Antimicrobial resistance in urinary *Escherichia coli* in Quebec, Canada

Jean-Paul R. Soucy

Department of Epidemiology, Biostatistics and Occupational Health
McGill University, Montréal

August, 2018

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

Abstract

Background: Urinary tract infections caused by the bacteria *Escherichia coli* are among the most common infections in the world. Resistance to the antimicrobials used to treat these infections is a growing concern. Given the lack of new drug development, it is critically important to understand the factors underlying patterns of antimicrobial resistance.

Methods: The individual-level predictors of resistance to six antimicrobials (ampicillin, gentamicin, ciprofloxacin, nitrofurantoin, trimethoprim/sulfamethoxazole, tobramycin) were investigated in community-acquired and nosocomial urinary *E. coli* isolates from three cities in the province of Quebec, Canada between April 2010 and December 2017. Hierarchical logistic regression models were used to account for correlations among the six types of resistance. We employed time series analysis in the form of dynamic linear models to explore the temporal association between oral fluoroquinolone use and ciprofloxacin resistance in isolates from the city of Montreal. Fluoroquinolone use in Montreal was estimated using a 25% sample of individuals insured under the public drug prescription plan up to December 2014.

Results: Both community-acquired and nosocomial isolates showed geographic variability in the prevalence of resistance. Male sex and recent hospitalization were predictors of increased resistance for most types of resistance; additionally, ciprofloxacin resistance increased sharply with age. Distinct seasonal patterns were noted for community-acquired and nosocomial infections, and resistance in the community setting has been rising since 2015. In Montreal, we found a positive correlation between total fluoroquinolone use lagged by 1 and 2 months and the monthly proportion of isolates resistant to ciprofloxacin.

Conclusions: These results demonstrate that hierarchical modelling of the prevalence of, and risk factors for, many types of antimicrobial resistance allows general and region-specific inference, which may inform empirical therapy. The observed correlation between fluoroquinolone use and ciprofloxacin resistance supports the rationale for antimicrobial stewardship campaigns to reduce fluoroquinolone prescriptions in the community setting.

Résumé

Contexte : Les infections urinaires causées par la bactérie *Escherichia coli* figurent parmi les infections les plus fréquentes au monde. La résistance aux antimicrobiens utilisés pour traiter ces infections est devenue une préoccupation croissante. Étant donné l'absence de mise au point de nouveaux médicaments, il est essentiel de comprendre les tendances sous-jacentes de la résistance aux antimicrobiens.

Méthode : Les prédicteurs individuels de la résistance à six antimicrobiens (ampicilline, gentamicine, ciprofloxacine, nitrofurantoïne, triméthoprime-sulfaméthoxazole, tobramycine) ont été étudiés à partir d'isolats d'*E. coli* associés à des infections urinaires nosocomiales et communautaires dans trois villes de la province de Québec, au Canada, entre avril 2010 et décembre 2017. Des modèles de régression logistique hiérarchique ont été utilisés pour expliquer les corrélations entre les six types de résistance. Nous avons utilisé l'analyse de séries temporelles sous la forme de modèles linéaires dynamiques pour explorer l'association temporelle entre l'utilisation des fluoroquinolones par voie orale et la résistance à la ciprofloxacine dans des isolats obtenus à Montréal. L'utilisation des fluoroquinolones à Montréal a été estimée en utilisant un échantillon correspondant à 25 % des personnes couvertes par le régime provincial d'assurance médicaments jusqu'en décembre 2014.

Résultats : Les isolats d'origine communautaire et les isolats d'origine nosocomiale ont démontré la variabilité géographique de la prévalence de la résistance. Le sexe masculin et l'hospitalisation récente étaient des facteurs de risque pour la plupart des types de résistance; de plus, la résistance à la ciprofloxacine augmentait fortement avec l'âge. Des tendances saisonnières distinctes ont été observées pour les infections nosocomiales et les infections communautaires. En outre, la résistance en milieu communautaire a augmenté depuis 2015. À Montréal, nous avons trouvé une corrélation positive entre l'utilisation totale de fluoroquinolones et la proportion mensuelle d'isolats résistants à la ciprofloxacine de 1 à 2 mois plus tard.

Conclusions : Ces résultats démontrent que l'emploi de modèles hiérarchiques de la prévalence et des facteurs de risque de nombreux types de résistance aux antimicrobiens permet de tirer des conclusions tant générales que spécifiques d'une région. Une telle démarche pourrait éclairer la prise de décision concernant le traitement empirique. La corrélation observée entre l'utilisation des fluoroquinolones et la résistance à la ciprofloxacine fournit la justification des campagnes de gestion des antimicrobiens qui visent à réduire les ordonnances de fluoroquinolones en milieu communautaire.

Preface

In this thesis, I investigate the extent to which individual-level and population-level factors explain variability in the prevalence of antimicrobial resistance in urinary *E. coli* isolates in the province of Quebec, Canada. First, I give a rationale for this research and outline the two main objectives of the thesis (Chapter 1). Chapter 2 introduces the topics of urinary tract infections and antimicrobial resistance. A summary of the epidemiological and clinical literature on risk factors for antimicrobial resistance in urinary *E. coli* isolates is given, as well as an overview of antimicrobial consumption in Canada and its connection to variation in the prevalence of antimicrobial resistance. Chapter 3 describes the study methodology, including study location, population, and rationale for the statistical analyses. The results are presented in the form of two manuscripts in Chapter 4. Finally, the results are discussed in Chapter 5, with concluding remarks in Chapter 6. References are provided in Chapter 7.

This thesis has been prepared according to the guidelines for a “Manuscript-Based Thesis”. The results are given in two manuscripts:

Jean-Paul R. Soucy, Alexandra M. Schmidt, Charles Frenette, Patrick Dolcé, Alexandre A. Boudreault, David L. Buckeridge, Caroline Quach. Joint modelling of resistance to six antimicrobials in urinary *Escherichia coli* isolates in Quebec, Canada.

Jean-Paul R. Soucy, Alexandra M. Schmidt, Caroline Quach, David L. Buckeridge. Fluoroquinolone use explains seasonal patterns in ciprofloxacin resistance in community-acquired urinary *Escherichia coli*: A dynamic linear model in a large urban community.

Contribution of Authors

The original research ideas were conceived by Dr. David L. Buckeridge, Dr. Caroline Quach, and Jean-Paul R. Soucy. The study designs were conceived by Dr. Alexandra M. Schmidt, Dr. David L. Buckeridge, Dr. Caroline Quach, and Jean-Paul R. Soucy. Jean-Paul R. Soucy wrote the protocol for ethics approval, with input and revisions from Dr. Caroline Quach and Dr. David L. Buckeridge. Dr. Charles Frenette, Dr. Patrick Dolcé, and Dr. Alexandre A. Boudreault assisted with acquisition of the antimicrobial resistance data from their respective institutions.

All non-manuscript chapters of this thesis were written by Jean-Paul R. Soucy and critically reviewed and revised by Dr. David L. Buckeridge, Dr. Caroline Quach, and Dr. Alexandra Schmidt.

The first manuscript (Chapter 4.2) was written by Jean-Paul R. Soucy and critically reviewed and revised by all aforementioned individuals.

The second manuscript (Chapter 4.3) was written by Jean-Paul R. Soucy and critically reviewed and revised by Dr. David L. Buckeridge, Dr. Caroline Quach, and Dr. Alexandra Schmidt.

Hélène Soucy a contribué à la révision du résumé en français.

Acknowledgements

Financial support for my studies has been provided through a Frederick Banting and Charles Best Canada Graduate Scholarship from the Canadian Institutes of Health Research, a Max. E. Binz Fellowship from the McGill University Faculty of Medicine, and stipend support from Dr. David Buckeridge. I would like to extend my sincere gratitude to my supervisor and these organizations for making this thesis possible.

First and foremost, I would like to thank my supervisor, Dr. David Buckeridge, my co-supervisor, Dr. Caroline Quach, and my committee member, Dr. Alexandra Schmidt, for their unwavering commitment and support not only on this project but also to my development as a young scholar. I am grateful to the members of the Surveillance Lab for fostering a friendly, intellectually stimulating working environment. I must also acknowledge Nosotech for providing the data for this thesis.

I would be remiss if I did not recognize the social and intellectual milieu cultivated by the members of McGill's Department of Epidemiology, Biostatistics and Occupational Health. I am grateful for the support of my friends, especially Stephen Kutcher and Emily MacLean, who have pushed me to become a better scientist and a better person. It has been a privilege to serve the McGill Epidemiology, Biostatistics and Occupational Health Student Society, particularly with my fellow executive team members Stephen Kutcher and Siyana Kurteva. I would like to thank Dr. Maida Sewitch for her dedication to student success and her support of the Current Events Epidemiology Journal Club.

Lastly, I would like to express a deep gratitude to my family for all they have done for me. Without them, I would not be where I am today.

Table of Contents

List of Tables

Chapter 4.2

Chapter 4.3

List of Figures

Chapter 4.2

Chapter 4.3

List of Appendices

Chapter 4.2

List of Abbreviations/Acronyms

ADT: Admission, discharge, transfer

AIC: Akaike information criterion

ARIMA: Autoregressive integrated moving average

CI: Credible interval

DDD: Defined Daily Dose

E. coli: *Escherichia coli*

FDA: Food and Drug Administration

MUHC: McGill University Health Centre

MCMC: Markov chain Monte Carlo

RAMQ: Régie de l'assurance maladie du Québec

TMP/SMX: Trimethoprim/sulfamethoxazole

USD: United States dollar

UTI: Urinary tract infection

WAIC: Widely applicable information criterion

1. Introduction

1.1. Rationale

The World Health Organization (1) has called antimicrobial resistance “one of the biggest threats to global health, food security, and development today.” Despite a widespread recognition of antimicrobial usage as the leading driver of resistance, unnecessary prescribing remains common (2–4). Given the paucity of new drug development, it is critically important to understand the patterns underlying resistance to existing drugs. Urinary tract infections, especially those caused by the pathogen *Escherichia coli*, are among the most common infections in both the community and hospital settings (5,6). Given the prevalence of these infections, UTIs are a major driver of antimicrobial consumption and thus a natural subject of study to elucidate patterns in antimicrobial resistance, antimicrobial consumption, and the connection between the two.

1.2. Objectives

This thesis will investigate antimicrobial resistance in urinary *Escherichia coli* isolates at both the individual and population levels in the province of Quebec, Canada. The first objective is to describe the association between patient-level characteristics (age, sex, and recent hospitalization) and the probability of resistance to six antimicrobials in community-acquired and hospital-acquired urinary *E. coli* isolates from three cities in the province of Quebec. As part of this objective, we will also describe annual, seasonal, and geographic variability in resistance to the aforementioned antimicrobials. The second objective is to investigate the association between community consumption of fluoroquinolones in the city of Montreal and the prevalence of ciprofloxacin resistance in community-acquired urinary *E. coli* isolates tested in the laboratory

of the McGill University Health Centre. Specifically, the focus of this objective is to identify the time lag(s) at which this association occurs.

2. Literature Review

2.1. Urinary tract infections

2.1.1. Definition and symptoms

Urinary tract infections (UTIs) are principally divided into infections of the lower urinary tract, cystitis (bladder infections), and infections of the upper urinary tract, pyelonephritis (kidney infections) (5). Cystitis is characterized by frequent urination, painful urination, the need to urinate despite an empty bladder, and/or suprapubic pain; pyelonephritis is characterized by the aforementioned symptoms plus fever, flank pain, and nausea (5). In severe cases, renal damage or sepsis may result (5). Bacteriuria, the presence of bacteria in urine, is considered asymptomatic when not accompanied by at least one symptom of urinary tract infection. This asymptomatic form is more common in women and the elderly (6).

2.1.2. Prevalence and etiology

Urinary tract infections are among the most common infections in both hospital and community settings, accounting for at least 150 million annual infections worldwide (7), including up to 40% of all nosocomial (hospital-acquired) infections (6). Infections are common among infants, the elderly, and women of all ages (5,6). In women, the lifetime risk of a UTI exceeds 50% (8). Recurrence of UTIs is common (5,9), with around a quarter of women in a cohort of 113 suffering a second infection within six months of an initial infection (10).

Urinary tract infections are further categorized as uncomplicated (patient has no structural or functional abnormalities, is not pregnant, and has not been instrumented, e.g., with a urinary catheter) or complicated (all other infections) (6). In uncomplicated infections, urinary tract infection is associated with sexual activity, which facilitates the movement of bacteria into the

bladder (11). In comparison to men, the periurethral area and vaginal cavity provide additional niches for bacterial growth; this fact, combined with a reduced distance between the urethral opening to the bladder, helps to explain the increased prevalence of UTIs among women (11). The frequency of bacteriuria is high among the very young, but otherwise incidence increases gradually with age, with the disparities between men and women being less pronounced in the elderly population (6). However, a higher proportion of bacteriuria is symptomatic (constituting urinary tract infection) in women between the ages of 15–29 (6). Most complicated infections are associated with indwelling urinary catheters (12), the cause of over 1 million infections in hospitals and nursing homes per year in the United States (13). UTI is also a common complication during pregnancy (9).

Urinary tract infections are caused by a wide variety of pathogens, including *Escherichia coli*, *Streptococcus*, Enterobacteriaceae species, and even several types of yeast (6,14). Among these, the gram-negative, facultatively anaerobic bacterium *E. coli* is by far the most common agent of infection, accounting for 80–85% of UTIs (6,14), although *E. coli* is seemingly responsible for a smaller proportion of infections in men compared to women (15,16).

2.1.3. Treatment

Urinary tract infections are generally treatable with a short course (1–7 days) of antimicrobials (11,17,18). For uncomplicated infections, nitrofurantoin, trimethoprim/sulfamethoxazole (TMP/SMX), fosfomycin, pivmecillinam, or one of a number of fluoroquinolones or β-lactams may be prescribed (17). The precise selection depends on a number of factors, including patient allergies, drug availability, local resistance rates, and local prescribing guidelines. An analysis of prescribing patterns for uncomplicated UTIs in the United States between 2002 and 2011 found that fluoroquinolones (mainly ciprofloxacin and levofloxacin) were the most commonly

prescribed antimicrobials, accounting for 49% of the total (19). In 2016, the United States Food and Drug Administration (FDA) recommended against prescribing fluoroquinolone antimicrobials for uncomplicated UTIs when other treatment options were available due to the possibility of disabling side effects (20). Complicated UTIs such as catheter-associated urinary tract infections generally call for longer treatment, from 5 to 14 days, depending on severity and etiology (18).

2.2. Antimicrobial resistance

2.2.1. Antimicrobials & antimicrobial resistance

Antimicrobials are a type of drug used to either kill or inhibit the growth of microorganisms like bacteria. Antibiotics are a sub-class of antimicrobials referring specifically to those that target bacteria. However, the strict definition of “antibiotic” includes only substances produced by other microorganisms, to the exclusion of drugs that are synthetic or semisynthetic. For this reason, this thesis uses the broader term “antimicrobial”, although we refer primarily to antimicrobials targeting bacteria (rather than fungi, viruses, or parasites). Antimicrobials are divided into several broad classes based on their chemical structures and mechanisms of action, with some of the more commonly used ones being β-lactams, tetracylines, macrolides, quinolones, and sulfonamides (for a comprehensive overview, see (21)). Some antimicrobials, such as penicillin and gentamicin, were isolated from microbes in nature, whereas others, such as quinolones, are fully synthetic (22).

Antimicrobial resistance refers to the capacity of some bacteria to tolerate or resist the effects of particular antimicrobial agents. Bacteria have evolved a number of methods to deal with these compounds in nature and in the clinical setting, such as by inactivating the antimicrobial, actively pumping it out of the cell, altering the target site, or otherwise confounding its effects

(23). Although it was once believed that resistance would be unlikely to develop against some classes of antimicrobials, like the fully synthetic quinolones with their complex mechanisms of action (22), resistance is in fact inevitable for all antimicrobials (24). Although antimicrobial resistance occurs in nature, antimicrobial consumption among humans and livestock is the leading driver of resistance (1,25–27).

2.2.2. Antimicrobial resistance as a public health problem

Antimicrobial resistance threatens our ability to treat infections in all parts of the world. The consequences of rising levels of resistance to patients and healthcare systems include higher costs, prolonged hospital stays, and worse health outcomes. A review commissioned by the government of the United Kingdom in 2014 concluded that in the absence of significant progress, antimicrobial (in this case encompassing antibacterials as well as antifungals, antivirals, and antiparasitics) resistance would contribute to 10 million deaths per year by 2050—greater than the current annual burden of cancer deaths (28). Additionally, the report estimated a 100 trillion USD loss in global production between now and 2050 that would be attributable to antimicrobial resistance (28). At existing levels, antimicrobial resistance contributes to an estimated 700,000 deaths per year and climbing (28). The report further states that *E. coli*, malaria, and tuberculosis were the most significant pathogens driving mortality and economic costs (29). *E. coli* alone accounted for a substantial proportion of the economic impact, and the ubiquity of *E. coli* meant that there was less regional variation in these effects (29).

Urinary tract infections, as one of the most common infections (largely caused by *E. coli*), impose a large burden on the healthcare system. For example, in the United States in 1996, UTIs accounted for approximately 7 million office visits, 1 million emergency room visits, and 100,000 hospitalizations (30); UTIs comprise also 40% of infections in hospitals (6). A study

analyzing data from 1995 estimated the direct and indirect costs of urinary tract infections among American adult women at 1.6 billion USD annually (8). UTIs leading to severe kidney infection are a severe threat to maternal and foetal health (31).

2.2.3. Antimicrobial resistance in urinary tract infections

Resistance has emerged to all drugs used to treat urinary tract infections. The prevalence of resistances depends on the time, place, and antimicrobial in question. For example, resistance to ampicillin and amoxicillin, two widely prescribed antimicrobials in the penicillin family, is now extremely prevalent and thus these drugs are no longer recommended for the treatment of urinary tract infections (17,32). In North America, ampicillin resistance ranges from 22% to over 50% (32,33). In contrast, nitrofurantoin, an antimicrobial used exclusively to treat urinary tract infections, has very low rates of resistance (~1%) despite decades of frequent use (17,32,33). Urinary *E. coli* resistant to multiple classes of antimicrobials, such as extended spectrum β-lactamase (ESBL)-producing *E. coli*, have grown in frequency over the last two decades (15,34,35).

The decision to treat, with any antimicrobial, depends very much on local rates of resistance, with the acceptable threshold of resistance standing at 20%. The example of TMP/SMX illustrates the importance of regional considerations in the empirical treatment of urinary tract infections. This antimicrobial would be recommended as a first-line treatment in some locations but not others (17,32,33,36,37). For example, Zhanel and colleagues (32) surveyed 10 Canadian medical centres between 2003–2004 and found TMP/SMX resistance in 6.4% of isolates in New Brunswick and 48.5% in Manitoba. Although it should be noted that a more recent survey of 23 acute care hospitals across 7 Canadian provinces found smaller differences between three broad geographic regions (resistance ranged from 17–27% (37)), it is nonetheless clear that the success

or failure of empirical treatment depends on the availability of a region-specific resistance profile (17,38). This wide range of resistance across settings is also seen with fluoroquinolones, such as ciprofloxacin, which are among the most prescribed antimicrobials in the world for any condition (39,40) and for urinary tract infections specifically (19). Given high antimicrobial concentrations found in urine, antimicrobial treatment of UTI has been highly effective. However, resistance has grown in the past few decades, potentially increasing the risk of treatment failure. Reported rates of ciprofloxacin resistance in North America range from 5% (in a sample of young women at an American college (41)) to over 50% (in a group of outpatients in Mexico City) (42) (see also other studies, e.g. (17,32,37,43,44)).

2.3. Risk factors for antimicrobial resistance

2.3.1. Individual-level risk factors

A number of individual patient characteristics have been associated with an increased risk of acquiring an antimicrobial resistant UTI. These characteristics include demographic, behavioural, and pharmacological factors but should not be confused with risk factors for urinary tract infection in general. A prime example of this distinction is the observation that men tend to have a higher probability of a resistant infection (15,16,45–47), despite experiencing far fewer UTIs (6). For example, in a study of 18,112 urinary *E. coli* specimens taken from a university hospital in the United Kingdom between 2006 and 2014, Toner and colleagues (47) found that male sex was associated with a 46% increase in odds (OR = 1.46; confidence interval: 1.26, 1.69) of having an ESBL-producing organism. The mechanism underlying this observation is not well understood.

Age has also been correlated with higher rates of resistance to certain antimicrobials (36,44–49). This relationship has been most consistently observed with the fluoroquinolone ciprofloxacin

(36,44,46,48,49), but has also been seen with other antimicrobials such as ceftriaxone and piperacilin-tazobactam, as well as multi-drug resistance to common antimicrobial agents (46,49). ESBL-producing organisms also seem to be more common among older adults (15,47). Mechanistically, cumulative consumption of broad-spectrum antimicrobials like ciprofloxacin are linked with profound changes in the gut microbiome (50), which may influence susceptibility to invasion by antimicrobial-resistant organisms (51); additionally, older individuals have, in general, greater cumulative exposure to the healthcare system, more comorbidities, and longer hospital stays (49).

Antimicrobial consumption, particularly recent antimicrobial consumption, is a notable risk factor for antimicrobial resistance (45,52–55). The reasons are two-fold: antimicrobial use exerts a strong selective pressure for resistance in existing microbiota and disrupt bacterial communities (especially in the gut), allowing foreign bacteria to colonize the body (51). Short courses of antimicrobials are capable of inducing both short-term and long-term changes in the body's microbiome (51).

Other individual risk factors for antimicrobial resistance in UTIs identified in previous research include recent hospitalization (36,45), presence of a long-term medical condition (54), previous UTI (45,55), ethnicity (45,53), and severity of symptoms (i.e. uncomplicated versus complicated infection or asymptomatic versus symptomatic infection) (44,53), although these findings are often nuanced and occasionally contradictory (e.g. see (48)). These differences may arise partly from differences in patient populations, case definitions, and exposure ascertainment.

Finally, much attention has been given to the setting of acquisition as a predictor of risk. Nursing home residents are a particularly vulnerable population for drug-resistant UTIs, especially given the high use of urinary catheters in this population (14,45,56–58). Importantly, this follows a

general trend where nosocomial (hospital-acquired) isolates are reported to have higher rates of antimicrobial resistance than community-acquired isolates (15,44,54,59) (but see (15,48) for counter-examples). Some reasons for this association may include urinary catheterization, a frequently identified risk factor (45,47) (but again, see (48) for counter-example), and the typical cause of infection in the healthcare setting. There may also be increased selective pressure arising from antimicrobial use in hospitals, as well as the possibility of being exposed to cross infection. Some of these differences may also be attributable to variation in demographic and behavioural factors in the patient populations, such as age, sex, and antimicrobial consumption.

