distribution of visits and urine cultures

	Females			Males			Total		
	Total # of visits (N)	% of female visits	% with urine cultures	Total # of visits (N)	% of male visits	% with urine cultures	Total # of visits (N)	% of total visits	% with urine cultures
Female	317,146	30.5	18.7	41,101	20.7	9.8	358,247	28.9	17.7
Male	722,265	69.5	14.3	157,382	79.3	8.8	879,647	71.1	13.4
n missing	1,225			111			1,336		
Physician's UTI volume (number of billed visits) in past 3 months									
Q1, under 13	275,222	26.5	13.7	41,593	20.9	8.1	316,815	25.6	13.0
Q2, 13-24	272,714	26.2	15.2	47,552	23.9	9.7	320,266	25.8	14.4
Q3, 25-45	269,156	25.9	16.5	54,581	27.5	9.4	323,737	26.1	15.3
Q4, 45+	223,544	21.5	17.9	54,868	27.63	8.9	278,412	22.5	16.1
Physician years of clinical experience									
0-5yrs	56,739	5.5	14.6	7,917	4.0	8.1	64,656	5.2	13.9
6-10yrs	99,105	9.5	13.7	16,225	8.2	8.1	115,330	9.3	12.9
11-15yrs	126,017	12.1	14.9	20,422	10.3	8.7	146,439	11.8	14.0
16-20yrs	169,951	16.3	17.6	32,155	16.2	10.1	202,106	16.3	16.4
21-25yrs	177,547	17.1	16.9	35,348	17.8	9.2	212,895	17.2	15.6

Table 5: Distribution of visits and urine cultures

	Females			Males			Total		
	Total # of visits (N)	% of female visits	% with urine cultures	Total # of visits (N)	% of male visits	% with urine cultures	Total # of visits (N)	% of total visits	% with urine cultures
26-30yrs	144,654	13.9	15.0	29,166	14.7	8.6	173,820	14.0	13.9
31-35yrs	134,938	13.0	16.5	27,536	13.9	10.3	162,474	13.1	15.5
36-40yrs	85,072	8.2	15.7	19,536	9.7	9.0	104,355	8.4	14.5
40+yrs	46,613	4.5	11.6	10,542	5.3	6.5	57,155	4.6	10.7
Physician place of medical school									
Canada	685,374	67.2	16.2	132,770	67.9	9.1	818,144	67.4	15.0
International	333,878	32.8	14.6	62,770	32.1	8.8	396,648	32.7	13.7
n missing	21,384			3,054			24,438		
Antibiotic therapy									
Amoxicillin	28,474	2.7	16.8	3,424	1.7	11.3	31,898	2.6	16.3
Cefalexin	16,674	1.6	17.2	2,361	1.2	11.8	19,19,035	1.5	16.5
Ciprofloxacin	239,810	23.0	19.4	34,790	17.5	17.8	275,600	22.2	19.2
Nitrofurantoin	201,633	19.4	21.2	9,416	4.7	14.1	211,049	17.0	20.9
No Rx	382,343	36.7	10.3	127,875	64.4	5.5	510,218	41.2	9.1
Norfloxacin	13,391	1.3	15.3	1,116	0.6	14.6	14,507	1.2	15.2

Table 5: Distribution of visits and urine cultures

	Females			Males			Total		
	Total # of visits (N)	% of female visits	% with urine cultures	Total # of visits (N)	% of male visits	% with urine cultures	Total # of visits (N)	% of total visits	% with urine cultures
Other	21,409	2.1	13.4	5,971	3.0	9.2	27,380	2.2	12.4
TMP-SMX	136,902	13.2	16.2	13,641	6.9	15.4	150,543	12.2	16.1

*Percent of all visits

Model results

Table 6 shows the results of the final models. Among female visits, there was a lower probability of culturing with increasing age: children under 15 years had higher odds of culture compared to adolescents 15-24 years old (adjusted odds ratio (aOR) 1.18, 95% CI 1.14-1.22), while adults 85 years and older had lower odds compared to adolescents (aOR 0.69, 95% CI 0.66-0.71). The same pattern was generally apparent among male patients as well. After accounting for all other variables, visits that were likely the result of prior treatment failure were associated with a decreased probability of culturing among female and male patients. Both male and female long-term care residents were less likely to have a culture submitted than community-dwelling individuals. Recent hospitalization was associated with lower odds of culture among females (aOR 0.73, 95% CI 0.65-0.81), but not among males (aOR 0.96, 95% CI 0.83-1.12). Both females and males with an antibiotic prescription in the past 6 months were less likely to have a culture. We explored whether this last finding was related to prior use of culture subsequently guiding the present treatment plan, but found no strong evidence to support that theory. Including a variable in our models to indicate whether a patient had a previous culture in the past 28 days had no effect on the parameter estimate for recent antibiotic use (results not shown).

Female physicians were significantly more likely to submit a culture for both female and male patients (aOR 1.62, 95 CI 1.32-1.98 for female patients and aOR 1.37, 95% CI 1.15-1.64 for male patients). International medical graduates were less likely than Canadian graduates to submit a culture. Compared to early-career physicians, those with 16-35 years of experience were generally more likely to culture their patients, although the effect was stronger with female patients. Physicians who saw more UTIs in their practice in the 3 months prior to the visit, generally cultured more.

Table 6: Urine culture model results

		Empty model				Model with patient covariates				Model with patient and physician covariates			
		Female patients		Male patients		Female patients		Male patients		Female patients		Male patients	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Intercept		0.01	0.01 - 0.01	0.02	0.02 - 0.02	0.01	0.01 - 0.02	0.03	0.02 - 0.03	0.01	0.01 - 0.01	0.02	0.02 - 0.03
Year of visit (reference: 2005)	**2006**					0.96	0.94 - 0.98	0.92	0.87 - 0.99	0.94	0.92 - 0.97	0.92	0.86 - 0.99
	2007					0.72	0.71 - 0.74	0.56	0.52 - 0.60	0.69	0.67 - 0.71	0.55	0.51 - 0.59
	2008					0.77	0.75 - 0.79	0.59	0.55 - 0.63	0.74	0.72 - 0.76	0.59	0.54 - 0.63
	2009					0.84	0.82 - 0.86	0.62	0.58 - 0.66	0.81	0.78 - 0.84	0.62	0.57 - 0.67
	2010					0.92	0.89 - 0.94	0.68	0.64 - 0.73	0.87	0.84 - 0.90	0.69	0.64 - 0.74
	2011					1.04	1.02 - 1.07	0.71	0.67 - 0.76	1.00	0.97 - 1.04	0.73	0.67 - 0.79
Patient age group (reference: 15-24)	**0-14**					0.98	0.95 - 1.01	1.18	1.07 - 1.29	1.18	1.14 - 1.22	1.32	1.20 - 1.46
	25-39					0.97	0.95 - 0.99	1.02	0.93 - 1.12	0.99	0.97 - 1.01	0.91	0.83 - 1.00
	40-54					0.94	0.92 - 0.96	1.07	0.98 - 1.17	0.95	0.93 - 0.97	0.91	0.83 - 0.99
	55-69					0.92	0.89 - 0.94	1.15	1.05 - 1.25	0.93	0.91 - 0.96	0.95	0.87 - 1.04
	70-84					0.84	0.82 - 0.86	1.12	1.02 - 1.22	0.87	0.84 - 0.89	0.94	0.85 - 1.03
	85+					0.64	0.62 - 0.66	1.01	0.91 - 1.12	0.69	0.66 - 0.71	0.85	0.76 - 0.95

Table 6: Urine culture model results

		Empty model				Model with patient covariates				Model with patient and physician covariates			
		Female patients		Male patients		Female patients		Male patients		Female patients		Male patients	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Follow up visit (within 28 days of a previous UTI treated with antibiotics)	**Yes**					1.08	1.05 - 1.11	1.12	1.02 - 1.24	0.86	0.84 - 0.89	0.67	0.61 - 0.74
Long term care resident	**Yes**					0.45	0.43 - 0.48	0.41	0.36 - 0.46	0.49	0.46 - 0.51	0.45	0.40 - 0.51
Patient has had an antibiotic prescription in the past 6 months	**Yes**					0.85	0.84 - 0.87	0.77	0.74 - 0.80	0.90	0.89 - 0.91	0.82	0.79 - 0.86
Patient was discharged from hospital in the previous 30 days	**Yes**					0.66	0.59 - 0.74	0.91	0.79 - 1.06	0.73	0.65 - 0.81	0.96	0.83 - 1.12
Diabetes	**Yes**					0.91	0.89 - 0.93	0.92	0.87 - 0.97	0.91	0.89 - 0.93	0.92	0.87 - 0.97

Table 6: Urine culture model results

		Empty model				Model with patient covariates				Model with patient and physician covariates			
		Female patients		Male patients		Female patients		Male patients		Female patients		Male patients	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Proportion of patient's visits in last 3 years that were with this physician (reference: >7.3%)	**Patient had no medical visits in the past 3 years**									1.01	0.97 - 1.05	1.09	0.99 - 1.20
	<= 7.3%									1.00	0.98 - 1.02	1.08	1.03 - 1.13
Physician sex (reference: male)	**Female**									1.62	1.32 - 1.98	1.37	1.15 - 1.64
Medical school graduation location (reference: Canada)	**International (outside of Canada)**									0.55	0.44 - 0.69	0.74	0.62 - 0.89
Number of years of clinical experience/years since graduating medical school	**6-10yrs**									1.07	1.02 - 1.13	1.12	0.96 - 1.30

Table 6: Urine culture model results

		Empty model				Model with patient covariates				Model with patient and physician covariates			
		Female patients		Male patients		Female patients		Male patients		Female patients		Male patients	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
	11-15yrs									1.16	1.07 - 1.25	1.10	0.92 - 1.32
	16-20yrs									1.31	1.20 - 1.42	1.19	0.98 - 1.44
	21-25yrs									1.31	1.18 - 1.44	1.20	0.98 - 1.47
	26-30yrs									1.30	1.16 - 1.46	1.18	0.95 - 1.46
	31-35yrs									1.28	1.12 - 1.46	1.31	1.04 - 1.65
	36-40yrs									1.17	1.01 - 1.36	1.14	0.89 - 1.46
	40+yrs									1.20	1.01 - 1.44	0.91	0.68 - 1.22
Physician's UTI volume - number of UTIs seen in the previous 3 months (reference: Q1, <13)	Q2, 13-24									1.07	1.05 - 1.09	1.15	1.08 - 1.23
	Q3, 25-45									1.16	1.13 - 1.19	1.14	1.06 - 1.24
	Q4, 45+									1.15	1.11 - 1.19	1.19	1.09 - 1.31

Table 6: Urine culture model results

		Empty model				Model with patient covariates				Model with patient and physician covariates			
		Female patients		Male patients		Female patients		Male patients		Female patients		Male patients	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Antibiotic prescribed (reference: No antibiotic prescription)	**Amoxicillin**									1.73	1.66 - 1.80	1.87	1.64 - 2.12
	Cefalexin									1.87	1.77 - 1.97	2.11	1.81 - 2.46
	Ciprofloxacin									2.37	2.33 - 2.42	4.35	4.15 - 4.56
	Nitrofurantoin									2.22	2.17 - 2.26	3.11	2.87 - 3.36
	Norfloxacin									2.17	2.03 - 2.31	3.09	2.49 - 3.84
	Other									1.64	1.56 - 1.72	1.86	1.68 - 2.07
	TMPSMX									2.13	2.08 - 2.18	3.62	3.38 - 3.87
Number of observations			1,040,636		198,594		1,040,636		198,594		1,015,911		195,050
Number of patients			468,146		108,969		468,146		108,969		460,419		107,038
Number of doctors			5,752		4,865		5,752		4,865		5,637		4,763
Random intercept variance			11.04		6.09		11.06		6.23		11.01		4.32
Random effect standard error			0.38		0.29		0.39		0.29		0.39		0.20
Median Odds Ratio			23.78		10.52		23.86		10.81		23.68		7.26

Table 6: Urine culture model results

	Empty model				**Model with patient covariates**				**Model with patient and physician covariates**			
	Female patients		**Male patients**		**Female patients**		**Male patients**		**Female patients**		**Male patients**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Intraclass correlation coefficient		0.77		0.65		0.77		0.65		0.77		0.57

Variation across physicians

The intraclass correlation coefficient (ICC) for the female patient model was 0.77, implying that 77% of the total variation in culturing could be accounted for by differences between physicians. Among male patients, the ICC was slightly smaller, but still large, at 57%. The median odds ratio (MOR) was 23.7 among female visits, and 7.3 among male visits. This can be interpreted as indicating that a female patient visiting a higher culturing physician had a median odds 24 times higher of a culture being ordered compared to an otherwise similar female visiting a lower culturing physician. And similarly, a male patient had a median 7 times higher odds of culture when visiting a higher culturing as compared to lower culturing physician.

Sensitivity analyses

Parameter estimates from the model that did not control for HSDA (Table 7) were substantively similar to our original analysis. When we restricted the analysis to the two regions with greatest Lifelabs coverage, there were slightly larger differences in the parameter estimates as compared to the original analysis, although the directions of effects all remained the same. The small differences in magnitude would not lead to different conclusions in general. The random effect variances reflect the expected trend – larger variance with the exclusion of the HSDA control variable, and smaller variance with restriction to a smaller population of physicians.