2.3.2. Community-level risk factors

Perhaps even more important than individual antimicrobial use is antimicrobial use in the surrounding population (60). Numerous international or interregional comparisons have shown a strong tendency towards a higher prevalence of resistance in countries with higher overall levels of antimicrobial consumption (25–27,61). These differences can be quite dramatic. Between 1997 and 2002, France consumed 32.2 Defined Daily Doses (DDD) of antimicrobials per 1,000 inhabitant-days, whereas the Netherlands consumed only 10 DDDs per 1,000 inhabitant-days (26). In this same time period, the Netherlands had the lowest prevalence of penicillin-resistant *Streptococcus pneumoniae* (< 5%) among the 19 European countries in the study and France had by far the highest (> 40%). In this sample, average penicillin consumption explained around 84% of variance in the prevalence of resistance in the sample (Spearman correlation = 0.84; 95% confidence interval: 0.62, 0.94).

Another population-level factor that has been proposed to contribute to the prevalence of resistance is population density. Briefly, the hypothesis contends that increased migration and urbanization offers more opportunities for human-to-human contact, facilitating the spread of

resistance bacteria and genes (62). The idea has intuitive appeal, but is difficult to prove due to the large number of confounding factors present between cities of differing population densities.

2.4. Antimicrobial consumption

2.4.1. Antimicrobial consumption in Canada

Antimicrobial consumption happens in four settings: in the community, in hospitals, in veterinary medicine, and in agriculture/aquaculture. In 2016, an estimated 22.6 million prescriptions for antimicrobials were dispensed to patients in Canada, at a cost of nearly 700 million dollars (37). This amounts to just under 20 DDDs/1,000 inhabitant-days. A vast majority of these doses were dispensed in the community (92%) rather than hospital setting (8%). Among community-dispensed antimicrobials, 65% were dispensed by general and family practitioners. Compared to the 30 European countries participating in the European Surveillance of Antimicrobial Consumption Network, Canada ranked 13/31 for outpatient antimicrobial use when ranked from lowest to highest use (37). Antimicrobial consumption by companion animals and especially livestock is an enormous and pressing issue (37,63), but falls mostly outside of the realm of this thesis because it is harder to track.

2.4.2. Distribution of antimicrobial consumption

Unsurprisingly, the distribution of antimicrobial use is not uniform in the population. In 2016 in Canada, individuals 60 years of age and above had an average of 856.1 prescriptions dispensed in community pharmacies per 1,000 inhabitants (37). Usage was lower among younger age groups, with 546.5 prescriptions dispensed per 1,000 inhabitants for those aged 15–59 and 597.9 prescriptions dispensed per 1,000 inhabitants for the 0–14 age group. Overall prescribing rates have remained relatively constant since 2010 after a substantial decline beginning in 1995 (37).

There exist persistent, stable differences in rates of community prescribing across the ten Canadian provinces (37). In British Columbia, the overall community dispensation rate for 2016 was 546.0 prescriptions per 1,000 inhabitants. At the other end of the spectrum, Newfoundland's prescribing rate is 955.2 per 1,000 inhabitants. In the province of Quebec, the focus of this thesis, the prescribing rate is 602.8 per 1,000, just under the national average of 625.5 prescriptions per 1,000 inhabitants.

2.4.3. Antimicrobial consumption and antimicrobial resistance

It is intuitive that variation in resistance is driven by changes in antimicrobial use, but rigorously studying this relationship is challenging. The Public Health Agency of Canada notes that "there is a significant gap in understanding the linkages between [antimicrobial use] and the observed patterns of resistance and the spread of pathogens in Canada (64)." Simple comparisons of rates of consumption and resistance across countries are limited in their ability to draw causal inferences due to the large number of potential confounding factors between countries. Time series analysis is better suited to exploring this relationship, by being able to model the correlation through time between rates of antimicrobial use and the prevalence or incidence of resistant infections in the same region.

Several time series studies have been done, looking at how short-term fluctuations in the consumption of particular antimicrobials are reflected in the prevalence or incidence of infections resistant to closely-related antimicrobials. *E. coli*, a common pathogen, is the focus of much of this research. Other popular infections to study with this methodology include *Staphylococcus aureus* (65–68), *Clostridium difficile* (68–70), and ESBL-producing bacteria (71).

Sun and colleagues (67) studied the seasonality of the prevalence of ampicillin and ciprofloxacin resistance in *E. coli* isolates in the United States between 1999–2007 and found that patterns of resistance to these two drugs lagged aminopenicillin consumption and fluoroquinolone consumption, respectively, by 1 month. Vernaz et al. (72), studying the incidence of resistant *E. coli* infections in Geneva, reported that community use of ciprofloxacin lagged by 1 month and community use of moxifloxacin lagged by 4 months both correlated with the incidence of community-acquired ciprofloxacin-resistant isolates. The incidence of isolates resistant to cefepime (a fourth-generation cephalosporin antimicrobial, resistance to which was used as a marker of ESBL production) correlated with outpatient and inpatient use of ciprofloxacin, as well as the inpatient use of a number of other antimicrobials, with time lags ranging from 0–4 months. Outpatient use of TMP/SMX weakly correlated with the incidence of hospital-acquired TMP/SMX-resistant *E. coli* with a lag of 4 months but did not correlate with the incidence of community-acquired infections. Gallini et al. (73) investigated how the consumption of antimicrobials in the community was connected with ciprofloxacin resistance in *E. coli* infections acquired in a French university hospital. We would expect community consumption to take longer to affect hospital infections than community infections, and indeed, the study reported an association with levofloxacin use lagged by 12 months.

3. Study Methodology

3.1. Study location

For objective 1, we examined antimicrobial susceptibility testing results from three cities across the province of Quebec, Canada. The large urban centre of Montreal was represented by the laboratory of the McGill University Health Centre (MUHC). Specifically, we analyzed data from the following hospitals in the network: Royal Victoria Hospital, Montreal General Hospital, Montreal Neurological Hospital, and Montreal Children's Hospital, accounting for over a thousand hospital beds. We did not have data from the Hôpital de Lachine, one of the smaller hospitals in the network. The McGill University Health Centre is one of the two major teaching healthcare networks in the city; additionally, it provides specialized and ultra-specialized care to the surrounding area and the rest of the province. The smaller urban centre of Quebec City was represented by two hospital laboratories, those of the Centre hospitalier affilié universitaire de Quebec and the Centre hospitalier universitaire de Quebec. These two cities are by far the largest in the province. Finally, the small, remote city of Rimouski was represented by the Hôpital régional de Rimouski.

For objective 2, we considered data from the MUHC exclusively, as antimicrobial consumption data were only available for the health region of Montreal. In 2011 (near the beginning of the study period), the health region of Montreal had a census population of 1,886,480, which includes the city proper but not the surrounding metropolitan area (74).

3.2. Study population

3.2.1. Antimicrobial resistance data

The four aforementioned institutions have adopted a common infection control software (Nosokos; Nosotech, Rimouski, Canada). This software extracts data in each hospital from the laboratory system, including antimicrobial susceptibility testing results, and connects it with the ADT (admission, discharge, transfer) system, where demographic information and admission and discharge data are stored. These results can then be collated and compared using a standardized dictionary. For this project, Nosotech extracted susceptibility testing results for urinary *E. coli* isolates from each of the four participating institutions between April 2010 and December 2017.

For each isolate, the following data were available: date of collection and susceptibility testing results classified as sensitive, intermediate, or resistant. Additionally, the following information was available for patients with urine samples included in the study: age, sex, unique identifier, and date of previous admission/localization in the hospital (e.g., emergency room). Patient identifiers were unique to each laboratory and could not be used to track patients across hospital laboratories in the dataset. Species identification was performed according to local procedures and susceptibility testing was done following Clinical and Laboratory Standards Institute breakpoints and guidelines (75).

We first classified each isolate as community-acquired or nosocomial (hospital-acquired) and then filtered isolates on a number of criteria. We considered samples taken at least 48 hours after hospital admission or within 48 hours after hospital discharge as potentially nosocomial (based on National Healthcare Safety Network guidelines (76)); other samples (e.g., from emergency departments, outpatient clinics, and community clinics) were classified as community-acquired.

We excluded contaminated samples, considered as those with more than two bacterial species (77). We also excluded a small subset of samples with missing information on patient sex.

In Quebec, adult urinary *E. coli* isolates are regularly tested for resistance to six antimicrobials belonging to five classes of antimicrobials: ampicillin (penicillin), gentamicin (aminoglycoside), ciprofloxacin (fluoroquinolone), nitrofurantoin (nitrofuran), trimethoprim/sulfamethoxazole (combination dihydrofolate reductase inhibitor/sulfonamide), and tobramycin (aminoglycoside). Fluoroquinolones are not typically prescribed to children, leading to susceptibility testing results for ciprofloxacin being regularly suppressed in the hospital information system for this group of patients. Thus, we restricted our sample to patients aged 18 years or older for both community-acquired and nosocomial isolates. Our first objective was to investigate the association between age and probability of resistance for these six antimicrobials, so we wanted to avoid extrapolating results to ages not well-represented in the dataset. There were very few patients over the age of 95, and a small number of unrealistic values (i.e., older than the oldest person in the country), so we also excluded ages over 95. In the nosocomial dataset, people aged 65 and older accounted for 70% of samples, so we restricted the dataset to people in this age group to avoid unwarranted extrapolation on the association with age. For the purpose of analysis, we grouped the small percentage of intermediate susceptibility results with susceptible isolates ("non-resistant" isolates; e.g., see (67,78,79) for precedent; see also (72,73,80) for the alternative "non-susceptible" classification).

In objective 1, our analysis used the raw, individual-level data as originally extracted. We were interested accounting for correlations between the six types of antimicrobial resistance, so we considered only isolates with susceptibility testing results for all six types of resistance. Finally,

we retained only the first sample from each patient in order to meet the assumption of statistical independence between samples.

In objective 2, we considered only ciprofloxacin resistance in community-acquired isolates from the MUHC in Montreal and therefore did not exclude samples without results for all six antimicrobials, only samples without results for ciprofloxacin susceptibility. Prior to calculating the proportion of resistant samples within each month, we retained only the first sample from each patient, as in objective 1.

Further descriptive statistics and filtering results of the resistance dataset are available in the methods and results sections of the two manuscripts.

3.2.2. Fluoroquinolone dispensation data

In objective 2, we examined the association between short-term fluctuations in community fluoroquinolone use in Montreal and resistance to a common fluoroquinolone antimicrobial, ciprofloxacin, in UTIs in the community setting. We considered outpatient oral fluoroquinolone use (Anatomical Therapeutic Chemical Classification: J01MA), which in Quebec comprises the following drugs: ciprofloxacin, levofloxacin, ofloxacin, norfloxacin, and moxifloxacin. We also considered total fluoroquinolone use. We used drug dispensation data as a proxy for community consumption, although not all dispensed drugs are consumed as directed.

Drug dispensation data were procured for a randomly sampled, open cohort of 25% of people covered by the Régie de l'Assurance Maladie du Québec's Public Prescription Drug Insurance Plan for the health region of Montreal. Our subsample, covering the years 2004–2014, is drawn from a larger cohort covering 25% of the population of the Census Metropolitan Area of Montreal, described in detail elsewhere (81). The province of Quebec, through the Régie de l'assurance maladie du Quebec (RAMQ), insures all residents for medical care and

hospitalizations. Prescriptions are also covered for residents ineligible for a private plan. These individuals are covered under three main insurance programs: individuals 65 years of age or older, individuals receiving social assistance, and workers and family members without access to private drug insurance (e.g. self-employed, students, etc.). In the second quarter of 2011, these programs covered 258,774, 173,102, and 486,201 people, respectively (as reported in tables AM.01–AM.03 (82)), comprising nearly 49% of the health region of Montreal's population.

The claims database included the nature, quantity, and date of every drug dispensed to each individual covered under the plan, as well as demographic information including sex, month and year of birth, first three digits of their postal code, and type of insurance. The number of grams of each unique product (as defined by the Drug Identification Number from Health Canada) dispensed each month was tallied and then converted to Defined Daily Doses (DDDs) (83) for each active ingredient (e.g., ciprofloxacin, moxifloxacin). One DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" (83). We calculated DDDs assuming that all dispensed drugs were consumed, as antimicrobials are generally prescribed to provide one course of treatment for common infections. Next, for each active ingredient, we calculated monthly DDDs per 1,000 inhabitant-days for each insured group defined by five-year age category, sex, and insurance program type (e.g., men aged 65–69 covered under the old-age insurance plan). To produce a single monthly estimate for each active ingredient, we calculated a weighted average of the estimates for each insured group based on the composition of individuals enrolled in the public drug plan, which is reported quarterly (82).

Prior to analysis, we de-trended the antimicrobial consumption times series using loess smoothing, as implemented in the "stl" function in R 3.4.4 (84). This function decomposes the time series into three components: trend (time-varying mean), seasonal, and random. We

subtracted the trend component from the time-series, keeping only the seasonal and random components, which represents short-term, seasonal fluctuations in the consumption of antimicrobials.

3.3. Analysis

3.3.1. Objective 1

Antimicrobial susceptibility profiles are typically presented in the form of tables with resistance proportions for each antimicrobial, often broken down into sub-groups (e.g., men vs. women, elderly vs. non-elderly). These tables provide a simple, intuitive way to present local susceptibility results, but are limited in their ability to make inferences about risk factors for resistance for two reasons. First, it is difficult to simultaneously consider more than two factors in a table, making it difficult to appreciate the relative contributions of covariates or consider correlations between covariates. Second, each type of antimicrobial resistance is usually considered independently, even though different types of resistance are often related. To address these limitations, we propose to use a hierarchical, model-based approached to simultaneously consider each potential covariate and outcome (type of resistance). A model-based approach has the further advantage over tables of being easier to apply in clinical practice, as it facilitates the development of tools to predict risk and to make these predictions available when they are needed.

In this analysis, we modelled community-acquired and nosocomial isolates separately, with one independent model for each of the two groups. Within each model, we have six binary outcomes for each isolate *i*, the presence or absence of resistance to each of the six antimicrobials *a* ($Y_{i,a}$). Each isolate *i* has a corresponding set of covariates X_i, which is a vector of length *p*, where *p* is the total number of covariates. Covariates included in the model were: community (Quebec City

and Rimouski compared to Montreal), sex (male compared to female), age (quadratic), hospitalization in the past 30 days (yes compared to no), month (compared to January), and year (compared to 2010). The age variable was centred prior to analysis.

We model the association between covariates and outcomes using a Bayesian hierarchical logistic regression model (for an overview of this method, see (85)). In this framework, each outcome (type of resistance) is allowed to have its own intercept and set of regression coefficients ($\beta_{p,a}$). We impose a correlation structure on these coefficients by assuming that all coefficients for covariate *p* are normally distributed around a common mean value for that covariate (β_p) with standard deviation σ_p. This assumption allows the "borrowing of strength" across outcomes. The model is as follows:

$$Y_{i,a} \mid \pi_{i,a} \sim \text{Bernoulli}(\pi_{i,a})$$
$$\text{logit}(\pi_{i,a}) = \beta_{p,a} X_i \qquad \beta_{p,a} \sim N(\beta_p, \sigma_p^2).$$

Each common mean β_p was assigned a diffuse normal prior (mean = 0, variance = 10,000); each standard deviation σ_p was assigned a diffuse half-Cauchy prior (scale = 25) (86). The resultant posterior distribution of the parameters was estimated using Markov chain Monte Carlo (MCMC) as implemented in the nimble (87) package (version 0.6-10) in R. MCMC chains were run for 30,000 iterations and 95% posterior credible intervals for each parameter were extracted after discarding 10% of samples as burn-in. Chains were visually inspected for convergence; a second chain was run using different initial values and results were compared to verify convergence had occurred.

3.3.2. Objective 2

Studies of the temporal association between antimicrobial use and antimicrobial resistance are typically performed using the autoregressive integrated moving average (ARIMA) framework

(67,72,73). This class of models is widely used for a variety of time series problems and is implemented in all popular statistical packages. However, ARIMA models have several drawbacks. First, they require time series data to be stationary (constant mean and variance across time), an artificial requirement that often calls for extensive data transformation prior to analysis (88). Second, the approach is a “black box”: purely data-driven, without regard for prior analysis of the structure of the data.

Here, we propose an explicitly structural approach to studying the question of fluoroquinolone use and ciprofloxacin resistance in urinary *E. coli* samples in Montreal. Dynamic linear models, a form of state-space model, offer great flexibility. We used a dynamic linear model to decompose the ciprofloxacin resistance time series into several components (for an overview of this method, see (89) or (90) for worked examples with R). These components comprise a time-varying mean, a seasonal component, and averaged patient characteristic component. Changes in averaged patient characteristics between monthly samples have not been incorporated into previous research on this topic.

The outcome, the proportion of isolates resistant to ciprofloxacin in month t (Y_t), is normally distributed after a logit transformation. Using a Bayesian dynamic linear model, we modelled the expected proportion of resistant samples in month t (θ_t) with Gaussian white noise observation errors (v_t):

$$\text{logit}(Y_t) = \theta_t + v_t \qquad\qquad v_t \sim N(0, \sigma_v^2).$$

The expected value (θ_t) is decomposed as the sum of three independent components: a time-varying mean (μ_t), averaged patient characteristics (P_t), and a seasonal component (S_t):

$$\theta_t = \mu_t + P_t + S_t.$$

The time-varying mean component is treated as a random walk. The value of μ_t depends on the previous value, μ_{t-1}, plus a white noise with unknown variance σ_μ^2. Both the variance and the value of μ_t are jointly estimated from the data with other model parameters.

The averaged patient characteristic component includes three covariates: percentage of samples where the patient is male, mean age of patients, and percentage of samples where the patient was admitted to the hospital in the past 30 days. This component was estimated in the model as a multiple regression on the values of these three covariates in the current month.

The seasonal component can be modelled in one of two ways. First, as seasonal fluctuations in fluoroquinolone use (as described in section 3.2.2). Second, as a neutral comparison to the first option, we could instead employ a first-order harmonic, without reference to fluoroquinolone use. In this case, a first-order harmonic models seasonality as a sinusoidal function of time (period = 12 months):

$$S_t = h_t \cos(2\pi/12t) + \widetilde{h}_t \sin(2\pi/12t).$$

The coefficients of the harmonic (h_t , $\widetilde{h}_t$) control the amplitude and phase of the resulting curve. These coefficients can be defined as constant with respect to time ($h_t = h$, $\widetilde{h}_t = \widetilde{h}$) or be allowed to vary according to random walks with variances σ_h^2 and $\sigma_{\widetilde{h}}^2$, respectively. This latter option produces a non-constant sinusoidal curve that can respond to changes in the seasonal pattern over time, but also increases model complexity by adding additional model parameters.

Modelling the seasonal component as a function of changing fluoroquinolone use is achieved through the use of a transfer function (for an overview of transfer functions, see (91)), which describes how the association between the two variables evolves over time. For each of the five

fluoroquinolones described in section 3.2.2 (plus total fluoroquinolone use), we fit four types of distributed lag models, each of which considers the association between fluoroquinolone use in the current month ($D_{t,0}$) up to fluoroquinolone use five months ago ($D_{t,5}$). The sole exception is the Koyck model, which does not fix the lag *a priori*.

$$S_t = \sum_{i=0}^{5} \beta_i D_{t,i} \qquad \text{(Finite distributed lag model)}$$

$$S_t = \sum_{m=0}^{M} a_m Z_{m,t} \qquad \text{(Almon model of order } M\text{)}$$

$$Z_{m,t} \begin{cases} m = 0 & \sum_{i=0}^{5} D_{t,i} \\ m \neq 0 & \sum_{i=1}^{5} i^m D_{t,i} \end{cases}$$

$$S_t = \lambda S_{t-1} + \psi D_{t,0} \qquad 0 \leq \lambda \leq 1 \qquad \text{(Koyck model)}$$

The finite distributed lag model requires one parameter (regression coefficient) for each lagged value of antimicrobial use (92). The Almon model reparametrizes the finite distributed lag model by assuming the regression coefficients form a polynomial curve of order *M* (93). This means that fewer parameters must be estimated compared to the previous model. The raw beta coefficients, in the form one would expect from a standard finite distributed lag model, can be recovered through the following transformation:

$$\beta_i = a_0 + i^1 \times a_1 + \ldots + i^M a_M \qquad i \in 0, \ldots, 5.$$

For this study, we considered Almon transfer functions of order 2 (quadratic) and 3 (cubic). The final transfer function is the Koyck model, where the magnitude of association with the independent variable is greatest in the current time ($t = 0$) and decays exponentially with the length of the lag (92,94).

A total of 26 models (6 types of fluoroquinolone use × 4 possible transfer functions + static harmonic model + random harmonic model) were fit. Model selection was performed using

widely applicable information criterion (WAIC), a generalization of Akaike information criterion (AIC), which assesses model fit while penalizing complexity (smaller values are better) (95). For each model, we estimated the posterior distribution of the parameters using Markov chain Monte Carlo (MCMC) as implemented in the nimble (87) package in R. MCMC chains were run for 500,000 iterations and 95% posterior credible intervals for each parameter were extracted after discarding 10% of samples as burn-in and with a thinning interval of 5. The time-varying mean (μ_t) and transfer function (S_t) parameters were estimated in a block using automated factor slice sampling, which substantially speeds convergence in correlated state-space models (96,97).

3.4. Ethics

We obtained ethics approval from each participating institution according to the Multi-Centre Research Ethics Review Mechanism of the Quebec Ministry of Health and Social Services (MP-37-2018-3758).

4. Study Results

4.1. Preface

The results of this thesis are presented in two manuscripts. These manuscripts include:

Jean-Paul R. Soucy, Alexandra M. Schmidt, Charles Frenette, Patrick Dolcé, Alexandre A. Boudreault, David L. Buckeridge, Caroline Quach. Joint modelling of resistance to six antimicrobials in urinary *Escherichia coli* isolates in Quebec, Canada.

Jean-Paul R. Soucy, Alexandra M. Schmidt, Caroline Quach, David L. Buckeridge. Fluoroquinolone use explains seasonal patterns in ciprofloxacin resistance in community-acquired urinary *Escherichia coli*: A dynamic linear model in a large urban community.

The first manuscript has been targeted at a clinical-focused journal. It addresses the first objective of the thesis, to describe the association between patient-level characteristics and the prevalence of antimicrobial resistance in urinary *E. coli* isolates from three Quebec cities as well as annual, seasonal, and geographic variability in the prevalence of resistance. The second manuscript has been targeted at an epidemiology-focused journal. It addresses the second objective of the thesis, to investigate the temporal association between community consumption of fluoroquinolones in Montreal and the prevalence of ciprofloxacin resistance in community-acquired urinary *E. coli* isolates tested in the city.

4.2. Manuscript 1: Joint modelling of resistance to six antimicrobials in urinary *Escherichia coli* isolates in Quebec, Canada

Joint modelling of resistance to six antimicrobials in urinary *Escherichia coli* isolates in Quebec, Canada

Jean-Paul R. Soucy[1,2], Alexandra M. Schmidt[1], Charles Frenette[3], Patrick Dolcé[4], Alexandre A. Boudreault[5,6], David L. Buckeridge[1,2], Caroline Quach[7,8*]

[1] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, QC, Canada

[2] Surveillance Laboratory, McGill Clinical and Health Informatics, McGill University, Montréal, QC, Canada

[3] Infectious Disease Department, McGill University Health Centre, Montréal, QC, Canada

[4] Department of Medical Microbiology and Infectious Diseases, Centre Hospitalier Régional de Rimouski, Rimouski, QC, Canada

[5] Département de Microbiologie-infectiologie et d'Immunologie, Université Laval, Québec, QC, Canada

[6] CHU de Québec, Université Laval, Québec, QC, Canada

[7] Department of Microbiology, Infectious Diseases & Immunology, Université de Montréal, Montréal, QC, Canada

[8] Infection Prevention & Control Unit, Department of Pediatric Laboratory Medicine, CHU Sainte-Justine, Université de Montréal, Montréal, QC, Canada

* Corresponding author

Telephone: 1-514-345-4931, ext. 7430

Email: c.quach@umontreal.ca

Short running title: Resistance to six antimicrobials in urinary *Escherichia coli*

Abstract

Objectives: Empirical treatment of urinary tract infections should be based on susceptibility profiles specific to the locale and patient population. Additionally, estimates for the prevalence of antimicrobial resistance should account for correlation between different types of resistance. We aimed to use a model-based approach to estimate the probabilities of multiple types of antimicrobial resistance in various patient populations.

Methods: We used hierarchical logistic regression models to investigate geographic, temporal, and demographic trends in resistance to six antimicrobials in community-acquired and nosocomial urinary *E. coli* isolates from three communities in the province of Quebec, Canada procured between April 2010 and December 2017.

Results: A total of 74,986 community-acquired and 4,384 nosocomial isolates were analyzed. In both community-acquired and nosocomial isolates, we found geographic variation in the prevalence of resistance; we also found male sex (top-level community OR 1.24, 95% credible interval: 1.00–1.53; top-level nosocomial OR 1.16, 95% CI: 0.95–1.42) and recent hospitalization (top-level community OR 1.48, 95% CI: 1.32–1.66; top-level nosocomial OR 1.29, 95% CI: 0.98–1.78) to be associated with a higher risk of resistance to most types of antimicrobials. We found distinct seasonal trends in both community-acquired and nosocomial isolates, but only community-acquired isolates showed a consistent annual pattern. Ciprofloxacin resistance increased sharply as patient age increased.

Conclusions: We found clinically relevant differences in antimicrobial resistance in urinary *E. coli* isolates between locales and patient populations in the province of Quebec. These results could help inform empirical treatment decisions for urinary tract infections.

Introduction

Urinary tract infections (UTIs) are among the most common infections encountered in community and hospital settings.[1,2] These infections occur primarily in women, with a lifetime risk in excess of 50%[3], but UTIs also occur frequently in infant and elderly males[2]. Many pathogens cause UTIs, but by far the most prominent agents are the gram-negative, facultatively anaerobic bacteria *Escherichia coli*.[2,4] In the community setting, UTIs occur frequently in sexually active women, whereas nosocomial infections are associated mainly with urinary catheters and urogenital procedures.[2,5] Although UTIs are generally treatable with a short course of antimicrobials, the prevalence of urinary tract pathogens resistant to one or more drugs, such as extended spectrum β-lactamase-producing (ESBL) *E. coli*, appears to be rising.[6–8] Given their high incidence, UTIs drive antimicrobial use in both hospitals and their surrounding communities. Understanding the mediators of resistance is therefore important to inform empirical therapy for this class of infections.

Previous research has identified several potential risk factors for antimicrobial resistance in urinary *E. coli* isolates, including age, male sex, hospitalization, previous UTI infection, antimicrobial use, and residence in a nursing home.[4,5,9–17] These studies often suggest differences in rates of resistance between community-acquired and hospital-associated infections, reflecting variation in host characteristics, underlying mechanics of transmission, and pathogen phenotypes.[2,6,18,19] Strong geographic and temporal variation in the prevalence of antimicrobial resistance in *E. coli* has been noted in North America, at both the national and sub-national levels. For example, Zhanel and colleagues[20] reported that isolates of *E. coli* from urinary tract samples of US outpatients had higher resistance than isolates from Canadian patients in 2003–2004, a trend that has also been observed in recent years with the rapid emergence of ESBL isolates in the United States[6]. The prevalence of resistance also varies between Canadian

provinces.[21,22] For uncomplicated UTIs, 20% resistance is cited as a threshold passed which empirical treatment with that drug is compromised.[23] Given the variation across regions, treatment decisions should be made with the most locally relevant information available.[24] The relative importance of risk factors may also differ depending on the phenotypic composition of pathogen source populations, motivating investigation into local trends rather than relying on less regionally specific estimates.

Much of the previous research on variation in rates of antimicrobial resistance suffers from a small sample size and a short window of sample collection, with results being limited to tables of resistance proportions for various sub-groups (e.g. men vs. women, children vs. adults). Thus, it can be difficult to appreciate the relative contributions of each characteristic to observed variation in rates of resistance between times, places, and settings of acquisition (community-acquired or nosocomial). With sufficient data and appropriate methods, we can build a model simultaneously considering these various demographic, temporal, and geographic characteristics. Another issue is that previous research generally treats resistance to each type of antimicrobial as an independent process, although this is clearly not the case. For example, the ESBL genes conferring penicillin and cephalosporin resistance often co-occur on plasmids with genes granting resistance to other classes of antimicrobials [25–27]. Thus, a modelling approach explicitly accounting for correlations between different types of resistance, arising from a common phenotype within each organism, is both clinically relevant and statistically expedient.

In the province of Quebec, adult urinary *E. coli* isolates are regularly tested for resistance to six antimicrobials representing five classes of antimicrobial drugs: ampicillin (penicillin), gentamicin (aminoglycoside), ciprofloxacin (fluoroquinolone), nitrofurantoin (nitrofuran), trimethoprim/sulfamethoxazole (combination dihydrofolate reductase inhibitor

/sulfonamide), and tobramycin (aminoglycoside). Here, we developed joint logistic regression models to investigate geographic, temporal, and demographic trends in resistance to these six antimicrobials in a large sample of community-acquired and nosocomial urinary *E. coli* isolates from three communities in the province of Quebec, Canada.

Materials and Methods

Study population

We examined antimicrobial resistance in urine samples positive for *E. coli*, analyzed in four hospital laboratories in three cities across the province of Quebec, Canada between April 2010 and December 2017. The large urban centre of Montreal and the small, remote city of Rimouski were each represented by one laboratory (the McGill University Health Centre and the Hôpital régional de Rimouski, respectively), whereas Quebec City was represented by two laboratories (the Centre hospitalier affilié universitaire de Quebec and the Centre hospitalier universitaire de Quebec). These institutions have adopted a common infection control software (Nosokos; Nosotech, Rimouski, Canada) which facilitates aggregation of results from different institutions using a standardized dictionary.

For each isolate, the following data were available: date of collection, age, sex, and unique patient identifier, date of previous admission/localization in the hospital (e.g., emergency room), and antimicrobial testing results classified as sensitive, intermediate, or resistant. Species identification was performed according to local procedures and susceptibility testing was done following CLSI breakpoints and guidelines.[28] Samples taken at least 48 hours after hospital admission or within 48 hours after discharge were considered potentially nosocomial (based on National Healthcare Safety Network guidelines[29]); other samples (e.g., from emergency departments, outpatient clinics, and community clinics) were considered community-acquired.

Samples with more than two bacterial species were excluded, considered as contaminated.[30] We also excluded samples without results for all six antimicrobials of interest. Since fluoroquinolones are not typically prescribed for children[31], results for ciprofloxacin resistance were regularly suppressed in the hospital information system; thus, we restricted our sample to patients aged 18 years and older. To avoid unwarranted extrapolation, we excluded patients with ages over 95 (very few individuals and some unrealistic ages); by the same logic, we limited nosocomial isolates to those obtained from patients aged 65 years and older, which accounted for over 70% of the dataset. To meet the assumption of statistical independence between samples, we retained only the first sample from each patient in the dataset.

Analysis

Six antimicrobials were routinely tested for resistance in the adult population during the study period: ampicillin, gentamicin, ciprofloxacin, nitrofurantoin, trimethoprim/sulfamethoxazole (TMP/SMX), and tobramycin. The small percentage of susceptibility results classified as intermediate (1.7%) were grouped with the susceptible isolates for the purpose of analysis ("non-resistant" isolates; e.g., see [32–34]). We jointly modelled each binary outcome ($Y_{i,a}$, the presence or absence of resistance in a particular isolate *i* to antimicrobial *a*) using hierarchical logistic regression in a Bayesian framework (for an overview of this approach, see Gelman and Hill[35]). We allowed each outcome (type of resistance) to have its own intercept and set of regression coefficients $\beta_{p,a}$ while imposing a correlation structure on these coefficients by assuming each coefficient for antimicrobial *a* and covariate *p* was normally distributed around a common mean value for that covariate (β_p) with standard deviation σ_p. By assuming, for example, that the association between male sex and the probability of resistance is related for different types of antimicrobial resistance, we allow for the "borrowing of strength" across outcomes. Each common mean β_p was assigned a diffuse normal prior (mean = 0, variance

= 10,000); each standard deviation σ_p was assigned a diffuse half-Cauchy prior (scale = 25)[36]. Two models were fitted independently: one for community-acquired isolates and another for nosocomial isolates. The model is as follows:

$$Y_{i,a} \mid \pi_{i,a} \sim \text{Bernoulli}(\pi_{i,a})$$
$$\text{logit}(\pi_{i,a}) = \beta_{p,a} X_i \qquad \beta_{p,a} \sim N(\beta_p, \sigma_p^2).$$

Covariate values for each isolate *i* are given as a *p*-dimensional vector X_i. Covariates included in the model were: community (Quebec City and Rimouski compared to Montreal), sex (male compared to female), age (quadratic), hospitalization in the past 30 days (yes compared to no), month (compared to January), and year (compared to 2010). The resultant posterior distribution of the parameters was estimated using Markov chain Monte Carlo (MCMC) as implemented in the nimble[37] package (version 0.6-10) in R 3.4.4[38]. The 95% posterior credible intervals for each parameter is presented after 10% burn-in of MCMC samples. See the supplementary methods for full details on how the model was estimated.

Ethics

We obtained ethics approval from each participating institution according to the Multi-Centre Research Ethics Review Mechanism of the Quebec Ministry of Health and Social Services (MP-37-2018-3758).

Results

Study population

The initial database of urinary *E. coli* samples contained 163,541 entries. We excluded contaminated samples (1,484). When samples contained with more than one isolate of the same species, we retained one isolate and excluded the rest (4,817). We further excluded samples without test results (911), samples with missing sex (4,585), and samples with age under 18

(15,357) or over 95 (1,336). For nosocomial isolates, we also excluded samples with age under 65 (3,468). We were left with 131,583 entries, 111,153 (85%) of which had complete information for all six antimicrobials of interest. Finally, we retained only the first sample from each of the 79,370 unique patients (71% unique samples). Demographic characteristics of these samples are described in Table 1.

Community-acquired isolates

Similar yearly (Figure 1) and seasonal (Figure 2) patterns were observed across most types of resistance. Compared to 2010, the odds of resistance held steady or slightly declined between 2011–2014, after which resistance increased from 2015–2017. The exceptions to this pattern were gentamicin, where resistance remained relatively constant throughout the study period, and nitrofurantoin, where resistance declined in 2016–2017. A seasonal trend was observed, with resistance generally peaking between February and May compared to January.

Resistance differed strongly by geography (Figure 3; Figure 4). Male sex and recent prior hospitalization were universal risk factors (Figure 3; Figure 5). Increasing age was strongly associated with increased resistance to ciprofloxacin, whereas TMP/SMX resistance declined slightly with age (Figure 3; Figure 5). Exact values for model coefficients on the odds ratio scale are given in Supplementary Table 1.

Nosocomial isolates

Nosocomial isolates lacked a coherent yearly trend (Figure 1). Seasonally, there was a weak tendency for resistance to be lower in February and July–September compared to January (Figure 2).

In contrast with community-acquired isolates, female sex and location were predictive of risk in only three or four resistance types (Figure 3). Recent prior hospitalization was usually a

risk factor. Increasing age was again associated with ciprofloxacin resistance (Figure 5). Exact values for model coefficients on the odds ratio scale are given in Supplementary Table 2.

Discussion

In this study, we jointly modelled the temporal, geographic, and patient-level associations with resistance to six antimicrobials in urinary *E. coli* isolates from inpatients and outpatients from three cities across the province of Quebec. Our hierarchical modelling approach allowed for correlations between regression coefficients across different types of antimicrobial resistance. It revealed commonalities in risk factors across drugs and patient populations, with location, male sex, and recent prior hospitalization being associated with increased resistance in most cases. Conversely, the strong effect of age on ciprofloxacin resistance was a notable departure from the weaker trends observed in other types of resistance. This hierarchical approach also made it possible to estimate risk factors for nitrofurantoin and tobramycin resistance through the borrowing of strength across antimicrobials despite a low overall prevalence of resistance to these particular antimicrobials. The markedly different levels of resistance in our three communities underscores the importance of making available to physicians the most locally relevant information on rates of resistance, rather than relying on provincial or national estimates.

This study's results support some of the findings from previous research. Both male sex and recent hospitalization have been previously identified as risk factors for resistance[9,10,16]. The mechanism underlying increased male susceptibility is not well understood; differences in etiology between men and women may be important, as UTIs are common in otherwise healthy women[5] but in men are often associated with anatomical abnormality such as an enlarged prostate[39]. Nonetheless, male sex as a risk factor persisted in the nosocomial setting, despite the

similarity in route of acquisition (catheterization). Rising rates of resistance over time are consistent with trends in urinary *E. coli*[40] and pathogens in general[41].

Increased age has been linked to greater ciprofloxacin resistance in adults[6,42,43], as observed here. This may be linked to cumulative changes in the gut microbiome which occur as a result of the use of broad-spectrum antimicrobials like ciprofloxacin[44], changing an individual's susceptibility to invasion by antimicrobial-resistant organisms[45]. A previous study of 403 women with uncomplicated pyelonephritis found no differences in TMP/SMX resistance in patients older than 55 compared with younger patients[14], whereas we found a negative relationship with age. Resistance rates were remarkably higher in the urban facilities of Montreal than the other two sites, with the more remote Rimouski generally showing the lowest. Our results are consistent with the hypothesized positive association between population density and resistance[46], although we cannot draw general conclusions from only three sites. It should be noted, however, that the McGill University Health Centre serves as a major reference centre for urology in Montreal and may receive complex cases from other hospitals, which could be over-representing the prevalence of resistance in the city.

Surprisingly, our model does not generally predict significantly different rates of antimicrobial resistance among elderly (65+) individuals based on setting of acquisition (community or nosocomial). A meta-analysis of 54 observational studies by Fasugba et al.[40] concluded that ciprofloxacin resistance was higher in hospital-acquired (38%; 95% confidence interval: 36%, 41%) compared with community-acquired (27%; 95% CI: 24%, 31%) infections, although they did not directly control for sex, previous hospitalization, or age among adults. Fleming et al.[11] reported that in 156 urinary *E. coli* taken from a Georgia hospital, prevalence of resistance to TMP/SMX (and several other antimicrobials) was higher in the hospital-acquired (34.6%) than community-acquired (25.2%) isolates, but did not adjust for demographic factors.

Other studies[6,14,17] also report differences in rates of resistance between these two sub-populations (interestingly, Lob et al.[6] reports these differences in the United States but not Canada), but it is also necessary to note the wide variation in estimated rates of resistance between studies. Geographic differences, as well as the demographic associations detected in our large database of isolates, help to explain this variation.

Our study had several limitations. First, the lack of supplementary clinical data (e.g., symptoms) meant that we were unable to distinguish asymptomatic bacteriuria from symptomatic UTI, or tMain Thesis Fullhe type and severity of infections. Since our sampling frame included only patients for which clinical specimens had been taken, and specimens may not be systematically taken for uncomplicated UTIs, our sampling frame may not be reflective of all treated UTIs. Additionally, changes in physician behaviour over time or between locations could explain some of the variability in rates of resistance. We make no attempt to draw inferences about factors influencing the incidence of UTIs, only the underlying prevalence of antimicrobial resistance among urinary *E. coli* isolates. Finally, since we cannot confirm the length of catheter use in hospitalized patients or identify when a patient was hospitalized in a hospital outside of where their sample was tested (more likely in Montreal and Quebec City, which have many hospitals), there is a possibility of misclassifying nosocomial isolates as community-acquired, as well as incorrectly identifying previous hospitalization status. This could obscure the differences we observed between nosocomial and community-acquired isolates and blunt the increased risk of resistance seen in recently hospitalized patients.

This study demonstrates the utility of standardized antimicrobial resistance data from multiple institutions to produce locally relevant profiles of antimicrobial resistance. Our joint modelling approach allowed us to make inferences about demographic associations with six types of antimicrobial resistance, as well as temporal and geographic trends in resistance.

Clinically relevant differences in resistance within the province of Quebec, as well as between different patient populations, could inform empirical treatment decisions. In the future, a model-based approach for antimicrobial resistance informed by local, provincial, and national trends could be incorporated into decision-support systems for clinicians.

Funding

AMS acknowledges the support of the Natural Sciences and Engineering Research Council of Canada. CQ is supported by a Chercheur boursier de mérite career award from the Fonds de recherche du Québec - Santé.

Transparency declarations

None to declare. Nosotech provided the data for this project, but had no input into the design of the study, the analysis of the data, or the production of this manuscript.

References

1. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol* 2015; **13**: 269–84.

2. Foxman B. The epidemiology of urinary tract infection. *Nat Rev Urol* 2010; **7**: 653–60.

3. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary Tract Infection: Self-Reported Incidence and Associated Costs. *Ann Epidemiol* 2000; **10**: 509–15.

4. Dielubanza EJ, Schaeffer AJ. Urinary Tract Infections in Women. *Med Clin North Am* 2011; **95**: 27–41.

5. Foxman B. Chapter 36 - Urinary Tract Infection. In: Goldman MB, Troisi R, Rexrode KM, eds. *Women and Health (Second Edition)*. Cambridge, MA: Academic Press, 2013; 553–64.

6. Lob SH, Nicolle LE, Hoban DJ, Kazmierczak KM, Badal RE, Sahm DF. Susceptibility patterns and ESBL rates of *Escherichia coli* from urinary tract infections in Canada and the United States, SMART 2010–2014. *Diagn Microbiol Infect Dis* 2016; **85**: 459–65.

7. Zilberberg MD, Shorr AF. Secular Trends in Gram-Negative Resistance among Urinary Tract Infection Hospitalizations in the United States, 2000–2009. *Infect Control Hosp Epidemiol* 2013; **34**: 940–6.

8. Lagacé-Wiens PRS, Adam HJ, Low DE, *et al.* Trends in antibiotic resistance over time among pathogens from Canadian hospitals: results of the CANWARD study 2007-11. *J Antimicrob Chemother* 2013; **68**: i23–9.

9. Tenney J, Hudson N, Alnifaidy H, Li JTC, Fung KH. Risk factors for aquiring multidrug-resistant organisms in urinary tract infections: A systematic literature review. *Saudi Pharm J* 2018; **26**: 678–84.

10. den Heijer CDJ, Penders J, Donker GA, Bruggeman CA, Stobberingh EE. The Importance of Gender-Stratified Antibiotic Resistance Surveillance of Unselected Uropathogens: A Dutch Nationwide Extramural Surveillance Study Thumbikat P, ed. *PLoS ONE* 2013; **8**: e60497.

11. Fleming VH, White BP, Southwood R. Resistance of *Escherichia coli* urinary isolates in ED-treated patients from a community hospital. *Am J Emerg Med* 2014; **32**: 864–70.

12. Lagacé-Wiens PRS, Simner PJ, Forward KR, *et al.* Analysis of 3789 in- and outpatient *Escherichia coli* isolates from across Canada—results of the CANWARD 2007–2009 study. *Diagn Microbiol Infect Dis* 2011; **69**: 314–9.

13. Calbo E, Romaní V, Xercavins M, *et al.* Risk factors for community-onset urinary tract infections due to *Escherichia coli* harbouring extended-spectrum β-lactamases. *J Antimicrob Chemother* 2006; **57**: 780–3.

14. Talan DA, Krishnadasan A, Abrahamian FM, Stamm WE, Moran GJ, EMERGEncy ID NET Study Group. Prevalence and Risk Factor Analysis of Trimethoprim-Sulfamethoxazole– and Fluoroquinolone-Resistant *Escherichia coli* Infection among Emergency Department Patients with Pyelonephritis. *Clin Infect Dis* 2008; **47**: 1150–8.

15. Delisle G, Quach C, Domingo M-C, *et al. Escherichia coli* antimicrobial susceptibility profile and cumulative antibiogram to guide empirical treatment of uncomplicated urinary tract infections in women in the province of Québec, 2010–15. *J Antimicrob Chemother* 2016; **71**: 3562–7.

16. Toner L, Papa N, Aliyu SH, Dev H, Lawrentschuk N, Al-Hayek S. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in hospital urinary tract infections: incidence and antibiotic susceptibility profile over 9 years. *World J Urol* 2016; **34**: 1031–7.

17. Khawcharoenporn T, Vasoo S, Ward E, Singh K. High rates of quinolone resistance among urinary tract infections in the ED. *Am J Emerg Med* 2012; **30**: 68–74.

18. Toval F, Köhler C-D, Vogel U, *et al.* Characterization of *Escherichia coli* Isolates from Hospital Inpatients or Outpatients with Urinary Tract Infection. *J Clin Microbiol* 2014; **52**: 407–18.

19. Sabir N, Ikram A, Zaman G, *et al.* Bacterial biofilm-based catheter-associated urinary tract infections: Causative pathogens and antibiotic resistance. *Am J Infect Control* 2017; **45**: 1101–5.

20. Zhanel G, Hisanaga T, Laing N, *et al.* Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents* 2006; **27**: 468–75.

21. McIsaac WJ, Moineddin R, Meaney C, Mazzulli T. Antibiotic-resistant *Escherichia coli* in women with acute cystitis in Canada. *Can J Infect Dis Med Microbiol* 2013; **24**: 143–9.

22. Public Health Agency of Canada. *Canadian Antimicrobial Resistance Surveillance System – 2017 Report*. 2017.

23. Gupta K, Hooton TM, Naber KG, *et al.* International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011; **52**: e103–20.

24. Grignon O, Montassier E, Corvec S, Lepelletier D, Hardouin JB, Caillon J. *Escherichia coli* antibiotic resistance in emergency departments. Do local resistance rates matter? *Eur J Clin Microbiol Infect Dis* 2015; **34**: 571–7.

25. Song S, Lee EY, Koh E-M, *et al.* Antibiotic Resistance Mechanisms of *Escherichia coli* Isolates from Urinary Specimens. *Korean J Lab Med* 2009; **29**: 17.

26. Mammeri H, Van De Loo M, Poirel L, Martinez-Martinez L, Nordmann P. Emergence of Plasmid-Mediated Quinolone Resistance in *Escherichia coli* in Europe. *Antimicrob Agents Chemother* 2005; **49**: 71–6.