Table 7: LifeLabs coverage sensitivity analyses

		Without controlling for HSDA				Restricted to VCHA and FHA			
		Female patients		Male patients		Female patients		Male patients	
		OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Intercept		0.01	0.01 - 0.01	0.01	0.01 - 0.01	0.03	0.02 - 0.03	0.03	0.02 - 0.04
Year of visit (reference: 2005)	**2006**	0.94	0.92 - 0.97	0.92	0.86 - 0.99	0.94	0.91 - 0.97	0.91	0.85 - 0.99
	2007	0.69	0.67 - 0.71	0.55	0.51 - 0.59	0.61	0.59 - 0.63	0.49	0.45 - 0.53
	2008	0.74	0.72 - 0.76	0.58	0.54 - 0.63	0.63	0.61 - 0.66	0.51	0.46 - 0.55
	2009	0.81	0.78 - 0.83	0.62	0.57 - 0.67	0.68	0.65 - 0.70	0.52	0.48 - 0.57
	2010	0.87	0.84 - 0.90	0.68	0.63 - 0.74	0.75	0.72 - 0.77	0.59	0.54 - 0.64
	2011	1.00	0.97 - 1.04	0.72	0.66 - 0.78	0.84	0.81 - 0.88	0.61	0.56 - 0.66
Patient age group (reference: 15-24)	**0-14**	1.18	1.15 - 1.22	1.36	1.23 - 1.50	1.19	1.14 - 1.23	1.38	1.24 - 1.54
	25-39	0.99	0.97 - 1.01	0.93	0.85 - 1.03	0.99	0.96 - 1.01	0.94	0.84 - 1.04
	40-54	0.95	0.93 - 0.97	0.93	0.85 - 1.02	0.94	0.92 - 0.97	0.95	0.86 - 1.05
	55-69	0.93	0.91 - 0.96	0.98	0.89 - 1.07	0.92	0.89 - 0.95	0.99	0.89 - 1.09
	70-84	0.87	0.85 - 0.89	0.96	0.88 - 1.05	0.84	0.82 - 0.87	0.96	0.87 - 1.07
	85+	0.69	0.66 - 0.71	0.87	0.78 - 0.97	0.67	0.64 - 0.70	0.88	0.77 - 0.99
Follow up visit (within 28 days of a previous UTI treated with antibiotics)	**Yes**	0.86	0.84 - 0.89	0.67	0.61 - 0.74	0.83	0.80 - 0.86	0.66	0.59 - 0.74

Table 7: LifeLabs coverage sensitivity analyses

		Without controlling for HSDA				Restricted to VCHA and FHA			
		Female patients		Male patients		Female patients		Male patients	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Long term care resident	**Yes**	0.49	0.46 - 0.51	0.45	0.40 - 0.51	0.57	0.54 - 0.61	0.54	0.48 - 0.62
Patient has had an antibiotic prescription in the past 6 months	**Yes**	0.90	0.89 - 0.91	0.82	0.78 - 0.85	0.90	0.88 - 0.91	0.80	0.76 - 0.84
Patient was discharged from hospital in the previous 30 days	**Yes**	0.73	0.65 - 0.81	0.97	0.83 - 1.13	0.70	0.62 - 0.80	0.97	0.81 - 1.15
Diabetes	**Yes**	0.91	0.89 - 0.94	0.92	0.87 - 0.97	0.92	0.89 - 0.94	0.92	0.86 - 0.98
Proportion of patient's visits in last 3 years that were with this physician (reference: >7.3%)	**no visits**	1.01	0.97 - 1.05	1.10	0.99 - 1.21	1.03	0.99 - 1.08	1.08	0.97 - 1.20
	<= 7.3%	1.00	0.98 - 1.02	1.08	1.03 - 1.14	1.05	1.03 - 1.07	1.09	1.03 - 1.15
Physician sex (reference: male)	**Female**	1.62	1.32 – 1.98	1.53	1.26 - 1.87	1.55	1.30 - 1.85	1.49	1.23 - 1.80

Table 7: LifeLabs coverage sensitivity analyses

		Without controlling for HSDA				Restricted to VCHA and FHA			
		Female patients		Male patients		Female patients		Male patients	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Medical school graduation location (reference: Canada)	**International (outside of Canada)**	0.56	0.44 - 0.69	0.65	0.53 - 0.79	0.73	0.60 - 0.88	0.75	0.62 - 0.92
Number of years of clinical experience/years since graduating medical school	**6-10yrs**	1.07	1.05 - 1.13	1.12	0.96 - 1.31	1.00	0.94 - 1.06	1.09	0.92 - 1.29
	11-15yrs	1.16	1.08 - 1.25	1.12	0.93 - 1.35	1.05	0.97 - 1.14	1.10	0.90 - 1.34
	16-20yrs	1.30	1.19 - 1.42	1.24	1.01 - 1.51	1.16	1.06 - 1.28	1.13	0.91 - 1.39
	21-25yrs	1.31	1.18 - 1.44	1.27	1.02 - 1.56	1.19	1.07 - 1.33	1.19	0.96 - 1.49
	26-30yrs	1.30	1.16 - 1.44	1.29	1.03 - 1.62	1.15	1.02 - 1.31	1.16	0.92 - 1.47
	31-35yrs	1.28	1.12 - 1.46	1.48	1.16 - 1.88	1.16	1.00 - 1.33	1.28	1.00 - 1.65
	36-40yrs	1.17	1.01 - 1.36	1.30	1.00 - 1.71	1.03	0.88 - 1.21	1.10	0.84 - 1.45
	40+yrs	1.20	1.01 - 1.43	1.09	0.79 - 1.49	1.12	0.93 - 1.35	0.98	0.71 - 1.35
Physician's UTI volume - number of UTIs seen in the previous 3 months (reference: Q1, <13)	**Q2, 13-24**	1.07	1.05 - 1.09	1.17	1.10 - 1.25	1.06	1.03 - 1.09	1.12	1.03 - 1.21

Table 7: LifeLabs coverage sensitivity analyses

		Without controlling for HSDA				Restricted to VCHA and FHA			
		Female patients		Male patients		Female patients		Male patients	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
	Q3, 25-45	1.16	1.13 - 1.19	1.17	1.09 - 1.27	1.14	1.11 - 1.18	1.12	1.02 - 1.22
	Q4, 45+	1.16	1.12 - 1.20	1.23	1.12 - 1.35	1.11	1.06 - 1.15	1.15	1.03 - 1.28
Antibiotic prescribed (reference: No antibiotic prescription)	**Amoxicillin**	1.73	1.67 - 1.81	1.86	1.63 - 2.11	1.68	1.60 - 1.76	1.74	1.50 - 2.02
	Cefalexin	1.87	1.78 - 1.97	2.1	1.80 - 2.45	1.84	1.74 - 1.95	2.12	1.79 - 2.52
	Ciprofloxacin	2.37	2.33 - 2.42	4.33	4.12 - 4.54	2.39	2.34 - 2.44	4.50	4.26 - 4.75
	Nitrofurantoin	2.22	2.17 - 2.26	3.08	2.85 - 3.33	2.19	2.14 - 2.24	3.12	2.84 - 3.42
	Norfloxacin	2.17	2.03 - 2.31	3.11	2.50 - 3.86	2.04	1.87 - 2.24	3.21	2.41 - 4.26
	Other	1.64	1.56 - 1.73	1.88	1.69 - 2.09	1.62	1.53 - 1.72	1.88	1.66 - 2.12
	TMPSMX	2.13	2.09 - 2.18	3.59	3.36 - 3.84	2.13	2.08 - 2.19	3.70	3.43 – 3.99
N observations			1,018,207		195,429		627,914		128,597
Random intercept variance			11		6.1		6.02		3.56
Random effect standard error			0.39		0.29		0.23		0.19

Costs of urine cultures

The cost of urine cultures performed by LifeLabs was estimated to be approximately $813,716 per year between 2005 and 2011 (Figure 7). Considering that LifeLabs has an approximate 61% share of the outpatient laboratory testing market (estimated from publicly available financial statements; data not shown) (194), it could be extrapolated that the province spends upwards of $1.33 million on urine cultures per year.