27. Paterson DL, Bonomo RA. Extended-Spectrum -Lactamases: a Clinical Update. *Clin Microbiol Rev* 2005; **18**: 657–86.

28. CLSI. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—Twelfth Edition. CLSI document M02-A12.* Wayne, PA: Committee for Clinical Laboratory Standards; 2015.

29. CDC. *Catheter-Associated Urinary Tract Infection (CAUTI) Event; National Healthcare Safety Network Patient Safety Component Manual.* Centers for Disease Control and Prevention; 2012.

30. Girard R, Perraud M, Herriot HE, *et al. Prevention of hospital-acquired infections: A Practical Guide, 2nd Edition*. World Health Organization; 2002.

31. Choi S-H, Kim EY, Kim Y-J. Systemic use of fluoroquinolone in children. *Korean J Pediatr* 2013; **56**: 196.

32. Sun L, Klein EY, Laxminarayan R. Seasonality and temporal correlation between community antibiotic use and resistance in the United States. *Clin Infect Dis* 2012; **55**: 687–94.

33. Jeon K, Kwon OJ, Lee NY, *et al.* Antibiotic Treatment of *Mycobacterium abscessus* Lung Disease: A Retrospective Analysis of 65 Patients. *Am J Respir Crit Care Med* 2009; **180**: 896–902.

34. Benedict KM, Gow SP, Checkley S, Booker CW, McAllister TA, Morley PS. Methodological comparisons for antimicrobial resistance surveillance in feedlot cattle. *BMC Vet Res* 2013; **9**: 216.

35. Gelman A, Hill J. *Data Analysis Using Regression and Multilevel/Hierarchical Models*. Cambridge: Cambridge University Press; 2006.

36. Gelman A. Prior distributions for variance parameters in hierarchical models (Comment on Article by Browne and Draper). *Bayesian Anal* 2006; **1**: 515–34.

37. de Valpine P, Turek D, Paciorek CJ, Anderson-Bergman C, Lang DT, Bodik R. Programming With Models: Writing Statistical Algorithms for General Model Structures With NIMBLE. *J Comput Graph Stat* 2017; **26**: 403–13.

38. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018. Available at: https://www.R-project.org/.

39. Lipsky BA. Urinary Tract Infections in Men: Epidemiology, Pathophysiology, Diagnosis, and Treatment. *Ann Intern Med* 1989; **110**: 138.

40. Fasugba O, Gardner A, Mitchell BG, Mnatzaganian G. Ciprofloxacin resistance in community- and hospital-acquired *Escherichia coli* urinary tract infections: a systematic review and meta-analysis of observational studies. *BMC Infect Dis* 2015; **15**.

41. World Health Organization. *Antimicrobial resistance: global report on surveillance*. Geneva: World Health Organization; 2014.

42. Blaettler L, Mertz D, Frei R, *et al.* Secular Trend and Risk Factors for Antimicrobial Resistance in *Escherichia coli* Isolates in Switzerland 1997–2007. *Infection* 2009; **37**: 534–9.

43. Karlowsky JA, Lagacé-Wiens PRS, Simner PJ, *et al.* Antimicrobial Resistance in Urinary Tract Pathogens in Canada from 2007 to 2009: CANWARD Surveillance Study. *Antimicrob Agents Chemother* 2011; **55**: 3169–75.

44. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci* 2011; **108**: 4554–61.

45. Carlet J. The gut is the epicentre of antibiotic resistance. *Antimicrob Resist Infect Control* 2012; **1**: 39.

46. Bruinsma N. Influence of population density on antibiotic resistance. *J Antimicrob Chemother* 2003; **51**: 385–90.

47. Gelman A, Hill J. Logistic regression. In: *Data Analysis Using Regression and Multilevel/Hierarchical Models*. Cambridge: Cambridge University Press, 2006; 79–108.

Table 1. Characteristics of 79,370 urinary *E. coli* isolates collected from three communities in Quebec, Canada (April 2010–December 2017).

Characteristic	Community	Nosocomial
All	74,986	4,384
Sex		
Male	11,079 (14.8%)	1,310 (29.9%)
Female	63,907 (85.2%)	3,074 (70.1%)
Age category		
18–64	44,981 (60%)	-
65–95	30,005 (40%)	4,384
Prior hospitalization in the past 30 days	1,743 (2.3%)	392 (8.9%)
Community		
Montreal	16,396 (21.9%)	1,478 (33.7%)
Quebec City	51,942 (69.3%)	2,296 (52.4%)
Rimouski	6,648 (8.9%)	6,10 (13.9%)
Resistance		
Ampicillin	24,713 (33%)	1,683 (38.4%)
Ciprofloxacin	9,930 (13.2%)	896 (20.4%)
Gentamicin	4,572 (6.1%)	375 (8.6%)
Nitrofurantoin	719 (1%)	60 (1.4%)
Tobramycin	1,340 (1.8%)	120 (2.7%)
TMP/SMX	13,037 (17.4%)	819 (18.7%)

Figure 1. Log odds ratios (with 95% credible intervals) for years compared to 2010 for resistance to six antimicrobials in urinary *E. coli* isolates. Some credible intervals for nitrofurantoin have been truncated at -1.0 to facilitate comparison.

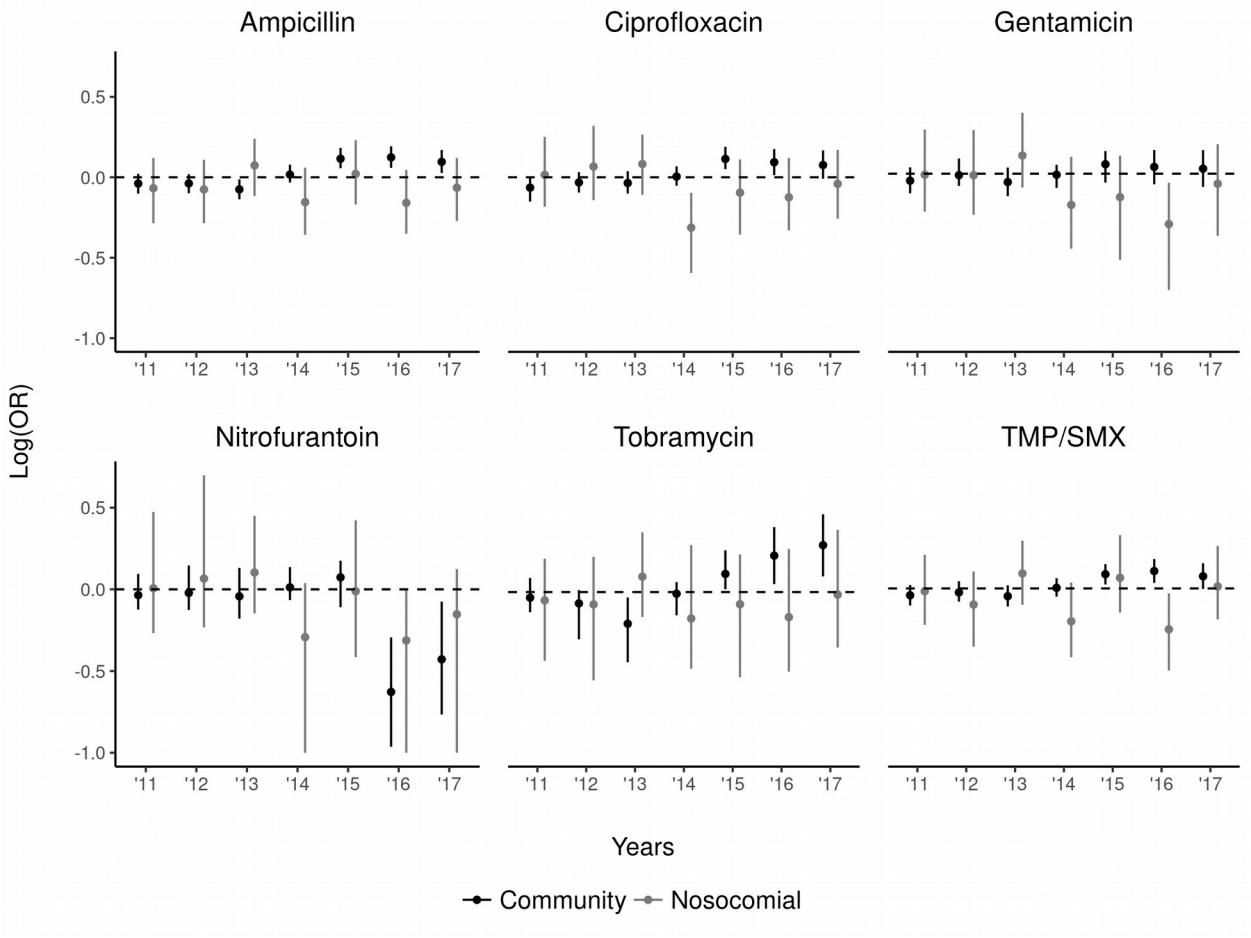


Figure 2. Log odds ratios (with 95% credible intervals) for months compared to January for resistance to six antimicrobials in urinary *E. coli* isolates. Some credible intervals for gentamicin, nitrofurantoin, and tobramycin have been truncated at -1.0 to facilitate comparison.

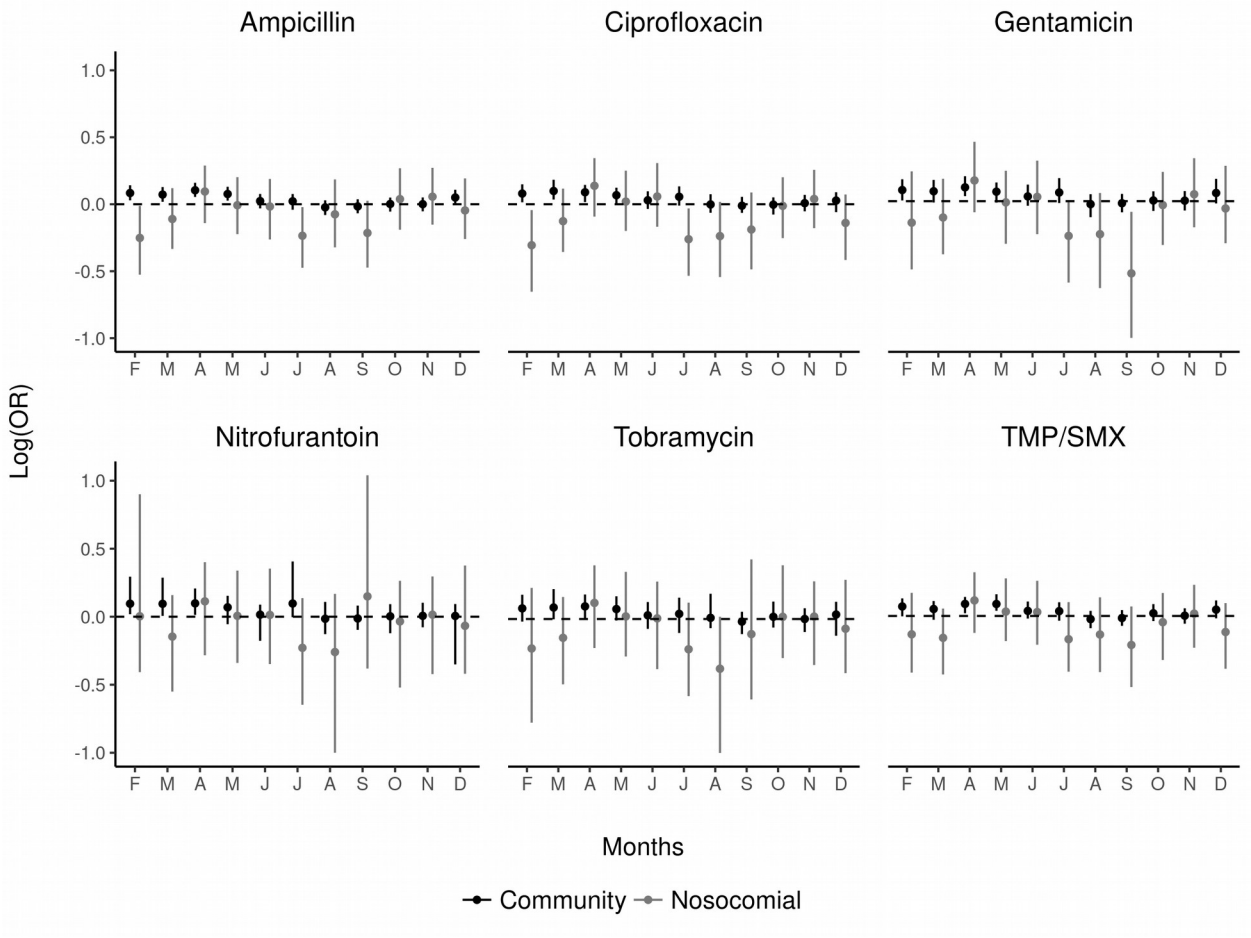


Figure 3. Log odds ratios (with 95% credible intervals) for patient characteristics and community (compared to Montreal) for resistance to six antimicrobials in urinary *E. coli* isolates. The intercept corresponds to female patients aged approximately 55 and 80 years old for community-acquired and nosocomial isolates, respectively. The intercepts for gentamicin, nitrofurantoin, and tobramycin are not shown, as the base odds of resistance are very low.

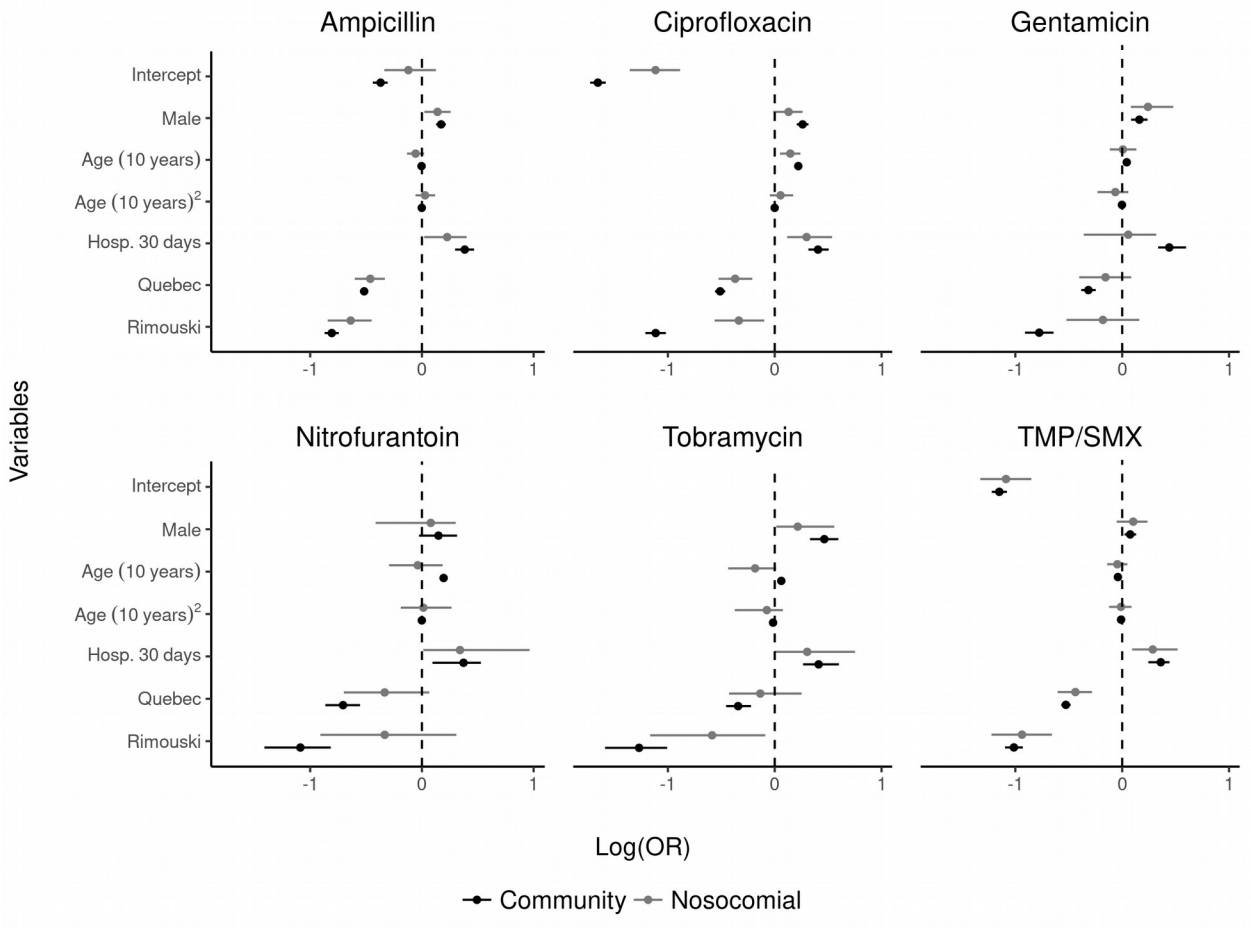


Figure 4. Fitted probability of resistance to six antimicrobials (with 95% credible intervals) for community-acquired urinary *E. coli* isolates from three communities in Quebec, Canada. January probability of resistance is presented for women aged approximately 55 and not hospitalized in the past 30 days.

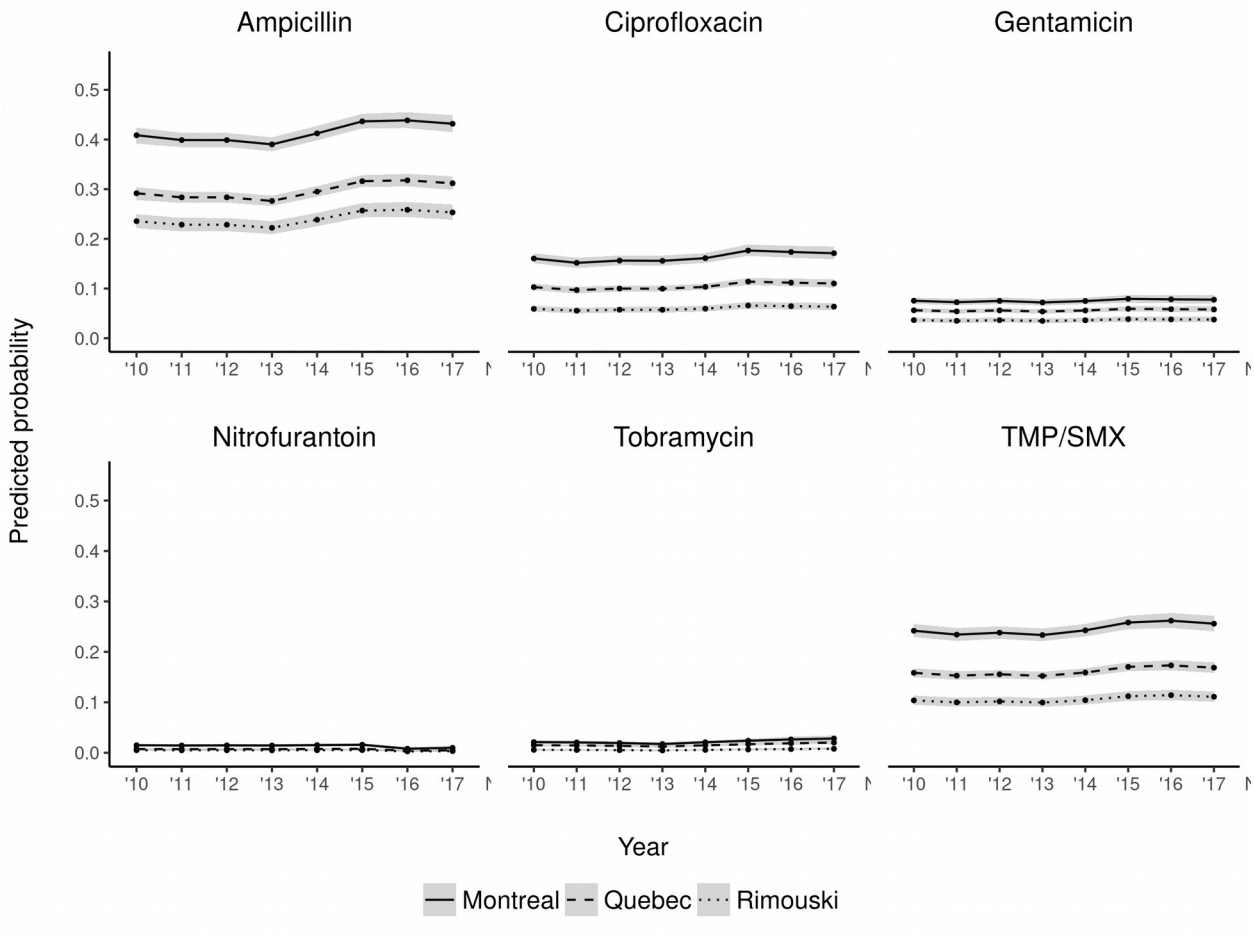
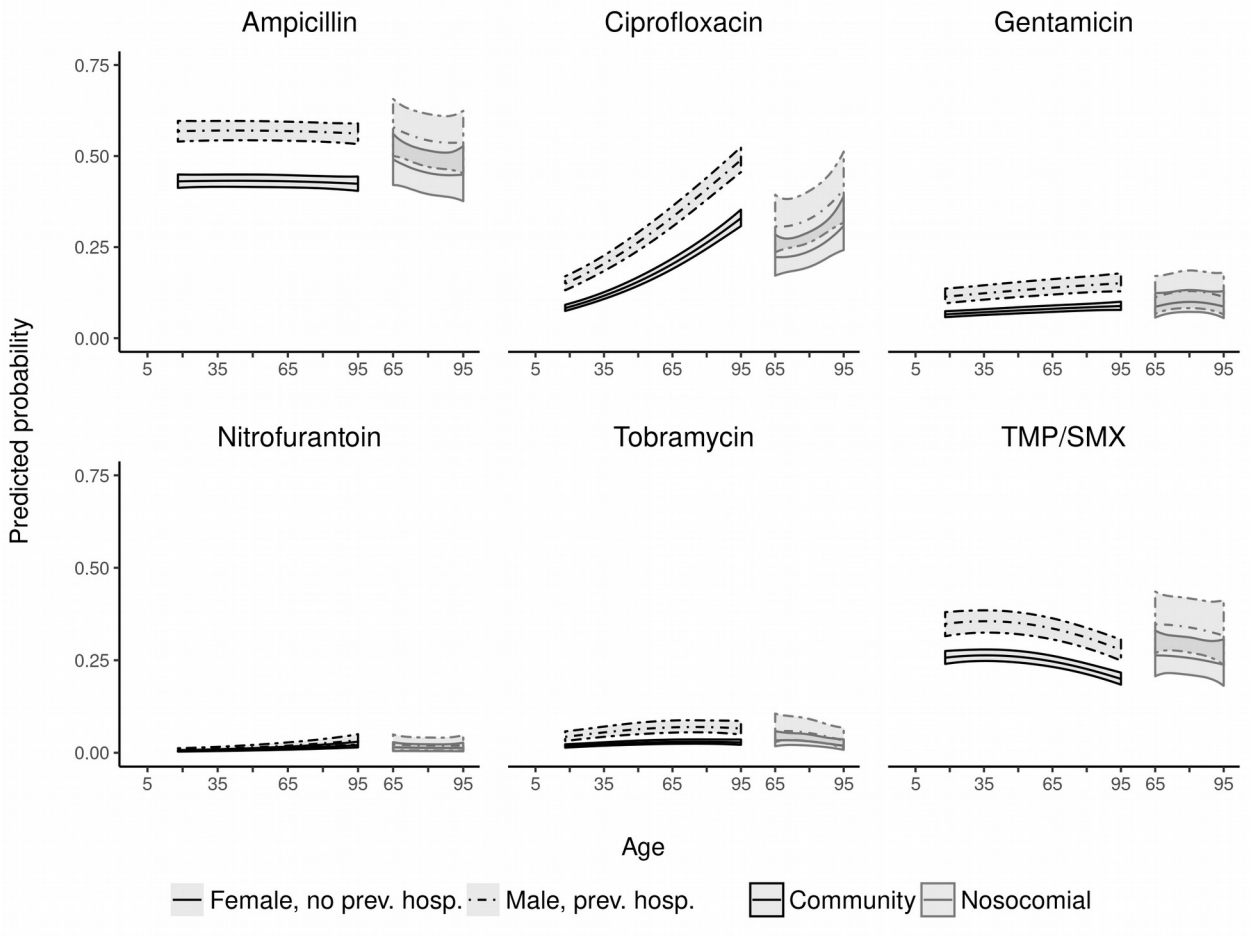


Figure 5. Fitted probability of resistance to six antimicrobials (with 95% credible intervals) for community-acquired and nosocomial urinary *E. coli* isolates, comparing female, not recently hospitalized patients versus male, recently hospitalized patients. Patients are assumed to be in Montreal during January of 2017.