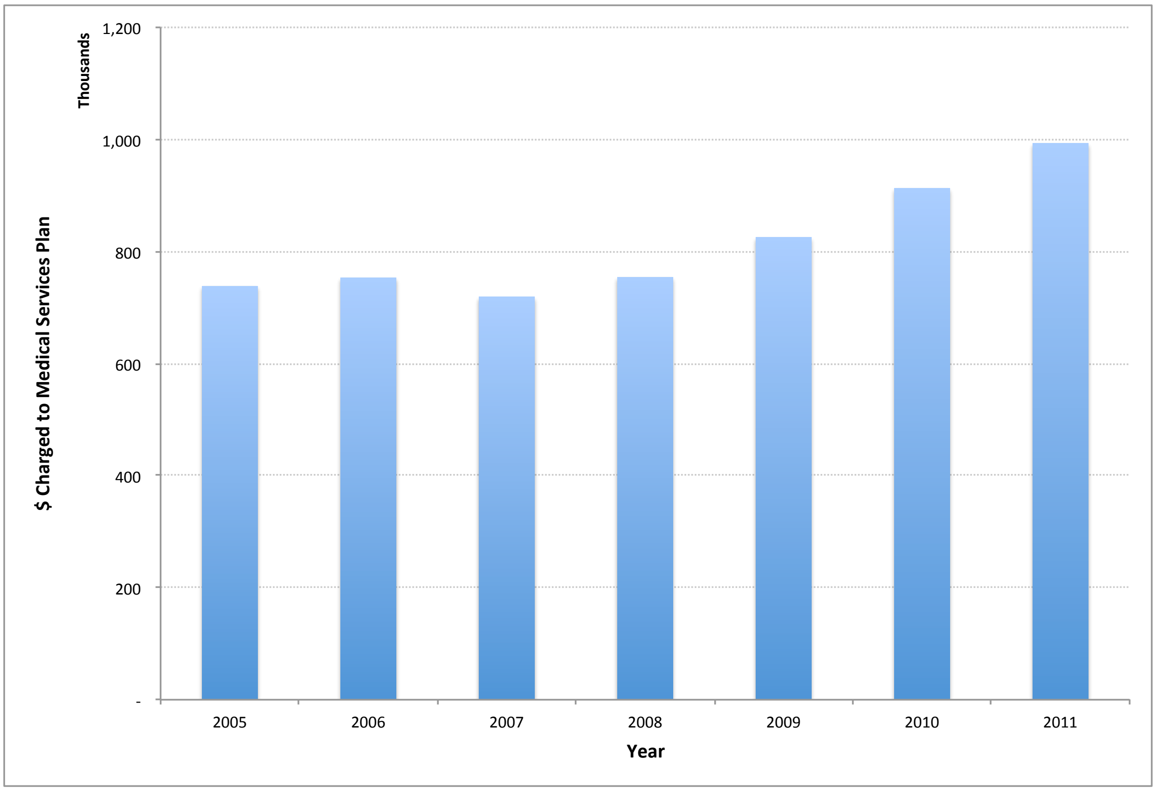

Figure 7: Approximate cost of outpatient urine cultures submitted to LifeLabs, 2005-2011, based on 2017 pricing

Interpretation

Rising antibiotic resistance among uropathogens complicates the treatment of urinary tract infections. Culturing a UTI specimen can facilitate treatment through identification of the organism and susceptibility profile; however, given the stability of organism distribution and predictability of susceptibility probabilities, there is good evidence that there is no clinical advantage from routinely sending urine cultures from suspected uncomplicated cystitis for testing (189,198). Microbiology services support optimal clinical care when used appropriately, and are an essential component of antimicrobial stewardship (199,200). Overuse of culturing in uncomplicated UTI may represent potential system waste. However, in complicated cases, where the distribution of organisms and resistance patterns is less predictable, a urine culture can be important – both in terms of targeting the clinical management of the patient with the goal of reducing symptoms quickly, and for minimizing undue selection pressure for antibiotic resistance. Therefore, encouraging the appropriate balance of use is both a patient care and health system issue. This study found large variations between physicians in their propensity to culture, and these variations were larger than the marginal effect of any of our observed characteristics of patients or physicians.

There are three aspects of these findings worth focusing on here. First, there were several patient-level variables that would be expected to be positively associated with urine culturing, that were in fact negatively associated. Particularly among female patients, this analysis found that recent antibiotic use, a history of diabetes, recent hospitalization, and older patients had lower odds of a urine culture, despite these being indications for culture (181,201,202). This suggests potential underuse of the microbiology resource among those who might benefit, or alternatively, potential overuse among those who likely would not. However, we cannot rule out the possibility that physicians had access to a recent previous culture (for instance, in hospital, or through a different laboratory) that was guiding treatment decisions.

Second, a number of variables at the physician level were independently associated with the probability of a urine culture, which highlights the complexity of clinical decision-making. In principle, a patient's clinical characteristics and medical need would be the only relevant factors in diagnostic and treatment decisions. However, a number of studies have demonstrated differences in physician practice on the basis of the physician's sex (203,204), or years in medical practice and international medical graduation (81), and the results of the present study support the conclusion that there can be differences in practice associated with these characteristics.

Third, and perhaps most importantly, the variations between physicians in the decision to culture a UTI are substantial. A female patient presenting with a UTI to a physician with a higher propensity to culture has a median 20 times the odds of a urine culture compared to a similar patient presenting to a physician with a lower propensity. This has relevant implications for resource use and patient care. Medical practice variations have been documented across a range of procedures and conditions (191,205), and have been explained in terms of clinical uncertainty and varying individual clinical thresholds at which physicians act (206). While the estimated costs are not of the highest magnitude, the results presented here would generally support these explanations.

The implications of these findings on our understanding of community-level resistance rates reported by the laboratory should also be considered. First, I did not find that complicated UTIs appeared to be predictably overrepresented among cultures – suggesting that resistance rates based on these cultures are not systematically over-estimating the level of antibiotic resistance. Second, however, the wide variations in practice between physicians complicates our understanding of resistance rates: we cannot reliably describe the patient population from whom urine cultures – and hence resistance rates – derive. Our understanding of resistance rates in the community should take this limitation of passive surveillance into account.

Policy implications

The scope of variations in urine culturing described here suggests two potential implications: 1) urine cultures are not predictably being used when they apparently should be, and 2) physicians have practice styles that tend towards, or away from, culturing UTIs, over and above basic clinical considerations. Antibiotic stewardship programs aim to support judicious and effective antibiotic use; an important component of this effort is the accurate diagnosis of infection and targeting of treatment. Optimization of resource use is always a concern, but is of particular significance in this era of antibiotic resistance: recommendations to expand the indications for additional urine culturing may be required as the epidemiology of UTIs shifts towards increasingly resistant pathogens. A greater understanding of the factors underlying the observed variations is required in order to promote adherence to (and adaptations as necessary of) recommendations.