Supplementary Methods

Markov chain Monte Carlo methods

Age was centred at its mean value prior to modelling. Models were run for 30,000 iterations, discarding the first 10% as burn-in. Residuals were assessed using binned residual plots as described by Gelman & Hill[47]. Chains were visually inspected for convergence. Finally, a second chain was run using different initial values and results were compared to verify convergence had actually occurred.

Supplementary Table 1. Odds ratios (with 95% credible intervals) for all variables in the hierarchical model for resistance to six antimicrobials in community-acquired urinary *E. coli* isolates. The intercept refers to a female approximately 55 years of age and not hospitalized in the past 30 days in Montreal during January of 2010.

Coefficient	Top-level	Ampicillin	Ciprofloxacin	Gentamicin	Nitrofurantoin	Tobramycin	TMP/SMX
Intercept	0.10 (0.02, 0.65)	0.69 (0.64, 0.74)	0.19 (0.18, 0.21)	0.08 (0.07, 0.09)	0.02 (0.01, 0.02)	0.02 (0.02, 0.03)	0.32 (0.30, 0.34)
Sex (male)	1.24 (1.00, 1.53)	1.19 (1.14, 1.24)	1.30 (1.23, 1.37)	1.17 (1.09, 1.27)	1.16 (0.97, 1.37)	1.59 (1.39, 1.81)	1.08 (1.02, 1.14)
Age (10 years)	1.08 (0.95, 1.23)	1.00 (0.99, 1.00)	1.25 (1.23, 1.26)	1.04 (1.03, 1.06)	1.21 (1.17, 1.26)	1.06 (1.04, 1.09)	0.96 (0.95, 0.97)
Age^2 (10 years)	1.00 (0.98, 1.01)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	0.98 (0.97, 1.00)	0.99 (0.99, 0.99)
Hosp. past 30 days	1.48 (1.32, 1.66)	1.47 (1.35, 1.60)	1.50 (1.37, 1.66)	1.55 (1.40, 1.82)	1.45 (1.10, 1.70)	1.51 (1.30, 1.82)	1.44 (1.28, 1.56)
Quebec	0.62 (0.51, 0.74)	0.60 (0.57, 0.62)	0.60 (0.57, 0.63)	0.73 (0.68, 0.78)	0.49 (0.42, 0.57)	0.71 (0.63, 0.80)	0.59 (0.57, 0.62)
Rimouski	0.36 (0.27, 0.48)	0.45 (0.42, 0.48)	0.33 (0.30, 0.36)	0.46 (0.40, 0.53)	0.34 (0.24, 0.44)	0.28 (0.20, 0.37)	0.36 (0.33, 0.39)
2011	0.96 (0.90, 1.03)	0.96 (0.90, 1.02)	0.94 (0.86, 1.00)	0.96 (0.89, 1.04)	0.97 (0.88, 1.10)	0.97 (0.88, 1.09)	0.96 (0.90, 1.02)
2012	0.97 (0.88, 1.05)	0.96 (0.91, 1.02)	0.97 (0.91, 1.03)	0.99 (0.93, 1.10)	0.98 (0.88, 1.16)	0.93 (0.75, 1.01)	0.98 (0.92, 1.04)
2013	0.93 (0.81, 1.04)	0.93 (0.87, 0.99)	0.96 (0.90, 1.04)	0.95 (0.87, 1.04)	0.96 (0.84, 1.14)	0.82 (0.65, 0.97)	0.95 (0.90, 1.02)
2014	1.00 (0.94, 1.07)	1.02 (0.97, 1.08)	1.00 (0.95, 1.07)	0.99 (0.92, 1.06)	1.01 (0.94, 1.15)	0.99 (0.87, 1.06)	1.00 (0.95, 1.06)
2015	1.10 (1.00, 1.19)	1.12 (1.06, 1.20)	1.12 (1.05, 1.21)	1.06 (0.95, 1.15)	1.08 (0.90, 1.19)	1.12 (1.02, 1.30)	1.09 (1.02, 1.16)
2016	1.00 (0.66, 1.47)	1.13 (1.06, 1.21)	1.10 (1.01, 1.19)	1.04 (0.94, 1.16)	0.53 (0.38, 0.74)	1.25 (1.05, 1.50)	1.11 (1.03, 1.20)
2017	1.03 (0.72, 1.41)	1.10 (1.03, 1.19)	1.08 (0.99, 1.18)	1.03 (0.92, 1.15)	0.65 (0.46, 0.93)	1.34 (1.10, 1.62)	1.08 (1.00, 1.17)
Feb	1.08 (1.02, 1.17)	1.09 (1.03, 1.15)	1.08 (1.01, 1.16)	1.08 (1.01, 1.17)	1.10 (1.02, 1.34)	1.08 (0.98, 1.20)	1.07 (1.00, 1.14)
Mar	1.08 (1.01, 1.19)	1.07 (1.02, 1.14)	1.10 (1.04, 1.20)	1.08 (0.99, 1.17)	1.10 (1.01, 1.33)	1.09 (1.00, 1.25)	1.05 (0.97, 1.12)
Apr	1.10 (1.04, 1.17)	1.11 (1.06, 1.17)	1.09 (1.02, 1.16)	1.11 (1.04, 1.20)	1.10 (1.01, 1.23)	1.10 (1.00, 1.20)	1.09 (1.02, 1.15)
May	1.08 (1.01, 1.14)	1.08 (1.03, 1.14)	1.07 (1.00, 1.13)	1.07 (0.99, 1.15)	1.07 (0.95, 1.17)	1.08 (0.99, 1.18)	1.09 (1.04, 1.17)
Jun	1.03 (0.96, 1.09)	1.02 (0.97, 1.08)	1.03 (0.97, 1.10)	1.04 (0.97, 1.13)	1.02 (0.84, 1.09)	1.03 (0.93, 1.14)	1.04 (0.98, 1.11)
Jul	1.05 (0.97, 1.19)	1.02 (0.96, 1.08)	1.06 (0.99, 1.14)	1.07 (0.99, 1.18)	1.10 (1.00, 1.50)	1.04 (0.90, 1.17)	1.04 (0.97, 1.11)
Aug	0.99 (0.92, 1.07)	0.98 (0.92, 1.03)	1.00 (0.94, 1.08)	0.98 (0.89, 1.05)	0.99 (0.88, 1.12)	1.01 (0.93, 1.21)	0.98 (0.91, 1.04)
Sep	0.99 (0.93, 1.04)	0.98 (0.93, 1.04)	0.99 (0.94, 1.06)	0.99 (0.92, 1.05)	0.99 (0.91, 1.09)	0.98 (0.89, 1.06)	0.98 (0.93, 1.04)
Oct	1.01 (0.94, 1.07)	1.00 (0.95, 1.05)	1.00 (0.93, 1.05)	1.01 (0.93, 1.07)	1.00 (0.89, 1.10)	1.02 (0.94, 1.14)	1.02 (0.96, 1.09)
Nov	1.00 (0.95, 1.06)	1.00 (0.95, 1.05)	1.01 (0.95, 1.07)	1.00 (0.93, 1.08)	1.01 (0.93, 1.11)	1.00 (0.91, 1.08)	1.00 (0.94, 1.06)
Dec	1.04 (0.91, 1.11)	1.05 (0.99, 1.11)	1.03 (0.94, 1.09)	1.06 (0.98, 1.18)	1.01 (0.70, 1.10)	1.03 (0.88, 1.14)	1.05 (0.98, 1.12)

Supplementary Table 2. Odds ratios (with 95% credible intervals) for all variables in the hierarchical model for resistance to six antimicrobials in nosocomial urinary *E. coli* isolates. The intercept refers to a female approximately 80 years of age and not hospitalized in the past 30 days in Montreal during January of 2010.

Coefficient	Top-level	Ampicillin	Ciprofloxacin	Gentamicin	Nitrofurantoin	Tobramycin	TMP/SMX
Intercept	0.14 (0.02, 0.93)	0.89 (0.71, 1.13)	0.33 (0.26, 0.41)	0.11 (0.09, 0.15)	0.02 (0.01, 0.03)	0.03 (0.02, 0.05)	0.34 (0.26, 0.43)
Sex (male)	1.16 (0.95, 1.42)	1.15 (1.02, 1.29)	1.14 (0.99, 1.30)	1.27 (1.08, 1.61)	1.08 (0.66, 1.35)	1.24 (1.01, 1.75)	1.11 (0.95, 1.27)
Age (10 years)	0.97 (0.80, 1.15)	0.94 (0.87, 1.02)	1.16 (1.05, 1.27)	1.01 (0.89, 1.14)	0.96 (0.75, 1.20)	0.83 (0.65, 1.01)	0.96 (0.87, 1.05)
Age^2 (10 years)	0.99 (0.85, 1.13)	1.03 (0.94, 1.13)	1.06 (0.96, 1.19)	0.94 (0.79, 1.06)	1.01 (0.83, 1.30)	0.93 (0.69, 1.08)	0.99 (0.88, 1.09)
Hosp. past 30 days	1.29 (0.98, 1.78)	1.25 (1.02, 1.49)	1.35 (1.12, 1.71)	1.06 (0.70, 1.38)	1.41 (1.01, 2.62)	1.36 (1.00, 2.12)	1.33 (1.10, 1.68)
Quebec	0.73 (0.57, 0.98)	0.63 (0.55, 0.72)	0.69 (0.59, 0.81)	0.86 (0.67, 1.09)	0.72 (0.50, 1.07)	0.87 (0.65, 1.29)	0.65 (0.55, 0.75)
Rimouski	0.60 (0.38, 0.97)	0.53 (0.43, 0.64)	0.71 (0.57, 0.91)	0.83 (0.59, 1.17)	0.72 (0.40, 1.36)	0.56 (0.31, 0.92)	0.39 (0.29, 0.52)
2011	0.98 (0.80, 1.23)	0.93 (0.75, 1.13)	1.02 (0.83, 1.29)	0.99 (0.79, 1.31)	1.01 (0.76, 1.61)	0.95 (0.65, 1.23)	0.98 (0.80, 1.23)
2012	0.98 (0.76, 1.30)	0.93 (0.75, 1.11)	1.07 (0.87, 1.38)	0.99 (0.78, 1.30)	1.07 (0.79, 2.01)	0.93 (0.58, 1.25)	0.91 (0.70, 1.11)
2013	1.10 (0.91, 1.35)	1.08 (0.89, 1.27)	1.09 (0.90, 1.30)	1.12 (0.92, 1.45)	1.11 (0.86, 1.57)	1.10 (0.86, 1.45)	1.10 (0.91, 1.34)
2014	0.80 (0.56, 1.07)	0.86 (0.70, 1.06)	0.73 (0.55, 0.91)	0.83 (0.63, 1.11)	0.75 (0.27, 1.04)	0.85 (0.62, 1.34)	0.82 (0.66, 1.04)
2015	0.96 (0.72, 1.23)	1.02 (0.84, 1.26)	0.91 (0.70, 1.12)	0.87 (0.59, 1.12)	0.99 (0.66, 1.53)	0.93 (0.59, 1.26)	1.07 (0.86, 1.38)
2016	0.80 (0.55, 1.04)	0.85 (0.70, 1.05)	0.88 (0.72, 1.13)	0.74 (0.49, 0.95)	0.73 (0.30, 1.00)	0.86 (0.61, 1.31)	0.78 (0.61, 0.97)
2017	0.94 (0.63, 1.21)	0.94 (0.76, 1.13)	0.96 (0.77, 1.19)	0.94 (0.69, 1.20)	0.86 (0.26, 1.13)	0.98 (0.71, 1.47)	1.01 (0.83, 1.30)
Feb	0.84 (0.59, 1.28)	0.78 (0.59, 0.99)	0.74 (0.52, 0.96)	0.85 (0.61, 1.24)	1.00 (0.67, 2.46)	0.80 (0.46, 1.26)	0.87 (0.66, 1.18)
Mar	0.87 (0.69, 1.10)	0.90 (0.72, 1.13)	0.88 (0.70, 1.12)	0.89 (0.68, 1.18)	0.86 (0.58, 1.17)	0.87 (0.61, 1.18)	0.85 (0.65, 1.06)
Apr	1.13 (0.89, 1.38)	1.10 (0.87, 1.33)	1.15 (0.91, 1.41)	1.16 (0.92, 1.54)	1.12 (0.75, 1.49)	1.13 (0.81, 1.49)	1.12 (0.88, 1.38)
May	1.01 (0.80, 1.27)	0.99 (0.80, 1.22)	1.02 (0.82, 1.28)	0.99 (0.73, 1.25)	1.01 (0.71, 1.40)	1.02 (0.76, 1.42)	1.03 (0.83, 1.32)
Jun	1.02 (0.80, 1.28)	0.98 (0.77, 1.21)	1.06 (0.85, 1.36)	1.03 (0.79, 1.34)	1.01 (0.71, 1.42)	1.00 (0.69, 1.32)	1.03 (0.81, 1.29)
Jul	0.80 (0.61, 1.01)	0.79 (0.62, 0.98)	0.77 (0.59, 0.97)	0.78 (0.55, 1.00)	0.80 (0.52, 1.15)	0.80 (0.56, 1.13)	0.84 (0.67, 1.11)
Aug	0.80 (0.49, 1.08)	0.93 (0.72, 1.20)	0.79 (0.58, 1.02)	0.79 (0.53, 1.06)	0.77 (0.34, 1.18)	0.69 (0.27, 1.02)	0.87 (0.66, 1.15)
Sep	0.83 (0.53, 1.37)	0.81 (0.62, 1.03)	0.83 (0.61, 1.09)	0.59 (0.32, 0.92)	1.16 (0.68, 2.83)	0.89 (0.55, 1.56)	0.81 (0.59, 1.07)
Oct	0.99 (0.76, 1.23)	1.04 (0.83, 1.31)	0.99 (0.78, 1.22)	0.97 (0.73, 1.24)	0.97 (0.59, 1.30)	1.02 (0.75, 1.49)	0.96 (0.72, 1.18)
Nov	1.03 (0.81, 1.27)	1.06 (0.86, 1.31)	1.04 (0.84, 1.29)	1.05 (0.83, 1.37)	1.01 (0.66, 1.34)	1.02 (0.71, 1.32)	1.02 (0.79, 1.26)
Dec	0.92 (0.72, 1.17)	0.95 (0.77, 1.21)	0.87 (0.66, 1.08)	0.95 (0.74, 1.30)	0.94 (0.66, 1.46)	0.93 (0.67, 1.34)	0.89 (0.68, 1.10)

4.3. Manuscript 2: Fluoroquinolone consumption explains seasonal patterns in ciprofloxacin resistance in community-acquired urinary *Escherichia coli*: A dynamic linear model in a large urban community

Fluoroquinolone use explains seasonal patterns in ciprofloxacin resistance in community-acquired urinary *Escherichia coli*: A dynamic linear model in a large urban community

Jean-Paul R. Soucy, Alexandra M. Schmidt, Caroline Quach, David L. Buckeridge

Abbreviations: UTI, urinary tract infection

Correspondence: Dr. David L. Buckeridge, Department of Epidemiology, Biostatistics and Occupational Health, McGill University, 1020 Pine Avenue West, Montreal (QC) H3A 1A2 Canada; Email: david.buckeridge@mcgill.ca; Phone: 1-514-843-2831; Fax: 1-514-843-1551

Running head: Fluoroquinolone use and resistance in *E. coli*

ABSTRACT

Urinary tract infections caused by the bacteria *Escherichia coli* are among the most frequently encountered infections and a common reason for antibiotic prescriptions. Resistance to fluoroquinolone antimicrobials, and in particular ciprofloxacin, has increased in recent decades. It is intuitive that variation in resistance is driven by changes in antimicrobial use, but proper time series methods are necessary to study this association. We investigated the monthly proportion of ciprofloxacin resistance in community-acquired urinary *E. coli* isolates in Montreal, Quebec, Canada between April 2010 and December 2014 using a dynamic linear model. We found a positive correlation between total fluoroquinolone use lagged by 1 and 2 months and the proportion of isolates resistant to ciprofloxacin. Our results suggest that resistance to ciprofloxacin is responsive to changes in antimicrobial use. Thus, antimicrobial stewardship campaigns to reduce fluoroquinolone use, particularly in the community setting, are likely to be a value tool in the struggle against antimicrobial resistance.

Keywords: antimicrobial resistance, antimicrobial use, ciprofloxacin, dynamic linear models, *Escherichia coli*, fluoroquinolones, time series, urinary tract infections

Antimicrobial resistance has been recognized as one of the greatest threats to global health today (1). Rising levels of resistance to numerous classes of drugs threatens our ability to treat common infections, leading to higher costs, prolonged hospital stays, and worse outcomes for patients (1,2). Although antimicrobial resistance is a naturally occurring phenomenon, antimicrobial use is generally recognized as the leading driver of resistance (1,3–5). Given the paucity of new antimicrobials in the drug development pipeline, it is critical to understand the forces underlying patterns of resistance (6,7).

Urinary tract infections (UTIs) are among the most commonly encountered infections in both the hospital and community settings, affecting mainly women, as well as infant and elderly males (8,9). In fact, the lifetime risk for UTIs in women exceeds 50%, and many women will suffer more than one episode in their lifetime (10,11). Additionally, UTIs may account for up to 40% of infections in hospitals (9). Although UTIs are associated with a number of bacterial and even fungal species, *Escherichia coli* is by far the most prominent infectious agent (9,12). Given the high prevalence of these infections, it follows that UTIs are major drivers of antimicrobial use and potentially resistance.

The connection between antimicrobial use and antimicrobial resistance is certainly intuitive, and studies comparing patterns of use and resistance across countries support this notion (3–5). The demonstration of a temporal association between use and resistance provides stronger evidence for this connection, but this relationship is more difficult to study for both statistical and biological reasons. First, special time series methods are required to deal with the serial dependence of observations through time. Caution must be observed, as it is easy to observe strong yet spurious correlations between two variables by not accounting for the correlated nature of the data or due to hidden variables (13,14). Biologically, there are good reasons to expect antimicrobial resistance to imperfectly mirror patterns of antimicrobial

consumption. Generally, resistance mutations incur fitness penalties, such as reduced growth rate, competitive ability, and virulence (15,16). However, compensatory evolution (additional mutations relieving the fitness cost of resistance), co-selection with other traits, and complex interaction between genes can result in the persistence of antimicrobial resistance in bacterial populations even when the selective pressure of antimicrobials is alleviated (15–17).

Quinolone antimicrobials present a particularly interesting case of antimicrobial resistance. This class of drug, introduced in 1962, is fully synthetic and involves complex mechanisms of action; for these reasons, it was thought to be unlikely that resistance would emerge (18). Nonetheless, resistance to early quinolones quickly became widespread, and a more potent sub-class of quinolones, fluoroquinolones, was introduced in 1982 (18). This sub-class represents almost all quinolones still in use today, including the broad-spectrum antimicrobial ciprofloxacin, which is among the most commonly prescribed antimicrobials in the world (19,20). The prevalence of fluoroquinolone resistance has risen over the past two decades (21–23). Given the frequency at which fluoroquinolones (specifically ciprofloxacin and levofloxacin) have been prescribed for UTIs (24), as well as the ability for quinolone resistance to transfer horizontally via plasmids (18,25), this suggests that UTIs may play an important role in rising rates of resistance.

In the province of Quebec, Canada, ciprofloxacin resistance is routinely tested and reported for *E. coli* UTIs in adults (fluoroquinolones are not approved for use in children and thus rarely prescribed to them (26)). The prevalence of resistance to this drug shows both annual and seasonal patterns, as does the use of fluoroquinolones, making it an ideal candidate for time series analysis. Previous research has found correlations between time-lagged values of fluoroquinolone use in the community and the prevalence and incidence of ciprofloxacin resistance in community-acquired *E. coli* isolates using models under an autoregressive

integrated moving average framework (27–29). However, this class of models has several notable drawbacks, including a disregard for the structure of the data in favour of an untransparent, data-driven approach ("black box" model) and an artificial requirement for stationarity (constant mean and variance across time) prior to analysis, often requiring extensive transformation of the data (30). Additionally, the aforementioned studies did not consider averaged patient characteristics such as age and sex for explaining variation in observed rates of resistance between months.

Here, we propose the use of dynamic linear models (a type of state-space model—for an overview, see (31) or (32) for worked examples with R), an explicitly structural approach to time series analysis which offers greater flexibility than autoregressive integrated moving average models and allows us to decompose monthly ciprofloxacin resistance as a function of mean, seasonal, and averaged patient characteristic components. In this study, we investigated community fluoroquinolone use as a driver of observed seasonal trends in ciprofloxacin resistance in the city of Montreal, Quebec, Canada between April 2010 and December 2014.

METHODS

Setting

Montreal is a large city located in the province of Quebec, Canada. Near the beginning of the study period (2011), the health region of Montreal had a census population of 1,886,480, which includes the city proper but not the surrounding metropolitan area (33). The McGill University Health Centre is one of the two major teaching healthcare networks in the city, providing hospital services to the city as well as specialized and ultra-specialized care to the surrounding area and the rest of the province. This study included data from the following hospitals representing all but one in the network: Royal Victoria Hospital, Montreal General

Hospital, Montreal Neurological Hospital, and Montreal Children's Hospital, accounting for over a thousand hospital beds.

Antimicrobial resistance data

We examined resistance to ciprofloxacin in community-acquired urinary *E. coli* isolates for patients between the age of 18 and 95 tested in the laboratory of the McGill University Health Centre between April 2010 and December 2014. For each isolate, the following data were available: date of collection, age, sex, patient unique identifier, date of previous admission, and antimicrobial susceptibility testing results classified as sensitive, intermediate, or resistant. Species identification and susceptibility testing was done following Clinical and Laboratory Standards Institute breakpoints and guidelines (34). We excluded samples obtained 48 hours or more after hospital admission or within 48 hours after hospital discharge as potentially nosocomial based on National Healthcare Safety Network guidelines (35) and considered all other samples (e.g. from emergency departments, outpatient clinics, and community clinics) as community-acquired. Samples with more than two bacterial species were excluded, being considered as contaminated (36). Since our methodology presumes that samples are independent, we retained only the first urinary *E. coli* isolate from each patient. In total, we had 11,214 unique isolates (mean: 197/month). The small percentage of susceptibility results classified as intermediate (0.3%) were grouped with the susceptible isolates for the purpose of analysis ("non-resistant" isolates, e.g., see (29,37,38)). Finally, we calculated the monthly proportion of samples resistant to ciprofloxacin.

Fluoroquinolones dispensation data

Outpatient use of fluoroquinolones was estimated using dispensation data for a randomly sampled, open cohort of 25% of people covered by the Régie de l'Assurance Maladie du Québec's Public Prescription Drug Insurance Plan for the health region of Montreal. Our

subsample, covering the years 2004–2014, is drawn from a larger cohort covering 25% of the population of the Census Metropolitan Area of Montreal, described in detail elsewhere (39). In Quebec, all residents are covered for medical care and hospitalizations, and prescriptions are also covered for residents ineligible for a private plan. These groups, which comprised nearly 49% of Montreal's population in 2011 (40), include individuals 65 years of age or older, individuals receiving social assistance, and workers and family members without access to private drug insurance (e.g. self-employed, students, etc.). The claims database included the nature, quantity, and date of every drug dispensed to each individual covered under the plan, as well as demographic information.

We considered outpatient oral fluoroquinolone use (Anatomical Therapeutic Chemical Classification: J01MA) in Quebec, which comprises the following drugs: ciprofloxacin, levofloxacin, ofloxacin, norfloxacin, and moxifloxacin. We also considered total fluoroquinolone use. Antimicrobial use was expressed as monthly Defined Daily Doses (41) per 1,000 inhabitant-days, weighted by age, sex, and program type composition of individuals enrolled in the public drug plan, which is reported quarterly (40). We calculated DDDs assuming that all dispensed drugs were consumed, as antimicrobials are generally prescribed to provide one course of treatment for common infections.

Model fitting

For urinary *E. coli*, we modelled the monthly proportion of samples resistant to ciprofloxacin from April 2010 to December 2014 in a Bayesian dynamic linear model framework. The outcome (Y_t), is normally distributed after a logit transformation, so we modelled the logit of the expected proportion of resistant samples (θ_t) with Gaussian white noise observation errors (v_t):

$$\text{logit}(Y_t) = \theta_t + v_t \qquad\qquad v_t \sim N(0, \sigma_v^2).$$

The expected value (θ_t) is decomposed as the sum of three independent components: a time-varying mean (μ_t), averaged patient characteristics (P_t), and a seasonal component (S_t):

$$\theta_t = \mu_t + P_t + S_t.$$

We assumed the time-varying mean component follows a random walk with variance σ_μ^2. The averaged patient characteristic component was estimated in the model as a multiple regression on three values in the current month: percentage of samples where the patient is male, mean age of patients, and percentage of samples where the patient was admitted to the hospital in the past 30 days.

A standard way to account for seasonality is with a first-order harmonic, in our case with a period of 12 months. This models seasonality as a sinusoidal function of time without reference to antimicrobial use:

$$S_t = h_t \cos(2\pi/12t) + \widetilde{h}_t \sin(2\pi/12t).$$

We can allow the coefficients of the harmonic (h_t , $\widetilde{h}_t$) to remain statistic over time ($h_t = h$, $\widetilde{h}_t = \widetilde{h}$) or vary according to random walks with variances σ_h^2 and $\sigma_{\widetilde{h}}^2$, respectively.

Alternately, the seasonal component can be represented using a transfer function of antimicrobial use to model how the association between use and resistance evolves over time (for an overview of transfer functions, see (42)). Since we are interested in short-term, seasonal fluctuations in antimicrobial use (D_t), we first removed the trend (time-varying mean) component from the use series using loess smoothing ("stl" function in R 3.4.4 (43), subtracting the trend component from the overall series). We considered use of each of the fluoroquinolones mentioned above, as well as total fluoroquinolone use, in turn using a number of distributed lag models that consider the association of fluoroquinolone use in the current month ($D_{t,0}$) up to fluoroquinolone use five months ago ($D_{t,5}$) (a six month series).

$$S_t = \sum_{i=0}^{5} \beta_i D_{t,i} \qquad \text{(Finite distributed lag model)}$$

$$S_t = \sum_{m=0}^{M} a_m Z_{m,t} \qquad \text{(Almon model of order } M\text{)}$$

$$Z_{m,t} \begin{cases} m = 0 & \sum_{i=0}^{5} D_{t,i} \\ m \neq 0 & \sum_{i=1}^{5} i^m D_{t,i} \end{cases}$$

$$S_t = \lambda S_{t-1} + \psi D_{t,0} \qquad 0 \leq \lambda \leq 1 \qquad \text{(Koyck model)}$$

Briefly, the transfer functions considered are as follows: the finite distributed lag model requires one parameter for each lagged value of antimicrobial use (44); the Almon model reparametrizes the finite distributed lag model by assuming the regression coefficients form a polynomial curve of order *M* (raw beta coefficients can be recovered through a transformation) (45); finally, the Koyck model assumes the magnitude of association with the independent variable is greatest in the current time and decays exponentially with the length of the lag (44,46). The Koyck model does not fix the lag *a priori*. In this study, we considered Almon models of order 2 or 3. These models can easily be extended to consider the use of multiple antimicrobials simultaneously (multivariable transfer function).

For each model, we estimated the posterior distribution of the parameters using Markov chain Monte Carlo (MCMC) as implemented in the nimble (47) package (version 0.6-10) in R. The 95% posterior credible intervals for each parameter is presented after 500,000 iterations with a thinning interval of 5 and 10% burn-in. The time-varying mean (μ_t) and transfer function (S_t) parameters were estimated in a block using automated factor slice sampling, which substantially speeds convergence in correlated state-space models (48,49).

Model selection

We considered a total of 26 models (6 types of antimicrobial use × 4 possible transfer functions + static harmonic model + random harmonic model). Models were compared using

widely applicable information criterion (50), a generalization of Akaike information criterion commonly used to evaluate the model fit while penalizing complexity. Smaller values indicate better model fit.

Ethics

We obtained ethics approval from each participating institution according to the Multi-Centre Research Ethics Review Mechanism of the Quebec Ministry of Health and Social Services (MP-37-2018-3758).

RESULTS

Model selection

Table 1 shows the best transfer function model (using widely applicable information criterion) for each type of antimicrobial use, plus the two harmonic models. The overall best model included total fluoroquinolone use with a third order Almon model transfer function. Models for all but ofloxacin and norfloxacin use compared favourably to the harmonic models that did not consider antimicrobial resistance. The predicted values for resistance in the best model among the fitted ones are compared with the observed values in Figure 1A.

Time-varying mean

The mean level of resistance appeared to decrease from about 18.5% in the beginning of the study period (April 2010) until reaching a trough of about 17.2% in late 2011. After this, the mean climbed back to around 18.5% by mid-2012 (Figure 1B).

Patient characteristics

On the logit scale, the estimated regression coefficients (for a 1 unit increase) with 95% credible intervals (CI) were: mean age in years (0; 95% CI: -0.024, 0.024), percentage of isolates

where the patient was admitted to the hospital in the past 30 days (0.016; 95% CI: -0.012, 0.044), and percentage of isolates where the patient was male (0.013; 95% CI: -0.003, 0.030) (Figure 1C).

Seasonality

Fluoroquinolone resistance tended to show a seasonal pattern, with higher resistance between November to March and the lowest value around September (Figure 1A). Total fluoroquinolone use (Figure 2) was highly seasonal, with total use being lowest in July and highest from October to February (Figure 3). This suggests a time-lagged association of 1 to 2 months, which is exactly what is predicted by the model. A positive correlation was noted between total fluoroquinolone use lagged by 1 (0.257; 95% CI: 0.072, 0.438) and 2 (0.261, 95% CI: 0.110, 0.412) months (Figure 4A). These figures indicate the expected change in the logit of the proportion of resistance from a 1 unit change in total fluoroquinolone use in Defined Daily Doses per 1,000 inhabitant-days. The transfer function component of the model is plotted in Figure 4B.

The seasonality of levofloxacin use and moxifloxacin use closely followed the overall pattern of use for fluoroquinolones, whereas ciprofloxacin differed somewhat (Figure 3). Since ofloxacin and norfloxacin are prescribed much less compared to the other three drugs, estimation of their seasonal trends was more susceptible to sampling error.

DISCUSSION

In this study, we used a dynamic linear model to decompose ciprofloxacin resistance in community-acquired urinary *E. coli* infections in the city of Montreal, Quebec, Canada between April 2010 and December 2014 into three components: a time-varying mean, a component based on averaged patient characteristics, and seasonal variation as represented by lagged

fluoroquinolone use in Montreal. Compared to traditional autoregressive integrated moving average models for time series, this approach has the advantage of allowing us to estimate the long-term trend at the same time as the association between antimicrobial use and resistance across time. Additionally, the use of the Almon model to impose a biologically plausible correlation structure on the coefficients for lagged antimicrobial use allowed us to estimate these relationships using fewer parameters in the model.

Our three-component model captured the trend in ciprofloxacin resistance fairly well, although there was some variance left unexplained. The mean was relatively smooth, with a notable decrease in 2011 (Figure 1B). Although the patient characteristic component suggests a higher proportion of recently hospitalized individuals and a higher proportion of men are associated with greater resistance, the credible intervals of both coefficients included zero (Figure 1C). Both of these associations have been observed previously on an individual patient level (51,52), but the month-to-month differences in averaged patient characteristics (such as the proportion of women in the sample) is relatively small, making it more difficult to more precisely estimate these coefficients in a relatively short time series.

We found that community use of all but two fluoroquinolones (ofloxacin and norfloxacin) in our dataset predicted seasonal patterns in resistance better than generic harmonic models, but total fluoroquinolone use was the single best predictor. The observation that fluoroquinolone use is highest throughout the influenza season is not a coincidence, as these drugs are often prescribed for influenza, both inappropriately (for the viral infection) and appropriately (to combat secondary bacterial infections (53–55)). The association between use and resistance was lagged by 1 to 2 months. A particularly notable example of this relationship occurred in September of 2011, the lowest value in the series for ciprofloxacin resistance (Figure 1A), which

was preceded by a large drop in use in July of 2011 (Figure 2). Generally, the strength of this association translated into fluctuations within 2 percentage points from the mean.

The results regarding antimicrobial use are consistent with previous research. Sun and colleagues (29) reported that the strongest correlation between fluoroquinolone use and the prevalence of ciprofloxacin resistance occurred with a 1-month lag, which is similar to what we observed. Vernaz et al. (28), studying the incidence (rather than prevalence) of ciprofloxacin-resistant infections in Geneva, reported that use of ciprofloxacin lagged by 1 month and moxifloxacin lagged by 4 months showed the strongest correlations. Finally, Gallini et al. (27) investigated the correlation between levofloxacin use in the community and ciprofloxacin resistance in nosocomial infections in a French university hospital. This correlation occurred on a longer time scale, with a lag of 12 months. Individual fluoroquinolone use is also a risk factor for acquiring a resistant infection (56), although community use may be more important than individual use (57).

Our study had a number of limitations. First, with an ecological study, we cannot make causal inferences from our data, although the biological plausibility of the observed association is obvious. Our drug prescription database covers only those on the public prescription plan in Montreal, whereas our resistance dataset includes all community-acquired urinary *E. coli* isolates tested at the McGill University Health Centre, which may include individuals living outside of the city of Montreal. The public plan has near complete coverage for individuals 65 and older, where fluoroquinolone use is concentrated (e.g., in Canada, people aged 60+ account for approximately 70% of ciprofloxacin prescriptions (58)). People under 65 on the public plan probably differ from the general population in this age group (59), which may include their usage patterns of antimicrobials. Since we de-trended (removed the mean) antimicrobial use before analysis, these concerns would only be serious if they affected seasonal patterns, rather than

mean use. In our dataset, seasonal patterns of use were similar across age groups (Web Figure 1). A caveat to the use of a claims database is the assumption that drug dispensation reflects use, even though we cannot be sure who is actually consuming dispensed drugs. Finally, it would have been advantageous to be able to include consumption and resistance data from multiple communities across the province.

Despite the myriad ways in which resistance can be maintained in the absence of selective pressure from antimicrobial use, resistance mechanisms are still generally costly (15,60). Our study supports the notion that ciprofloxacin resistance responds to changes in fluoroquinolone use. While the strategy of restricting prescribing has had some success (61,62), cases like the rapid emergence of quinolone resistance in a remote Amazon community where quinolones were never prescribed (and antimicrobial usage is minimal) (63) should provoke urgency to find additional strategies for combating antimicrobial resistance (64). Nonetheless, antimicrobial stewardship campaigns to reduce fluoroquinolone usage, particularly in the community setting, are likely to be a valuable tool in the global struggle against this public health crisis.

REFERENCES

1. World Health Organization. Antibiotic resistance. 2018; (http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/). (Accessed March 11, 2018)

2. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T*. 2015;40(4):277–283.

3. Bell BG, Schellevis F, Stobberingh E, et al. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect. Dis.* 2014;14(1):13.

4. Goossens H. Antibiotic consumption and link to resistance. *Clin. Microbiol. Infect.* 2009;15(SUPPL. 3):12–15.

5. van de Sande-Bruinsma N, Grundmann H, Verloo D, et al. Antimicrobial Drug Use and Resistance in Europe. *Emerg. Infect. Dis.* 2008;14(11):1722–1730.

6. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect. Dis.* 2018;18(3):318–327.

7. World Health Organization. Antimicrobial resistance: global report on surveillance. Geneva: World Health Organization; 2014.

8. Flores-Mireles AL, Walker JN, Caparon M, et al. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat. Rev. Microbiol.* 2015;13(5):269–284.

9. Foxman B. The epidemiology of urinary tract infection. *Nat. Rev. Urol.* 2010;7(12):653–660.

10. Foxman B, Barlow R, D'Arcy H, et al. Urinary Tract Infection: Self-Reported Incidence and Associated Costs. *Ann. Epidemiol.* 2000;10(8):509–515.

11. Foxman B. Chapter 36 - Urinary Tract Infection. In: Goldman MB, Troisi R, Rexrode KM, eds. *Women and Health (Second Edition)*. Cambridge, MA: Academic Press; 2013:553–564.

12. Dielubanza EJ, Schaeffer AJ. Urinary Tract Infections in Women. *Med. Clin. North Am.* 2011;95(1):27–41.

13. Cowpertwait PSP, Metcalfe AV. Correlation. In: *Introductory Time Series with R*. New York: Springer; 2009:27–43.

14. Granger CWJ, Newbold P. Spurious regressions in econometrics. *J. Econom.* 1974;2(2):111–120.

15. Melnyk AH, Wong A, Kassen R. The fitness costs of antibiotic resistance mutations. *Evol. Appl.* 2015;8(3):273–283.

16. Basra P, Alsaadi A, Bernal-Astrain G, et al. Fitness Tradeoffs of Antibiotic Resistance in Extraintestinal Pathogenic *Escherichia coli*. *Genome Biol. Evol.* 2018;10(2):667–679.

17. Andersson DI, Hughes D. Persistence of antibiotic resistance in bacterial populations. *FEMS Microbiol. Rev.* 2011;35(5):901–911.

18. Robicsek A, Jacoby GA, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. *Lancet Infect. Dis.* 2006;6(10):629–640.

19. Durkin MJ, Jafarzadeh SR, Hsueh K, et al. Outpatient Antibiotic Prescription Trends in the United States: A National Cohort Study. *Infect. Control Hosp. Epidemiol.* 2018;1–6.

20. Williamson DA, Roos R, Verrall A, et al. Trends, demographics and disparities in outpatient antibiotic consumption in New Zealand: a national study. *J. Antimicrob. Chemother.* 2016;71(12):3593–3598.

21. Dalhoff A. Global Fluoroquinolone Resistance Epidemiology and Implictions for Clinical Use. *Interdiscip. Perspect. Infect. Dis.* 2012;2012:1–37.

22. Fasugba O, Gardner A, Mitchell BG, et al. Ciprofloxacin resistance in community- and hospital-acquired *Escherichia coli* urinary tract infections: a systematic review and meta-analysis of observational studies. *BMC Infect. Dis.* 2015;15(1).

23. Lautenbach E, Strom BL, Nachamkin I, et al. Longitudinal Trends in Fluoroquinolone Resistance among Enterobacteriaceae Isolates from Inpatients and Outpatients, 1989–2000: Differences in the Emergence and Epidemiology of Resistance across Organisms. *Clin. Infect. Dis.* 2004;38(5):655–662.

24. Kobayashi M, Shapiro DJ, Hersh AL, et al. Outpatient Antibiotic Prescribing Practices for Uncomplicated Urinary Tract Infection in Women in the United States, 2002–2011. *Open Forum Infect. Dis.* 2016;3(3).

25. Mammeri H, Van De Loo M, Poirel L, et al. Emergence of Plasmid-Mediated Quinolone Resistance in *Escherichia coli* in Europe. *Antimicrob. Agents Chemother.* 2005;49(1):71–76.

26. Choi S-H, Kim EY, Kim Y-J. Systemic use of fluoroquinolone in children. *Korean J. Pediatr.* 2013;56(5):196.

27. Gallini A, Degris E, Desplas M, et al. Influence of fluoroquinolone consumption in inpatients and outpatients on ciprofloxacin-resistant *Escherichia coli* in a university hospital. *J. Antimicrob. Chemother.* 2010;65(12):2650–2657.

28. Vernaz N, Huttner B, Muscionico D, et al. Modelling the impact of antibiotic use on antibiotic-resistant *Escherichia coli* using population-based data from a large hospital and its surrounding community. *J. Antimicrob. Chemother.* 2011;66(4):928–935.

29. Sun L, Klein EY, Laxminarayan R. Seasonality and temporal correlation between community antibiotic use and resistance in the United States. *Clin. Infect. Dis.* 2012;55(5):687–694.

30. Durbin J, Koopman SJ. Linear state space models. In: *Time Series Analysis by State Space Methods: Second Edition*. Oxford: Oxford University Press; 2012:43–75.

31. West M, Harrison J. Bayesian forecasting and dynamic models. 2nd ed. New York: Springer; 1997.

32. Petris G, Petrone S, Campagnoli P. Dynamic linear models With R. New York: Springer; 2009.

33. Statistics Canada. Health Profile, December 2013. Catalogue no. 82-228-XWE. 2013; (http://www12.statcan.gc.ca/health-sante/82-228/index.cfm?Lang=E). (Accessed May 7, 2018)

34. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—Twelfth Edition. CLSI document M02-A12. Wayne, PA: Committee for Clinical Laboratory Standards; 2015.

35. CDC. Catheter-Associated Urinary Tract Infection (CAUTI) Event; National Healthcare Safety Network Patient Safety Component Manual. Centers for Disease Control and Prevention; 2012.

36. Girard R, Perraud M, Herriot HE, et al. Prevention of hospital-acquired infections: A Practical Guide, 2nd Edition. World Health Organization; 2002.

37. Jeon K, Kwon OJ, Lee NY, et al. Antibiotic Treatment of *Mycobacterium abscessus* Lung Disease: A Retrospective Analysis of 65 Patients. *Am. J. Respir. Crit. Care Med.* 2009;180(9):896–902.

38. Benedict KM, Gow SP, Checkley S, et al. Methodological comparisons for antimicrobial resistance surveillance in feedlot cattle. *BMC Vet. Res.* 2013;9(1):216.

39. Shaban-Nejad A, Lavigne M, Okhmatovskaia A, et al. PopHR: a knowledge-based platform to support integration, analysis, and visualization of population health data: The Population Health Record (PopHR). *Ann. N. Y. Acad. Sci.* 2017;1387(1):44–53.

40. Régie de l’assurance maladie du Québec. Data and statistics. 2018; (http://www.ramq.gouv.qc.ca/en/data-statistics/pages/data-statistics.aspx). (Accessed January 22, 2018)

41. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2018. Oslo: 2017.

42. Alves MB, Gamerman D, Ferreira MA. Transfer functions in dynamic generalized linear models. *Stat. Model.* 2010;10(1):03–40.

43. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.(https://www.R-project.org/)

44. Ravines RR, Schmidt AM, Migon HS. Revisiting distributed lag models through a Bayesian perspective. *Appl. Stoch. Models Bus. Ind.* 2006;22(2):193–210.

45. Almon S. The Distributed Lag Between Capital Appropriations and Expenditures. *Econometrica*. 1965;33(1):178.

46. Koyck LM. Distributed Lags Models and Investment Analysis. Amsterdam: North-Holland; 1954.

47. de Valpine P, Turek D, Paciorek CJ, et al. Programming With Models: Writing Statistical Algorithms for General Model Structures With NIMBLE. *J. Comput. Graph. Stat.* 2017;26(2):403–413.

48. Tibbits MM, Groendyke C, Haran M, et al. Automated Factor Slice Sampling. *J. Comput. Graph. Stat.* 2014;23(2):543–563.

49. Turek D, de Valpine P, Paciorek CJ, et al. Automated Parameter Blocking for Efficient Markov Chain Monte Carlo Sampling. *Bayesian Anal.* 2017;12(2):465–490.

50. Watanabe S. Asymptotic Equivalence of Bayes Cross Validation and Widely Applicable Information Criterion in Singular Learning Theory. *J. Mach. Learn. Res.* 2010;11:3571–3594.

51. Tenney J, Hudson N, Alnifaidy H, et al. Risk factors for aquiring multidrug-resistant organisms in urinary tract infections: A systematic literature review. *Saudi Pharm. J.* 2018;26(5):678–684.

52. Toner L, Papa N, Aliyu SH, et al. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in hospital urinary tract infections: incidence and antibiotic susceptibility profile over 9 years. *World J. Urol.* 2016;34(7):1031–1037.

53. Polgreen PM, Yang M, Laxminarayan R, et al. Respiratory Fluoroquinolone Use and Influenza. *Infect. Control Hosp. Epidemiol.* 2011;32(07):706–709.

54. Glass SK, Pearl DL, McEwen SA, et al. A province-level risk factor analysis of fluoroquinolone consumption patterns in Canada (2000-06). *J. Antimicrob. Chemother.* 2010;65(9):2019–2027.

55. Rynda-Apple A, Robinson KM, Alcorn JF. Influenza and Bacterial Superinfection: Illuminating the Immunologic Mechanisms of Disease. *Infect. Immun.* 2015;83(10):3764–3770.