A simple audit and feedback intervention showed promising results in reducing antibiotic prescriptions (43). That intervention targeted the top 20% of prescribers with feedback from England's chief medical health officer. A similar intervention could be designed to address the use of cultures for urinary tract infections, adapted to include targeting of both potential over- and under-use of cultures. In British Columbia, family physicians are becoming more active in quality improvement activities. Understanding and reducing variations is one of the key topics of the professional development program for quality improvement, which is offered by the BC Patient Safety & Quality Council (https://bcpsqc.ca/documents/2016/11/Clinician-Quality-Academy-Cohort-2-Brochure.pdf, accessed July 12, 2017). Efforts to address unwarranted variation would therefore appear to have traction within the profession, which will strengthen the possibilities for implementation and action.

A recent study demonstrated that laboratory-based feedback on indications for culturing impacted culturing practices of physicians caring for nursing home residents (V. Leung, personal communication, July 10, 2017). Selective reporting of microbiology results has been shown to influence antibiotic treatment selection (207,208). Combining these ideas, laboratory reports to physicians could be designed to include general feedback about the indication for the specific culture (based on age and sex of the patient, for instance – which might reasonably be available in laboratory data), as well as a reminder of the appropriate indications for cultures in the general population.

Choosing Wisely initiatives aim to improve the quality of healthcare, in particular by reducing overuse of low-value services. Efforts to reduce overuse and underuse of urine cultures could integrate with the evaluation of these initiatives; for example, by following a framework to measure provider attitudes and awareness about the issue, assess unintended consequences of the campaign, and assess patient perceptions and outcomes (209).

In addition, sentinel physician networks – where a cohort of primary care physicians agrees to culture every patient with UTI seen in their practice – may be useful for surveillance of accurate antibiotic resistance rates. Alternatively, regular active surveillance studies may be required. Both of these would be costly endeavours.

Finally, while some reviews have revisited questions of appropriate diagnosis and management of UTI more recently (181,182), British Columbia's clinical practice guidelines have not been updated since 2009 (183). The results of this study suggest that there could be a benefit in re-stating clear and concise guidelines, even if the recommendations remain relatively unchanged.

Limitations

This was an exploratory study, and, to the best of our knowledge, is the first time that privately held outpatient microbiology data on urine cultures has been linked to population-based physician service data. Misclassification bias is an important consideration in our analysis, as LifeLabs is the largest but not the only outpatient laboratory service in the province. The market share is estimated to be approximately 60-62% province-wide, based on publicly available financial statements, during the time frame of this study (194). Non-differential misclassification bias in the outcome generally results in bias toward the null (210). It is unlikely that the presence of LifeLabs clinics, or indeed the compliance of a patient to proceed with sample submission, would differ systematically by the factors included in this analysis, other than geographic region. It can be expected that a patient will present for sampling at the closest clinic. As such, HSDA was included as a covariate in the models in an attempt to control for some of the coverage variability; however, the effect estimates for HSDA are potentially biased and should not be directly interpreted (and as such, are not reported in the table). The sensitivity analyses demonstrated some minor changes in parameter estimates, but nothing that would alter the overall conclusions.

Patient variability was not modeled. Around half of individuals had more than one UTI visit during the study period. However, the complex structure of the data precluded the inclusion of both a physician and a patient random effect (i.e. the models did not converge). Patient visits are not nested within physicians. Therefore, any attempt to handle this would necessarily mean a manipulation of the data (e.g. forcing the nesting of the patients within physicians). As another sensitivity analysis, one visit per person was randomly selected, thereby removing patient-level variability (as in the method in Chapter 3), and the results were substantively the same (results not shown).

The reason for the decrease in urine cultures in 2007 is unclear; no relevant change in policy or guidelines could be identified.

Finally, the cost estimates should be interpreted as a general estimate only. Using current fees to estimate past costs is not ideal, but more accurate information was not available to us for this analysis. Having a general sense of the costs helps with the overall interpretation of the variation findings, but accurate cost estimates were not the primary goal of the study.

Conclusion

This analysis suggests that physicians have highly variable tendencies to culture UTIs, and the appropriate and efficient use of urine cultures can likely be improved. Further research is necessary to confirm these exploratory findings. However, effort directed towards both promoting the use of urine cultures in relevant cases, and restricting their use when not required, would not be misplaced. This effort could involve targeted audit and feedback to primary care providers and alignment with Choosing Wisely initiatives.

Chapter 5: Conclusion

Relevance of this work

Antibiotic resistance poses a significant public health threat. Antibiotic stewardship programs have made some progress in reducing the amounts of antibiotics consumed in human medicine, but resistance continues to spread and further sustained effort is required. The goal of the research presented in this thesis has been to improve our understanding of the factors involved in the process of selecting antibiotics for common community-based infections, and of the variations between physicians in these practices.

Using rigorous methods, including systematic review of the literature, and generalized linear mixed models of population-level data, this thesis contributes new knowledge that contributes to achieving this goal. This is a timely topic, as antibiotic stewardship is increasingly being recognized as a necessary and integrated component of the health care system; the World Health Assembly recently endorsed a global action plan on antimicrobial resistance, which, among others, called on all member states to enact a national action plan by May, 2017 (25). As another example, Accreditation Canada added antimicrobial stewardship as a Required Organizational Practice in 2013 (211). The results of the research presented here will be useful to those tasked with developing and refining programs to slow the advance of antibiotic resistance.

In this concluding chapter, I review the objectives of this thesis, and summarize my findings. I discuss the strengths and limitations of the research, and then explore the potential implications of the results.

Objective 1: to identify factors associated with antibiotic use for respiratory tract infections and urine culture ordering for urinary tract infections

Patient factors

Both of the analytic studies presented in this thesis identified a measure of the patient's familiarity with the physician to be an important factor. Specifically, patients for whom fewer of their GP visits over the past 3 years had been with the current physician were more likely to receive an antibiotic for RTI, and more likely to have a urine culture for UTI. In both cases, patients who had not seen a GP in the prior 3 years were even more likely to receive the intervention. These findings can be considered in the context of discussions of continuity of care, and the benefits that arise from a consistent relationship between physician and patient (212) – it appears as though having some form of continuity between patient and provider is associated with less intervention, which could be related to increased confidence on the part of the provider who has past experience with a particular patient, or to easier communication between the patient-provider dyad.

Having had an antibiotic prescription in the past 6 months was associated, in both of the analyses, with a lower likelihood of the intervention. A recent antibiotic prescription has been shown to be a risk factor for resistance (213,214), and as such is an indication for culturing in UTI (181). The finding with respect to lower likelihood of urine culture in patients with recent antibiotic use is therefore surprising, or at least inconsistent with recommendations.

Previous research has also documented that diagnostic uncertainty can be related to the misuse, and in particular, overuse, of antibiotics (107,125,126). In the review of the literature, physical examination findings (such as fever, purulent sputum or nasal discharge, abnormal respiratory exam, tonsillar exudate, abnormal tympanic membrane) were generally associated with a higher likelihood of antibiotic prescribing for RTI. This may be due to increased diagnostic uncertainty that can arise from these findings. While there is no clear sign or symptom that distinguishes a bacterial from a viral infection, some findings may increase concern about an underlying bacterial cause. However, in the area of URI, guidelines recommend confirmation of bacterial infection before initiating antibiotic treatment in most cases (100-102).