56. Bolon MK, Wright SB, Gold HS, et al. The Magnitude of the Association between Fluoroquinolone Use and Quinolone-Resistant *Escherichia coli* and *Klebsiella pneumoniae* May Be Lower than Previously Reported. *Antimicrob. Agents Chemother.* 2004;48(6):1934–1940.

57. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat. Med.* 2004;10(12s):S122–S129.

58. Public Health Agency of Canada. Canadian Antimicrobial Resistance Surveillance System – 2017 Report. 2017.

59. Bérard A, Lacasse A. Validity of perinatal pharmacoepidemiologic studies using data from the RAMQ administrative database. *Can. J. Clin. Pharmacol.* 2009;16(2):e360–e369.

60. Basra P, Alsaadi A, Bernal-Astrain G, et al. Fitness Tradeoffs of Antibiotic Resistance in Extraintestinal Pathogenic Escherichia coli. *Genome Biol. Evol.* 2018;10(2):667–679.

61. Gottesman BS, Carmeli Y, Shitrit P, et al. Impact of Quinolone Restriction on Resistance Patterns of *Escherichia coli* Isolated from Urine by Culture in a Community Setting. *Clin. Infect. Dis.* 2009;49(6):869–875.

62. O'Brien KA, Zhang J, Mauldin PD, et al. Impact of a Stewardship-Initiated Restriction on Empirical Use of Ciprofloxacin on Nonsusceptibility of *Escherichia coli* Urinary Isolates to Ciprofloxacin. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* 2015;35(5):464–469.

63. Pallecchi L, Bartoloni A, Riccobono E, et al. Quinolone Resistance in Absence of Selective Pressure: The Experience of a Very Remote Community in the Amazon Forest. *PLoS Negl. Trop. Dis.* 2012;6(8):e1790.

64. Enne VI. Reducing antimicrobial resistance in the community by restricting prescribing: can it be done? *J. Antimicrob. Chemother.* 2010;65(2):179–182.

ACKNOWLEDGEMENTS

Author affiliations: Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, QC, Canada (JPRS, AMS, DLB); Surveillance Laboratory, McGill Clinical and Health Informatics, McGill University, Montréal, QC, Canada (JPRS, DLB); Department of Microbiology, Infectious Diseases & Immunology, Université de Montréal, Montréal, QC,

Canada (CQ); Infection Prevention & Control Unit, Department of Pediatric Laboratory Medicine, CHU Sainte-Justine, Université de Montréal, Montréal, QC, Canada (CQ)

AMS acknowledges the support of the Natural Sciences and Engineering Research Council of Canada. CQ is supported by a Chercheur boursier de mérite career award from the Fonds de recherche du Québec – Santé. The authors would like to thank Charles Frenette, Patrick Dolcé, and Alexandre A. Boudreault for their assistance in data acquisition for this project.

Conflict of interest: none declared.

Table 1. Model selection for the seasonal component of ciprofloxacin resistance in urinary *E. coli* isolates from Montreal, Quebec (2010–2014). D_t: antibiotic use; S_t: seasonal component; WAIC: widely applicable information criterion. The best transfer function model for each type of antimicrobial use, plus two harmonic models disregarding antimicrobial use, are contrasted with the best overall model (bolded).

S_t	D_t	WAIC
Harmonic (static)	None	-30.57
Harmonic (random)	None	-30.59
Almon (order 3)	Ciprofloxacin	-32.45
Almon (order 3)	Levofloxacin	-35.20
Almon (order 3)	Moxifloxacin	-33.48
Koyck	Norfloxacin	-29.84
Almon (order 2)	Ofloxacin	-30.52
Almon (order 3)	**Total fluoroquinolones**	**-35.98**

Figure 1. Expected value and non-seasonal components of the dynamic linear model for ciprofloxacin resistance in urinary *E. coli* samples from Montreal, Quebec (2010–2014). A) Expected proportion of resistance (solid) with 95% credible interval; observed proportion of resistance (dashed). B) Time-varying mean of proportion of resistance with 95% credible interval. C) Regression coefficients for averaged patient characteristics on the logit scale.

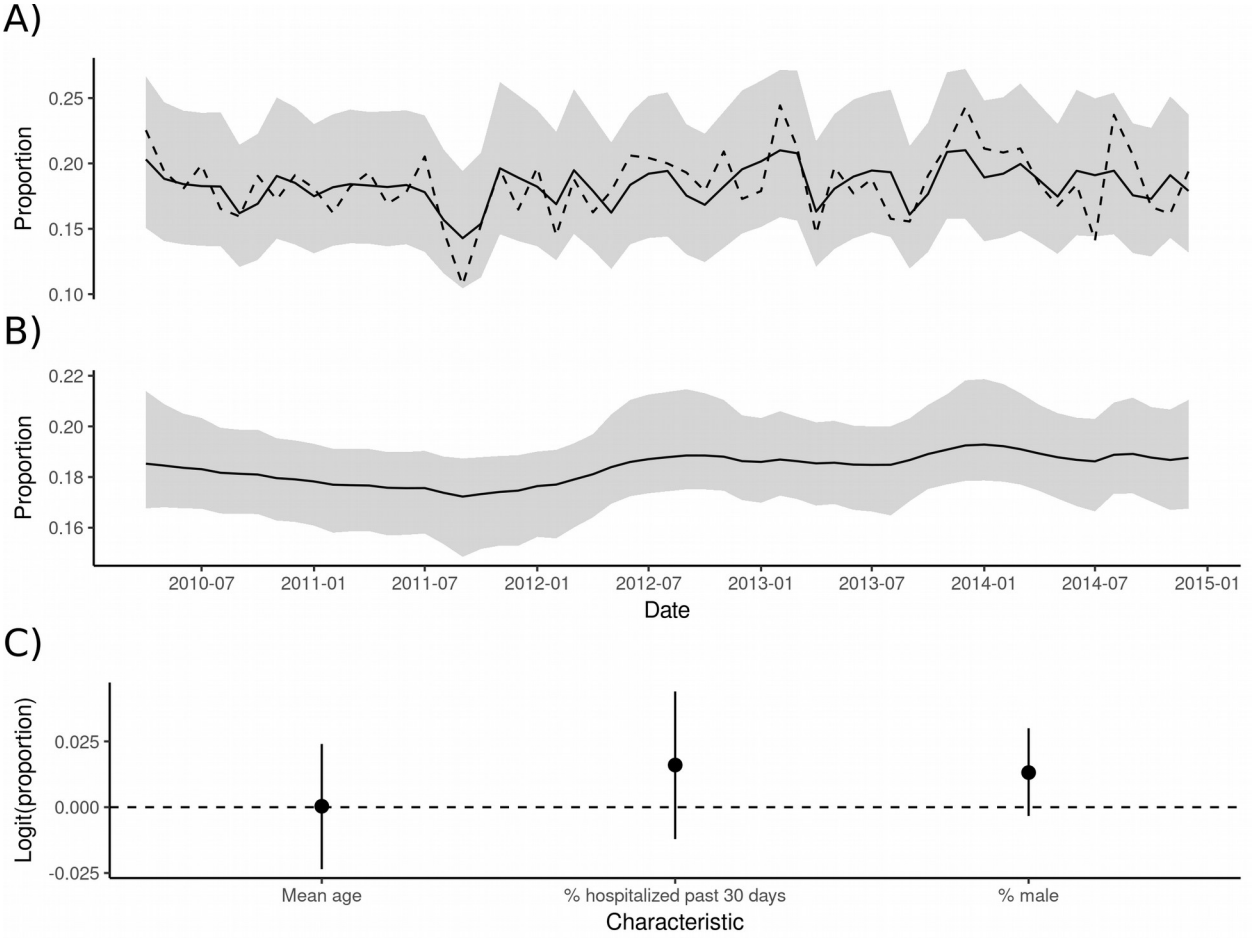


Figure 2. Total fluoroquinolone use in Montreal, Quebec (2010–2014), lagged by 2 months.

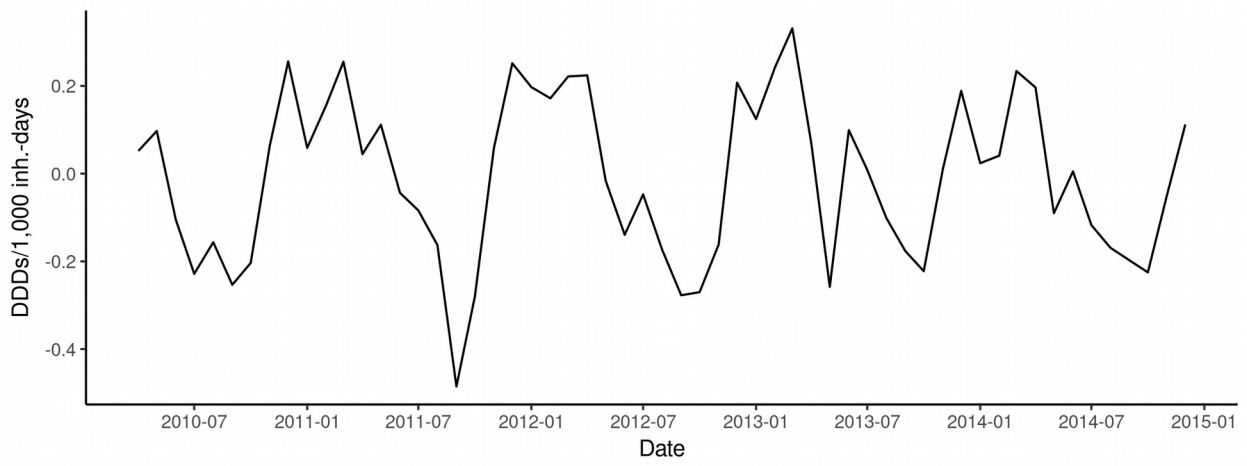


Figure 3. Seasonality of the use of several fluoroquinolones in Montreal, Quebec. Seasonality is calculated as the the average difference for each month between observed use and mean use (calculated by loess smoothing) in an 11-year time series (2004–2014). Values are given as Defined Daily Dose (DDD) per 1,000 inhabitant-days. A 95% confidence interval is given (n = 11 for all months).

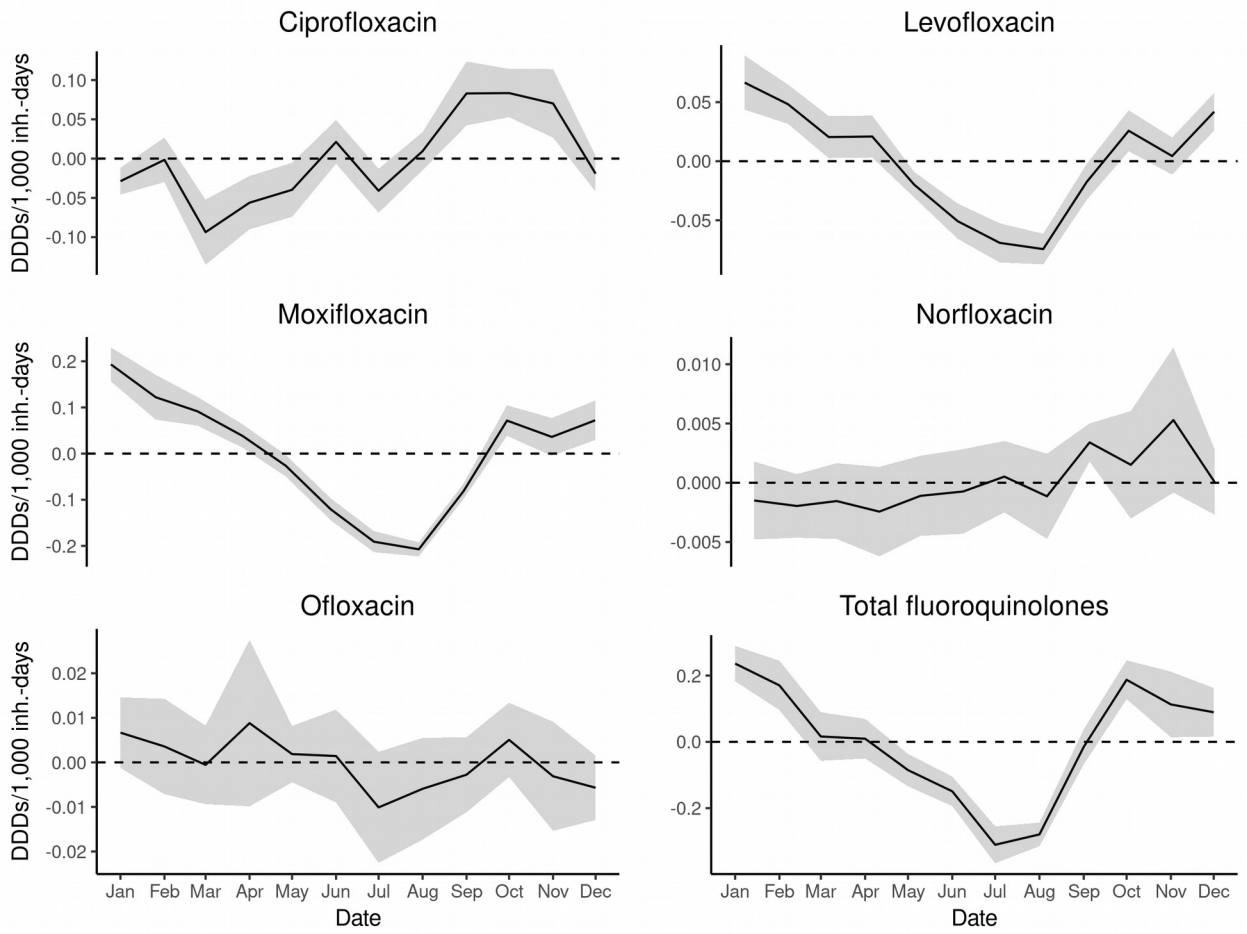
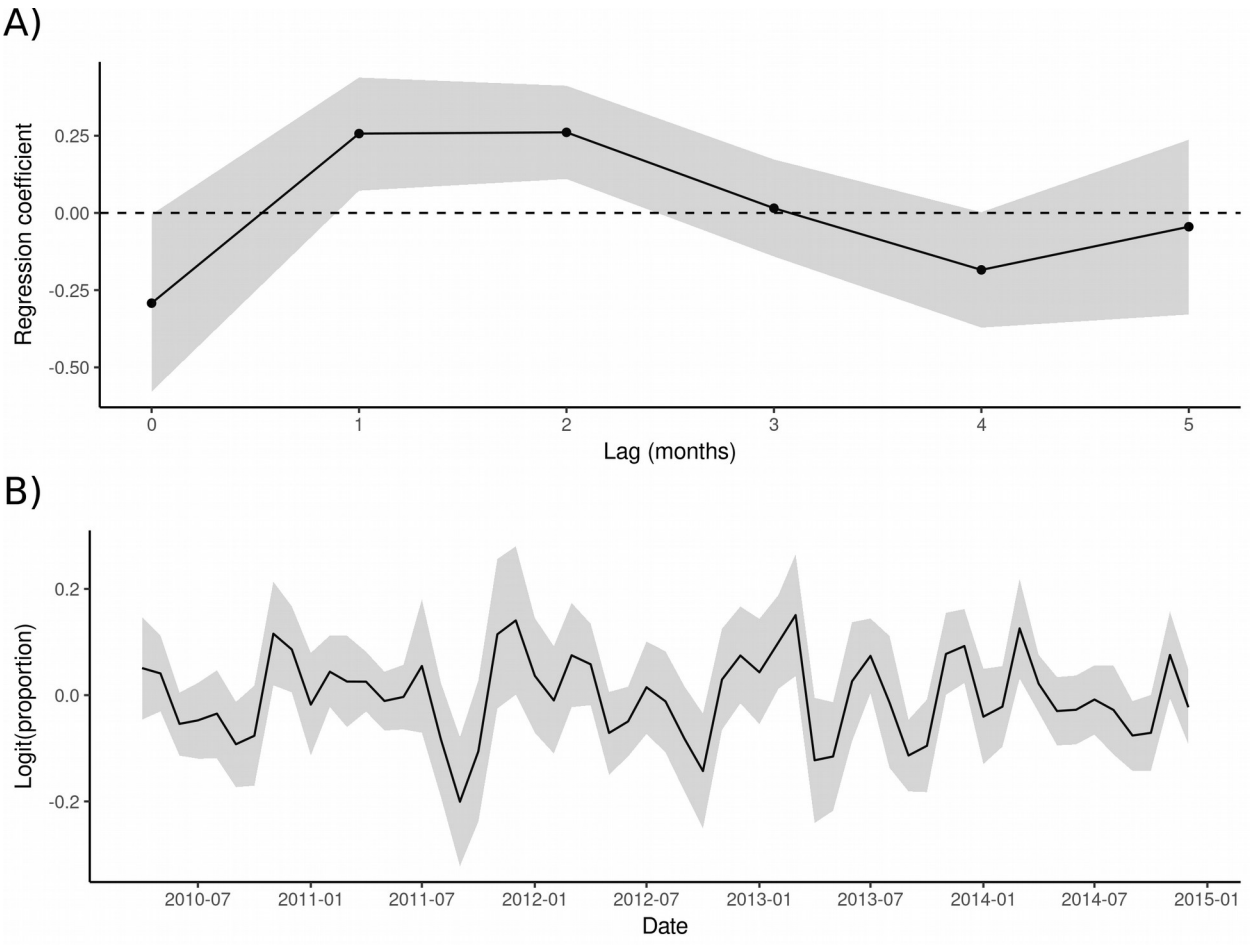
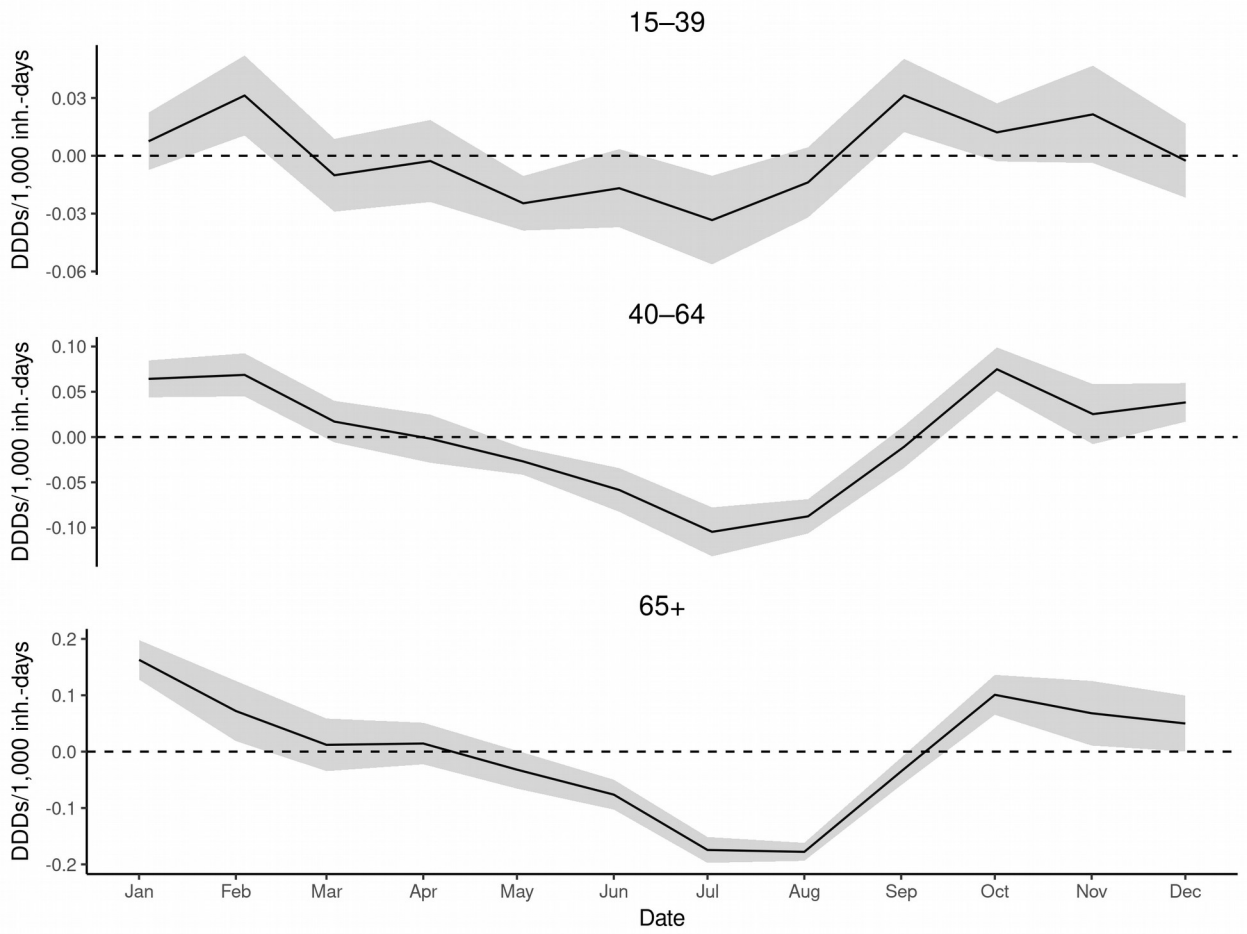


Figure 4. Correlation between time-lagged total fluoroquinolone use and monthly proportion of ciprofloxacin resistance in urinary *E. coli* isolates from Montreal, Quebec and the transfer function component of the dynamic linear model. A) Correlation between time-lagged fluoroquinolone use and the proportion of resistance on the logit scale. The regression coefficients represent the expected change in the logit of the proportion of resistance from a 1 unit change in total fluoroquinolone use in Defined Daily Doses per 1,000 inhabitant-days at a particular lag. B) The transfer function component of the dynamic linear model on the logit scale.



Web Figure 1. Seasonality of total fluoroquinolone use in Montreal, Quebec by age group. Seasonality is calculated as the the average difference for each month between observed use and mean use (calculated by loess smoothing) in an 11-year time series (2004–2014). Values are given as Defined Daily Dose (DDD) per 1,000 inhabitant-days. A 95% confidence interval is given (n = 11 for all months).



5. Discussion

5.1. Interpretation of results

The two manuscripts comprising this thesis examined the question of antimicrobial resistance in urinary *E. coli* from different angles. In the first manuscript, we examined several individual predictors of resistance to six different antimicrobials, namely age, sex, and recent hospitalization. We also looked at geographic, seasonal, and annual variability in three cities across the province of Quebec between the years of 2010 and 2017. In the second manuscript, we re-examined seasonal and temporal trends in ciprofloxacin resistance in Montreal, Quebec through the lens of time series analysis. In this second analysis, we considered population-level fluoroquinolone use as a potential predictor of monthly changes in resistance, comparing the model fit using fluoroquinolone consumption data to a generic sinusoidal model without reference to these data.