Physician factors

A number of physician factors were associated with antibiotic prescribing and urine culture ordering. There was an increasing trend towards prescribing antibiotics with more clinical experience. A recent study of antibiotic prescribing for RTI in patients over age 65 reported a similar finding (215). This trend was also apparent in the analysis of urine culturing, although not as strong, and it peaked at 31-35 years of experience. Finally, international medical school graduates were more likely to prescribe antibiotics, and less likely to submit urine cultures. The Silverman study also found that graduates of medical schools outside of North America had higher rates of antibiotic prescribing (215)

Patient-physician communication was also highlighted in the review as an important element in antibiotic prescribing decisions. Physician perception of patient expectations for antibiotics – rather than explicit patient expectation – was a relevant factor. This consistent finding raises important considerations about equipping prescribers with useful communication tools to elicit and discuss patient expectations, with the aim of reducing unnecessary prescriptions. Supporting good patient-provider communication and overall relationship is an important aspect of quality care provision (216). Education campaigns targeted to the public address the goal of reducing patient desire for antibiotic treatment.

Regional factors

These studies found differences in antibiotic prescribing between regions; however, the regional variables that were included did not account for a large proportion of the physician-level variation. In the RTI study, a set of specific population-based indicators was explored to determine the extent to which they accounted significantly for the regional-level variation in the models, but they generally did not. In the UTI study, Health Service Delivery Area was confounded with the outcome because of incomplete coverage of LifeLabs services around the province, thereby limiting statistical inference about the influence of regional-level factors.

Regional differences in antibiotic use have been reported previously. Research has explored cultural (217), country-level worldviews (218), climatic (130), and other (e.g. 218) influences on regional differences in antibiotic use. The research described in this thesis found a significantly higher chance of prescribing antibiotics for RTIs in the northern region of the province, which is characterized by rural and remote communities and few urban centres. While foreign-trained doctors are often recruited to these more remote regions, our models controlled for place of training. The north also has a higher relative proportion of first nations population than other regions, which has previously been correlated with higher antibiotic prescribing (130). The analyses presented here did not include this variable; as such, future research may need to explore this relationship in greater detail – i.e. to tease apart regional, cultural, and health service delivery effects. Our findings, although modest, reinforce that due consideration should be given to the contexts of health service delivery and practice logistics in different regions.

Objective 2: to explore the extent of variations related to physician practice styles

This thesis found evidence for substantial variation between physicians in practice style. The extent of variations was larger when it came to culturing for UTI than for antibiotic prescribing. Variations have been documented across a range of conditions and procedures (191), and so, to some extent, the findings presented here are not surprising. In fact, these findings reinforce what has been demonstrated in subsets of populations (123,124). The analyses presented in this thesis are novel in that large, population-based datasets spanning several years were employed, and indicators of healthcare usage and of physician's clinical practice were used that have not, to the best of our knowledge, been previously reported. In the RTI study, I found that nearly one-fifth of the variation in prescribing attributable to physicians could be explained by the observed patient and physician factors. In the UTI study, I found that between 57 and 77% of the variation in culture orders attributable to physicians could be explained by these factors.

Overall, observed physician-level factors had more of an effect on the variations in outcomes between physicians, than did patient factors, even after attempts to fully mitigate the impact of accessibility to services. This suggests that differences in patient composition – such as comorbidities, age, and health service use behaviour – do not explain differences in physician management of infections as well as physician characteristics do.

Strengths and limitations of this research

One of the most important strengths of this research is the large-scale, population-based administrative data we used for analyses. The use of administrative data for health services research has many advantages (219), including reduced cost for access to population-level, longitudinal data. The ability to observe an entire population precludes the need to adjust statistics for sampling variability. Additionally, these data lend themselves well to studies aiming to understand multiple levels of influence on an outcome (220,221) – the unit of analysis can differ from the unit of input variables, and appropriate analytic methods, like those employed herein, are available to handle this. We explored different ways of describing and investigating physician variation.

Important limitations must also be considered. First, one of the disadvantages of using administrative data for research is the reliance on variables collected independently of the research study, which can lead to missing data, inaccurate data, or unavailable data (222). In the studies presented here, data were missing in particular for physician demographics.

Second, the analytic cohorts were limited to patients with diagnoses of RTI and UTI, respectively, occurring in the MSP data. These diagnoses depend on physician coding (223). In these studies, potential misclassification of diagnosis was addressed by using an inclusive subset of RTI codes (138) and limiting the UTI cohort to diagnoses of cystitis.

Another limitation of this project is the incomplete outcome ascertainment in the UTI study due to the use of a private laboratory's urine culture data, which does not cover 100% of the population. However, other than geographically, I assume there is no systematic bias in coverage. I addressed this limitation by exploring sensitivity analyses (first, by assessing the impact of the geographic region variable on the estimated model parameters by running the model without this variable; and second, by restricting the analysis to the two health authorities with the greatest coverage, and comparing the estimated model parameters), which generally showed there was not a significant impact on the substantive conclusions of the original analysis, despite some differences in parameter estimates.

Due to the complexity of the data structure, it was not possible to simultaneously model patient-level and physician-level variation. Patient visits were not nested within physicians, as patients may see different physicians over time. While statistical models are available that can technically handle this situation (224), in practice the models would not converge in available statistical software. I approached this in different ways in the two analyses: in the RTI study, I randomly selected one visit per person, to eliminate the patient level variability; in the UTI study, I included all visits, and assumed the patient-level covariates adequately controlled for patient variability.

I had originally intended to use the systematic review to guide the selection of factors to include in the subsequent analyses. I actively aimed to identify factors at the levels of patient, physician, and region, in accordance with multilevel explorations of the production of behaviours (221,225-229). However, the review of the literature identified mostly patient-level factors, which were based primarily on the clinical examination. These factors cannot be ascertained from administrative data, and full clinical records are not available for linkage at this time due to the number of electronic medical health record systems in use around the province. Thus, the factors selected for the subsequent studies were based on known determinants, identified gaps, and theoretical reasoning. I note that the inability to include the patient's clinical presentation factors is a limitation of the analyses, and of analyses of administrative data in general.

Implications and recommendations

Variations in medical care have been documented between regions (230), practices (122), and physicians (231), and across a variety of diagnoses and procedures (191). A significant goal in health policy is to reduce the amount of unwarranted variation, in an effort to ensure a consistent standard of quality of care is provided to everyone. While it is important to appreciate that some degree of variation is inevitable, and likely desirable, as it represents the human and social nature of medical care interactions, the challenge lies in determining the extent of excess, or unnecessary, variations; and, of course, in defining the best approach for intervening on those variations. The research described in this thesis has the potential to contribute to the goal of reducing unwarranted variation in the management of common infections.

Intervention design

The behaviour change wheel is a framework that has been developed to assist the planning of effective interventions based on a model of behaviour (232). The framework centres on a 'behaviour system' comprising three primary components (capability, opportunity, and motivation) that interact to influence behaviour. These components are further subdivided into physical and psychological capability, physical and social opportunity, and reflective and automatic motivation (232). Considering these influences on behaviour can help to identify the specific target for a behaviour change intervention. The framework then identifies 9 intervention types (education, persuasion, incentivisation, coercion, training, restriction, environmental restructuring, modeling, and enablement) and 7 policy approaches (communication/marketing, guidelines, fiscal, regulation, legislation, environmental/social planning, and service provision) for effecting clinician behaviour change (232). This is a useful framework for considering the techniques available and their links with elements of behaviour change theories.

Antibiotic stewardship directions

The results presented in this thesis can help guide efforts to target effective intervention efforts towards physicians who have higher likelihoods of potentially inappropriate practice, and as such, greater room for improvement. Intervention research often focuses – not un-intuitively – on the premise that behaviour change is greatest where there is the most room for gain (43,233). From this perspective, identifying physicians who have been practicing for longer as demonstrating more potential overuse of resources offers a group to focus on.

Both reflective and automatic cognitive processes can be involved in clinical behaviours (234), and these are considered sources of behaviour motivation in the Behaviour Change Wheel framework (232). While reflective processes are often addressed by educational and other interventions, the automated or habitual processes are often not explicitly addressed (235). This may be pertinent in understanding why physicians with more experience have a greater tendency to prescribe antibiotics, or why some physicians have lower thresholds for prescribing, ordering tests, or making other medical decisions (206,236). The role of automated cognitive processing may also help to explain why higher recent volume of RTI-specific management is associated with lower prescribing; previous experience, and the accessibility of that experience, might prime decision-making in favour of more rational antibiotic use if those experiences suggest that RTIs are common and self-limiting conditions, thus increasing confidence in symptomatic management. Interventions that explicitly address automatic cognitive processes, such as persuasion, incentivisation, coercion, environmental restructuring, modeling, and enablement, may be more effective in changing these aspects of behaviour (232).

Feedback interventions aiming to engage clinicians in critical thinking about their clinical practice have demonstrated promising, although nuanced, results (43,237,238). Interventions such as audit and feedback, using the techniques of persuasion and modeling, are supported by the behaviour change wheel model and may be best targeted at groups of physicians with higher likelihoods of inappropriate or unnecessary resource use. The data presented in this thesis also suggests that routinely collected dispensing data can be vital for identifying such physicians.

While these findings suggest some possible targets for physician-directed interventions, the large observed variations also suggest that further consideration of the role of administrative levers to nudge use of resources in a more appropriate direction may be required. The challenge is balancing physician autonomy, and clinical expertise, with patient preferences, and socially responsible resource use (239). A stronger emphasis on social contexts of clinical behaviour has been advocated for understanding and intervening upon the determinants of medical practice variations (240). Our finding of significant regional-level variation in physician management of URI and UTI, even after accounting for physician and patient characteristics, is consistent with there being important contextual effects on physician behaviour, adding further support to this recommendation. While potentially more relevant in hospitals and other team-based clinical practices, social norms, and ‘prescribing etiquette’ are shown to impact clinical decisions (241-243). Efforts to actively shift social norms may be applicable to improving prescribing (43), and may ultimately help to embed the underlying determinants of practice into the collective system (244,245).

While RTIs and UTIs are common illnesses, individual physicians see such a variety of presenting complaints that the distribution of RTIs and UTIs becomes somewhat diluted. In the context of these visits comprising but a portion of a physician’s weekly workload, it is relevant to consider broader movements to reduce overuse and underuse of medical care (45,246). Reducing overuse in medical care has been called “the next quality frontier” by Donald Berwick (247). While interventions related to antibiotic prescribing frequently invoke the societal harm of antibiotic resistance as justification for required action, this may not be a necessary approach – at least in terms of presentation to primary care physicians. Rather, framing rational antibiotic prescribing in the same terms as most other prescribing interventions – a balance of the benefits and harms to the patient of treatment and no treatment, and erring on the side of less intervention where benefit is equivocal – should support the same goals in antibiotic stewardship. The growing significant threat of antibiotic resistance is certainly a compelling reason for action in this area, but the messages are ultimately in alignment with the broader goal of achieving reductions in overuse (and underuse) of medical care.

Future research

Overall, our results suggest that, while we may identify specific characteristics of physicians that could be worthwhile targets for focused interventions, more work is needed to understand the implications of the large observed variations in practice. To extend the usefulness of these results, future work should address the following objectives:

1) Further exploration of the reasons underlying variations in practice to determine, not just the extent of variations, but the processes through which variations manifest. This could be approached with a qualitative study of a sample of physicians with both high and low propensity to prescribe, and to order cultures, enabling a comparison of themes within and across these categories (high and low, antibiotic prescribing and culture ordering).
2) Exploration of the hypothesis that automatic cognitive processing is playing a competing role in infection management decisions, and possibly overpowering the rational thought stream in some situations. Experimental study designs would be best able to assess differences in cognitive processing and the impact on decision-making.

3) Further exploration of ways of understanding physician practice. For instance, recent work has been able to classify general practitioners into high responsibility, mixed practice, and low responsibility practice patterns, based on interactions with their patients (in terms of referral to specialists, prescribing, screening, oversight, and repeat visits) (205). Applying this classification to understanding antibiotic prescribing and urine culturing practices may yield new insights.
4) Simultaneous investigation of patient and physician variations in outcomes. Future studies could explore different ways of handling the data complexity, with a specific goal of assessing the contribution of between-patient variability in infection management outcomes. Administrative data is well suited for this, but further collaboration with statisticians to explore the best approaches to modeling is required.
5) Assessment of the components of interventions effective at reducing variations on a large scale. Targeting specific physician groups may improve "mean" infection management decisions, but an understanding of the effects of different approaches on reducing variations between physicians is also required. A careful randomized large-scale implementation of a policy intervention would allow for the study of effects on variations between physicians.
6) Investigation of the long-term sustainability of intervention effects. Randomized implementation of interventions can be evaluated with interrupted time series designs.
7) As personalized feedback appears to be effective in some circumstances, further work should explore the ways in which this could be implemented on a large scale in an ongoing, sustainable manner. Integrating feedback into the prescribing and test ordering process may reap more significant benefits.
8) Finally, rigorous evaluation of intervention efforts should be a mandatory part of any intervention design. As noted above, the careful planning of randomized interventions allows for high-quality evaluation.

Concluding remarks

The research described here has explored factors and variations associated with aspects of prescribing and test ordering in primary care. This research has found significant variations in practice, that remain even after controlling for a number of relevant demographic and other variables at the levels of patient and practitioner. These findings have implications for the design and implementation of effective antibiotic stewardship programs. Antibiotic resistance is a complex clinical and public health problem, and effort must be applied to continue to work to find appropriate solutions. Improving the practice patterns of physicians is one important way to address the issue. It is my hope that the research presented here will contribute to the ultimate goal of improving the judicious use of antibiotics and slowing the rise of antibiotic resistance, for the benefit of generations to come.

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Appendices

Appendix A: search strategy for systematic review

	Medline		Embase		International Phrmaceutical Abstracts
	Search terms	**Keywords**	**Search terms**	**Keywords**	**Keywords**
Cluster 1: Antibiotic	Antibacterial agents (explode)	antibiotic*	Antibiotic agent	antibiotic*	antibiotic*
Cluster 2: Community		community	Outpatient	outpatient	outpatient*
	Outpatients	outpatient	Outpatient care	ambulatory*	ambulatory care
	Ambulatory care	ambulatory	Primary health care	primary health care	primary health care
	Primary Health Care	primary health care	Ambulatory care	community	community
		Non-hospitalized		Non-hospitalized	Non-hospitalized
Cluster 3: Appropriateness	Guideline Adherence	inappropriate prescri*	Practice guideline	inappropriate prescri*	inappropriate prescri*
	Inappropriate prescribing	unjustified	Inappropriate prescribing	unjustified	practice guideline
	Clinical competence	variation*	clinical competence	variation*	unjustified
	Quality of health care		health care quality		variation*

	Medline		Embase		International Phrmaceutical Abstracts
	Search terms	**Keywords**	**Search terms**	**Keywords**	**Keywords**
Cluster 4: Prescribing	Drug Utilization	Drug prescri*	Prescription		drug prescri*
	Physician Practice Patterns	antibiotic prescri*	Clinical practice	prescri*	antibiotic prescri*
	Drug prescriptions		drug utilization		
Cluster 5: Factors	Risk Factors	risk factor*	Risk factor	risk factor	risk factor*
	Geography	geography	virus infection	geography	geography
	Demography	demography	geography	demography	demography
	Social class	social class	demography	social class	social class
	Patients	sociodemographic	geographic distribution	sociodemographic	sociodemographic
	Specialization	specialization	social class	specialization	specialization
		International medical graduate*		International medical graduate*	International medical graduate*
	Foreign medical graduates	foreign medical graduate*	patient	foreign medical graduate*	foreign medical graduate*
	Respiratory tract infections	respiratory infection*	foreign worker	respiratory infection*	respiratory infection*

	Medline		Embase		International Phrmaceutical Abstracts
	Search terms	**Keywords**	**Search terms**	**Keywords**	**Keywords**
	Urinary tract infections	urinary tract infection*	specialization	urinary tract infection*	urinary tract infection*
	Seasons	season*	respiratory tract infection	season*	season*
	Virus Diseases	vir* disease	urinary tract infection	vir* disease	vir* disease
	Bacterial Infections	vir* illness	season	vir* illness	vir* illness
		vir* infection*	bacterial infection	vir* infection*	vir* infection*
		bacteria* disease		bacteria* disease	bacteria* disease
		bacteria* infection*		bacteria* infection*	bacteria* infection*
		bacteria* illness		bacteria* illness	bacteria* illness
		predictor*		predictor*	predictor*
		determinant*		determinant*	determinant*
		contributing factor*		contributing factor*	contributing factor*

The search strategy combined search terms and keywords within each cluster with “OR”, and combined the results across clusters with “AND”.

Appendix B: full list of factors identified on systematic review

Factor	No. studies with positive association	No. studies with negative association	No. studies without significant association	Total number of studies
Patient age*	6	--	13	19
Patient sex	1	--	9	10
Comorbidity	2	--	7	9
Patient medical insurance type*	1	--	7	8
Physician specialty*	6	--	2	8
Geographic location*	1	--	6	7
Ethnicity*	1	--	6	7
Rural vs. urban	3	--	4	7
Black vs. white	--	1	5	6
Fever	5	--	1	6
Physician perception of desire for antibiotics	6	--	--	6
Bronchitis	5	--	--	5
Purulent sputum	5	--	--	5

Factor	No. studies with positive association	No. studies with negative association	No. studies without significant association	Total number of studies
Respiratory physical exam findings	5	--	--	5
Patient desire for antibiotics	3	--	1	4
Severity of illness	4	--	--	4
Smoker	3	--	1	4
Year of visit	--	--	4	4
Cough	1	--	2	3
Duration of illness	1	--	2	3
High volume practice	1	--	2	3
Household income	--	1	2	3
International medical graduate	2	1	--	3
Pharyngitis	3	--	--	3
Rhinorrhea	--	2	1	3
Sinus pain on exam	3	--	--	3

Factor	No. studies with positive association	No. studies with negative association	No. studies without significant association	Total number of studies
Tonsillar exudate	3	--	--	3
Tympanic membrane abnormality	3	--	--	3
Visit location (office, ED, hospital clinic)*	1	--	2	3
Ear drainage/ear pain	1	--	1	2
Increased provider age	1	--	1	2
Influenza	--	1	1	2
Lymphadenopathy	2	--	--	2
Nasopharyngitis	--	1	1	2
Physician is the primary care provider for the patient	1	--	1	2
Purulent nasal discharge	2	--	--	2
Resident vs staff	--	2		2
Shortness of breath	1	--	1	2
Sore throat	--	--	2	2

Factor	No. studies with positive association	No. studies with negative association	No. studies without significant association	Total number of studies
Wheezing	--	1	1	2
Acute otitis media	1	--	--	1
Before vs after CDC guidelines for antibiotic prescribing	1	--	--	1
Chest pain	1	--	--	1
Chest x-ray performed	--	--	1	1
Congestion	--	1	--	1
Daycare attendance	--	--	1	1
Diarrhea	--	1	--	1
Fatigue	--	--	1	1
Fee for service	--	--	1	1
Follow up	--	--	1	1
Headache	1	--	--	1
High risk patient as determined by physician	--	--	1	1

Factor	No. studies with positive association	No. studies with negative association	No. studies without significant association	Total number of studies
Increased years in practice	1	--	--	1
Laryngitis	--	1	--	1
Less time taken at visit	--	--	1	1
Loss of appetitie	--	--	1	1
Lower respiratory tract infection	1	--	--	1
Mean number of physician home visits	--	--	1	1
More educated patient	--	1	--	1
Myalgias	--	--	1	1
Number of patients in GP's practice with fever	1	--	--	1
Parents born abroad	1	--	--	1
Patient asking for antibiotics	--	--	1	1
Patient missed work	--	--	1	1
Patient taking supportive	--	--	1	1

Factor	**No. studies with positive association**	**No. studies with negative association**	**No. studies without significant association**	**Total number of studies**
medications				
Perceived parental concern about child's current illness	1	--	--	1
Percussion dullness	--	--	1	1
Periorbital edema	--	--	1	1
Physcian score on infectious diseases component of licencing exam	--	--	1	1
Physician clinical exams score female physician	--	1	--	1
Physician clinical exams score male physician	1	--	--	1
Physician works part time	--	--	1	1
Previous antibiotics for similar illness	--	--	1	1
Referral	--	1	--	1

Factor	No. studies with positive association	No. studies with negative association	No. studies without significant association	Total number of studies
Severity of illness in other patients within the GP practice	--	1	--	1
Signs of inflammation	1	--	--	1
Solo practice	--	--	1	1
Spirometer in office	--	1	--	1
Staff at nonteaching hospital vs teaching hospital	1	--	--	1
Time of year	--	1	--	1

* denotes categorical variable with different possible reference groups, and therefore the direction of effect is not always comparable. We have categorized any study that found a statistically significant association in one direction as a positive association for illustrative purposes.