The primary result of the first analysis was that there is clinically important variation in the probability of having a resistant infection across cities and patient populations. For most types of antimicrobials, men tended to be more vulnerable to resistant infections; this was also true of individuals hospitalized in the previous 30 days. In most cases, age did not strongly correlate with the probability of resistance, but ciprofloxacin was a notable exception. The cumulative effects of these covariates can result in dramatically different expected probabilities of resistance across patients requiring empirical antimicrobial therapy. For example, according to our model, a community-acquired isolate from an 18-year-old, not recently hospitalized, female patient in Montreal has an 8% (CI: 7%, 9%) probability of ciprofloxacin resistance, whereas a samples from a male, recently hospitalized patient of the same age has a 15% (CI: 13%, 17%) probability. If the male patient is instead 65 years of age, this probability jumps to 33% (CI: 31%, 36%).

Geographic variability was large, even though our study sites comprised three cities in the same province. For instance, after accounting for other factors, the prevalence of ciprofloxacin resistance community-acquired isolates in Montreal averaged around 20%, whereas Rimouski averaged around 8%, with Quebec City in the middle. The samples from Quebec City (covering both major hospital networks) and from Rimouski (covering the only area hospital) are expected to be relatively representative, whereas the sample from the MUHC (only one of the major hospital networks in Montreal), may not be representative of the prevalence of resistance in Montreal, especially given that the MUHC is a major reference centre for urology. Nonetheless, the MUHC serves a large portion of the population of Montreal, so these findings highlight the importance of local susceptibility profiles in making decisions about empirical therapy.

Annual trends in resistance were fairly consistent in community-acquired but not hospital-acquired samples. In community-acquired samples, resistance declined or held steady from the beginning of the study period (2010) until 2013, after which the prevalence of resistance increased. We noted a slight decline from 2010 to 2011 in ciprofloxacin resistance. Two distinct seasonal patterns emerged, one for community-acquired isolates and one for nosocomial isolates. In the former, resistance tended to peak in late winter and early spring; in the latter, resistance tended to slump in the summer, although this pattern was less pronounced.

These results generally replicated the results of previous findings about individual risk factors for antimicrobial resistance in urinary *E. coli*. However, the analysis did not generally show large differences in the prevalence of resistance between nosocomial and community-acquired isolates, which has been reported in many previous studies. Many previous studies did not directly account for differences in patient characteristics in their estimates of susceptibility between these two groups of isolates (as we have done here). We believe this explains a substantial proportion

of the variation between the two groups, at least in our study. The conclusion to draw from this first analysis and the previous weight of evidence is that there is a need for physicians, especially general practitioners, to be able to access region-specific antimicrobial resistance profiles. Ideally, a model-based clinical decision support system would integrate local, regional, and national data on antimicrobial resistance, as well as any available patient-specific data, in order to develop information to guide the selection of empirical therapy for UTIs and other infections.

The second analysis sought to illuminate the temporal trends noted in ciprofloxacin resistance for community-acquired *E. coli* isolates. The time series methods supported the temporal results of the first analysis using logistic regression (although we could only examine up to the end of 2014 in this analysis). Specifically, the dynamic linear model revealed a dip in the mean prevalence of resistance in 2011, as shown with the simpler method. The main result of the analysis showed that higher rates of resistance in late fall to early spring were preceded by elevated fluoroquinolone consumption in the 1 or 2 months prior, supporting the speculative explanation in the first analysis.

We were not able to fully replicate the results of the first analysis with respect to patient characteristics. Although the associations with the proportion of males and the proportion of recently hospitalized patients in the monthly sample trended in the expected directions, the credible intervals crossed the null. This can probably be explained by the fact that there was too little variance in averaged patient characteristics across months to reliably detect these associations in a time series of the length we modelled.

Historically, fluoroquinolones (specifically ciprofloxacin and levofloxacin) have been heavily prescribed for urinary tract infections, as well as being among the most commonly prescribed antimicrobials overall. This analysis supports the notion that fluoroquinolone resistance follows

fluoroquinolone use at the community level. These results should encourage the further adoption of antimicrobial stewardship campaigns to preserve the efficacy of these life-saving drugs. Currently, these campaigns are more commonplace in hospitals, but a strong effort must be made to reach general practitioners and specialists in the community, where the vast majority of drugs are dispensed. Prescribing practices regarding fluoroquinolones for UTIs are particularly ripe for change given the high volume prescriptions involved (and thus high potential for impact) and recent warnings by the FDA about the potentially disabling side effects of these antimicrobials, recommending against their use for uncomplicated infections. However, addressing the overuse of broad-spectrum fluoroquinolones alone is unlikely to slow the rising levels of resistance to more narrowly targeted therapies such as TMP/SMX. Due to the high economic costs and potential for serious sequelae (such as renal damage) resulting from UTIs, we must explore new ways of maintaining the effectiveness of these drugs, especially as novel pharmacological solutions remain elusive.

5.2. Strengths and limitations

The main advantage of this project was the use of rigorous statistical methods to analyze the associations of interest. Our hierarchical, model-based approach allowed us to transcend the dimensional limitations of contingency tables and to account for correlations between the six types of resistance in our analysis. This methodology was both biologically justified and statistically useful, especially when estimating associations for antimicrobials for which resistance is rare (e.g., nitrofurantoin and tobramycin). In the time series analysis, the use of dynamic linear models gave us a fuller picture of trends in ciprofloxacin resistance than we might have obtained using traditional ARIMA methods. We were able to decompose annual and

seasonal trends as well as investigate the role of averaged patient characteristics in the sample, which was a novel addition.

We also benefited from having access to three relatively long, complete datasets from four separate institutions in Quebec. Many previously published antimicrobial susceptibility profiles use a short time frame—often a year or less—at a single institution, which results in a small sample size and no possibility of making temporal inferences. Conversely, our antimicrobial resistance dataset spanned several institutions and nearly eight years.

Limitations in our dataset meant we were unable to explore some questions of clinical interest. For example, we had no information on symptoms, thus we were unable to separate asymptomatic bacteriuria from symptomatic UTI. It would have also been beneficial to be able to include personal antimicrobial use and comorbidities like diabetes in the analysis. The nature of the dataset also made misclassification of some nosocomial isolates as community-acquired likely, since we could not identify patients who were admitted to hospitals outside of the network where their samples were tested. We also likely misclassified some recently hospitalized patients as not having been hospitalized, which would diminish the magnitude of the association with this risk factor. These types of misclassification would have been more prevalent in the two major cities in our study, as opposed to Rimouski, where there are fewer hospitals in the surrounding region.

A limitation in the time series analysis concerned the source of the fluoroquinolone dispensation data, namely individuals enrolled in the public drug prescription plan. This group covers slightly less than half of the population of Montreal and may not be representative of the population under 65. However, the public plan is representative of individuals over 65, the age group in which fluoroquinolone use is concentrated. Furthermore, since we were interested in short-term,

seasonal fluctuations in consumption as opposed to the absolute amounts, the fact that seasonal patterns of use were similar across age groups provides yet more evidence that our database was sufficient to address our research question.

5.3. Areas for future research

The quotidian wish of every researcher is to have had more data. Longer antimicrobial resistance time series from more institutions in more places would allow risk factors for antimicrobial resistance to be calculated ever more precisely, and would help to illuminate the commonalities and differences in resistance risk across time and space. Additionally, longer time series would make it easier to study the association between community antimicrobial use and resistance in hospitals, a more indirect association that necessarily takes place on a longer time scale than the community-to-community association studied here.

The advent of large, standardized health databases makes research comparing health outcomes, like antimicrobial resistance, across geographic and patient populations easier than ever before. Bayesian hierarchical methods, which are more accessible and computationally feasible than ever before, are perfectly suited for a provincial or national system producing localized antimicrobial susceptibility profiles to support clinical decision making regarding empirical therapy. In this framework, physicians could have access to a locally relevant antimicrobial resistance profile specific to the patient population at hand, with the underlying model incorporating not only local but also provincial and national data to inform estimates.

Finally, the approaches used in the two analyses comprising this thesis are very applicable to infections other than urinary *E. coli* and could help inform empirical therapy in these contexts as well.

6. Conclusion

Resistance to common antimicrobials in urinary *E. coli* isolates in Quebec varied substantially by geography, time, and patient population. Resistance tended to be higher in men, patients who had been recently hospitalized, and in the case of ciprofloxacin resistance, older patients. The magnitude of these differences was significant enough to potentially influence the optimal selection of empirical therapy. In the future, this model-based approach to susceptibility profiles could be incorporated into a decision-support system for clinicians.

In Montreal, fluoroquinolone consumption explained seasonal fluctuations in ciprofloxacin resistance with a lag of 1 to 2 months. These results support the proposition that ciprofloxacin resistance is modifiable by limiting fluoroquinolone prescriptions, the rationale for antimicrobial stewardship campaigns.

This research demonstrates the utility of standardized susceptibility testing results and sophisticated modelling approaches to make general and locale-specific inferences about the prevalence of and risk factors for many types of antimicrobial resistance. There is a great opportunity for increased collaboration between hospitals, governments, and researchers in order to provide the most relevant resistance profiles to guide empiric therapy and target antimicrobial stewardship campaigns.

7. References

1. World Health Organization. Antibiotic resistance. 2018; (http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/). (Accessed March 11, 2018)

2. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among us ambulatory care visits, 2010-2011. *JAMA - J. Am. Med. Assoc.* 2016;315(17):1864–1873.

3. Wang EEL, Einarson TR, Kellner JD, et al. Antibiotic Prescribing for Canadian Preschool Children: Evidence of Overprescribing for Viral Respiratory Infections. *Clin. Infect. Dis.* 1999;29(1):155–160.

4. Cadieux G, Tamblyn R, Dauphinee D, et al. Predictors of inappropriate antibiotic prescribing among primary care physicians. *Can. Med. Assoc. J.* 2007;177(8):877–883.

5. Flores-Mireles AL, Walker JN, Caparon M, et al. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat. Rev. Microbiol.* 2015;13(5):269–284.

6. Foxman B. The epidemiology of urinary tract infection. *Nat. Rev. Urol.* 2010;7(12):653–660.

7. Harding GKM, Ronald AR. The management of urinary infections; what have we learned in the past decade? *Int. J. Antimicrob. Agents*. 1994;4(2):83–88.

8. Foxman B, Barlow R, D'Arcy H, et al. Urinary Tract Infection: Self-Reported Incidence and Associated Costs. *Ann. Epidemiol.* 2000;10(8):509–515.

9. Dwyer PL, O'Reilly M. Recurrent urinary tract infection in the female. *Curr. Opin. Obstet. Gynecol.* 2002;14(5):537–543.

10. Foxman B. Recurring urinary tract infection: incidence and risk factors. *Am. J. Public Health*. 1990;80(3):331–333.

11. Foxman B. Chapter 36 - Urinary Tract Infection. In: Goldman MB, Troisi R, Rexrode KM, eds. *Women and Health (Second Edition)*. Cambridge, MA: Academic Press; 2013:553–564.

12. Lo E, Nicolle LE, Coffin SE, et al. Strategies to Prevent Catheter-Associated Urinary Tract Infections in Acute Care Hospitals: 2014 Update. *Infect. Control Hosp. Epidemiol.* 2014;35(05):464–479.

13. Tambyah PA, Maki DG. Catheter-Associated Urinary Tract Infection Is Rarely Symptomatic: A Prospective Study of 1497 Catheterized Patients. *Arch. Intern. Med.* 2000;160(5).

14. Dielubanza EJ, Schaeffer AJ. Urinary Tract Infections in Women. *Med. Clin. North Am.* 2011;95(1):27–41.

15. Lob SH, Nicolle LE, Hoban DJ, et al. Susceptibility patterns and ESBL rates of *Escherichia coli* from urinary tract infections in Canada and the United States, SMART 2010–2014. *Diagn. Microbiol. Infect. Dis.* 2016;85(4):459–465.

16. den Heijer CDJ, Penders J, Donker GA, et al. The Importance of Gender-Stratified Antibiotic Resistance Surveillance of Unselected Uropathogens: A Dutch Nationwide Extramural Surveillance Study. *PLoS ONE*. 2013;8(3):e60497.

17. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin. Infect. Dis.* 2011;52(5):e103–e120.

18. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin. Infect. Dis.* 2010;50(5):625–663.

19. Kobayashi M, Shapiro DJ, Hersh AL, et al. Outpatient Antibiotic Prescribing Practices for Uncomplicated Urinary Tract Infection in Women in the United States, 2002–2011. *Open Forum Infect. Dis.* 2016;3(3).

20. U.S. Food and Drug Administration. FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. 2016;(https://www.fda.gov/Drugs/DrugSafety/ucm500143.htm). (Accessed May 16, 2018)

21. Sköld O. Antibiotics and antibiotic resistance. Hoboken, NJ: Wiley; 2011.

22. Robicsek A, Jacoby GA, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. *Lancet Infect. Dis.* 2006;6(10):629–640.

23. Davies J, Davies D. Origins and Evolution of Antibiotic Resistance. *Microbiol. Mol. Biol. Rev.* 2010;74(3):417–433.

24. Wright GD. The antibiotic resistome: The nexus of chemical and genetic diversity. *Nat. Rev. Microbiol.* 2007;5(3):175–186.

25. Bell BG, Schellevis F, Stobberingh E, et al. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect. Dis.* 2014;14(1):13.

26. Goossens H. Antibiotic consumption and link to resistance. *Clin. Microbiol. Infect.* 2009;15(SUPPL. 3):12–15.

27. van de Sande-Bruinsma N, Grundmann H, Verloo D, et al. Antimicrobial Drug Use and Resistance in Europe. *Emerg. Infect. Dis.* 2008;14(11):1722–1730.

28. The Review on Antimicrobial Resistance. Tackling Drug-resistant Infections Globally: Final Report and Recommendations. 2016.

29. The Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis For the Health and Wealth Of Nations. 2014.

30. Schappert SM. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1996. *Vital Health Stat. 13.* 1998;(134):1–37.

31. Macejko AM, Schaeffer AJ. Asymptomatic Bacteriuria and Symptomatic Urinary Tract Infections During Pregnancy. *Urol. Clin. North Am.* 2007;34(1):35–42.

32. Zhanel G, Hisanaga T, Laing N, et al. Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int. J. Antimicrob. Agents*. 2006;27(6):468–475.

33. McIsaac WJ, Moineddin R, Meaney C, et al. Antibiotic-resistant *Escherichia coli* in women with acute cystitis in Canada. *Can. J. Infect. Dis. Med. Microbiol.* 2013;24(3):143–149.

34. Zilberberg MD, Shorr AF. Secular Trends in Gram-Negative Resistance among Urinary Tract Infection Hospitalizations in the United States, 2000–2009. *Infect. Control Hosp. Epidemiol.* 2013;34(09):940–946.

35. Lagacé-Wiens PRS, Adam HJ, Low DE, et al. Trends in antibiotic resistance over time among pathogens from Canadian hospitals: results of the CANWARD study 2007-11. *J. Antimicrob. Chemother.* 2013;68(suppl 1):i23–i29.

36. Delisle G, Quach C, Domingo M-C, et al. *Escherichia coli* antimicrobial susceptibility profile and cumulative antibiogram to guide empirical treatment of uncomplicated urinary tract infections in women in the province of Québec, 2010–15. *J. Antimicrob. Chemother.* 2016;71(12):3562–3567.

37. Public Health Agency of Canada. Canadian Antimicrobial Resistance Surveillance System – 2017 Report. 2017.

38. Grignon O, Montassier E, Corvec S, et al. *Escherichia coli* antibiotic resistance in emergency departments. Do local resistance rates matter? *Eur. J. Clin. Microbiol. Infect. Dis.* 2015;34(3):571–577.

39. Durkin MJ, Jafarzadeh SR, Hsueh K, et al. Outpatient Antibiotic Prescription Trends in the United States: A National Cohort Study. *Infect. Control Hosp. Epidemiol.* 2018;1–6.

40. Williamson DA, Roos R, Verrall A, et al. Trends, demographics and disparities in outpatient antibiotic consumption in New Zealand: a national study. *J. Antimicrob. Chemother.* 2016;71(12):3593–3598.

41. Olson RP, Haith K. Antibiotic Resistance in Urinary Tract Infections in College Students. *J. Am. Coll. Health*. 2012;60(6):471–474.

42. Molina-López J, Aparicio-Ozores G, Ribas-Aparicio RM, et al. Drug resistance, serotypes, and phylogenetic groups among uropathogenic *Escherichia coli* including O25-ST131 in Mexico City. *J. Infect. Dev. Ctries.* 2011;5(12).

43. Dalhoff A. Global Fluoroquinolone Resistance Epidemiology and Implictions for Clinical Use. *Interdiscip. Perspect. Infect. Dis.* 2012;2012:1–37.

44. Fasugba O, Gardner A, Mitchell BG, et al. Ciprofloxacin resistance in community- and hospital-acquired *Escherichia coli* urinary tract infections: a systematic review and meta-analysis of observational studies. *BMC Infect. Dis.* 2015;15(1).

45. Tenney J, Hudson N, Alnifaidy H, et al. Risk factors for aquiring multidrug-resistant organisms in urinary tract infections: A systematic literature review. *Saudi Pharm. J.* 2018;26(5):678–684.

46. Lagacé-Wiens PRS, Simner PJ, Forward KR, et al. Analysis of 3789 in- and outpatient *Escherichia coli* isolates from across Canada—results of the CANWARD 2007–2009 study. *Diagn. Microbiol. Infect. Dis.* 2011;69(3):314–319.

47. Toner L, Papa N, Aliyu SH, et al. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in hospital urinary tract infections: incidence and antibiotic susceptibility profile over 9 years. *World J. Urol.* 2016;34(7):1031–1037.

48. Blaettler L, Mertz D, Frei R, et al. Secular Trend and Risk Factors for Antimicrobial Resistance in *Escherichia coli* Isolates in Switzerland 1997–2007. *Infection*. 2009;37(6):534–539.

49. Karlowsky JA, Lagacé-Wiens PRS, Simner PJ, et al. Antimicrobial Resistance in Urinary Tract Pathogens in Canada from 2007 to 2009: CANWARD Surveillance Study. *Antimicrob. Agents Chemother.* 2011;55(7):3169–3175.

50. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc. Natl. Acad. Sci.* 2011;108(Supplement_1):4554–4561.

51. Carlet J. The gut is the epicentre of antibiotic resistance. *Antimicrob. Resist. Infect. Control*. 2012;1(1):39.

52. Calbo E, Romaní V, Xercavins M, et al. Risk factors for community-onset urinary tract infections due to *Escherichia coli* harbouring extended-spectrum β-lactamases. *J. Antimicrob. Chemother.* 2006;57(4):780–783.

53. Talan DA, Krishnadasan A, Abrahamian FM, et al. Prevalence and Risk Factor Analysis of Trimethoprim-Sulfamethoxazole– and Fluoroquinolone-Resistant *Escherichia coli* Infection

among Emergency Department Patients with Pyelonephritis. *Clin. Infect. Dis.* 2008;47(9):1150–1158.

54. Khawcharoenporn T, Vasoo S, Ward E, et al. High rates of quinolone resistance among urinary tract infections in the ED. *Am. J. Emerg. Med.* 2012;30(1):68–74.

55. Killgore KM, March KL, Guglielmo BJ. Risk Factors for Community-Acquired Ciprofloxacin-Resistant *Escherichia coli* Urinary Tract Infection. *Ann. Pharmacother.* 2004;38(7–8):1148–1152.

56. Loeb MB. Risk Factors for Resistance to Antimicrobial Agents among Nursing Home Residents. *Am. J. Epidemiol.* 2003;157(1):40–47.

57. Vromen M, Van der Ven AJAM, Knols A, et al. Antimicrobial resistance patterns in urinary isolates from nursing home residents. Fifteen years of data reviewed. *J. Antimicrob. Chemother.* 1999;44(1):113–116.

58. Wiener J. Multiple Antibiotic–Resistant Klebsiella and *Escherichia coli* in Nursing Homes. *JAMA.* 1999;281(6):517.

59. Fleming VH, White BP, Southwood R. Resistance of *Escherichia coli* urinary isolates in ED-treated patients from a community hospital. *Am. J. Emerg. Med.* 2014;32(8):864–870.

60. Samore MH, Lipsitch M, Alder SC, et al. Mechanisms by which antibiotics promote dissemination of resistant pneumococci in human populations. *Am. J. Epidemiol.* 2006;163(2):160–170.

61. MacDougall C, Powell JP, Johnson CK, et al. Hospital and Community Fluoroquinolone Use and Resistance in *Staphylococcus aureus* and *Escherichia coli* in 17 US Hospitals. *Clin. Infect. Dis.* 2005;41(4):435–440.

62. Bruinsma N. Influence of population density on antibiotic resistance. *J. Antimicrob. Chemother.* 2003;51(2):385–390.

63. Sköld O. Distribution of Antibiotics. In: *Antibiotics and Antibiotic Resistance*. Hoboken, NJ: Wiley; 2011:21–28.

64. Public Health Agency of Canada. Canadian Antimicrobial Resistance Surveillance System – 2016 Report. 2016.

65. Bosso JA, Mauldin PD. Using interrupted time series analysis to assess associations of fluoroquinolone formulary changes with susceptibility of gram-negative pathogens and isolation rates of methicillin-resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 2006;50(6):2106–2112.

66. Charbonneau P, Parienti J-J, Thibon M, et al. Fluoroquinolone Use and Methicillin-Resistant *Staphylococcus aureus* Isolation Rates in Hospitalized Patients: A Quasi Experimental Study. *Clin. Infect. Dis.* 2006;42(6):778–784.

67. Sun L, Klein EY, Laxminarayan R. Seasonality and temporal correlation between community antibiotic use and resistance in the United States. *Clin. Infect. Dis.* 2012;55(5):687–694.

68. Kaier K, Hagist C, Frank U, et al. Two Time-Series Analyses of the Impact of Antibiotic Consumption and Alcohol-Based Hand Disinfection on the Incidences of Nosocomial Methicillin-Resistant *Staphylococcus aureus* Infection and *Clostridium difficile* Infection. *Infect. Control Hosp. Epidemiol.* 2009;30(04):346–353.

69. Gilca R, Fortin É, Frenette C, et al. Seasonal variations in *Clostridium difficile* infections are associated with influenza and respiratory syncytial virus activity independently of antibiotic prescriptions: A time series analysis in Québec, Canada. *Antimicrob. Agents Chemother.* 2012;56(2):639–646.

70. Aldeyab MA, Kearney MP, Scott MG, et al. An evaluation of the impact of antibiotic stewardship on reducing the use of high-risk antibiotics and its effect on the incidence of *Clostridium difficile* infection in hospital settings. *J. Antimicrob. Chemother.* 2012;67(12):2988–2996.

71. Kaier K, Frank U, Hagist C, et al. The impact of antimicrobial drug consumption and alcohol-based hand rub use on the emergence and spread of extended-spectrum β-lactamase-producing strains: A time-series analysis. *J. Antimicrob. Chemother.* 2009;63(3):609–614.

72. Vernaz N, Huttner B, Muscionico D, et al. Modelling the impact of antibiotic use on antibiotic-resistant *Escherichia coli* using population-based data from a large hospital and its surrounding community. *J. Antimicrob. Chemother.* 2011;66(4):928–935.

73. Gallini A, Degris E, Desplas M, et al. Influence of fluoroquinolone consumption in inpatients and outpatients on ciprofloxacin-resistant *Escherichia coli* in a university hospital. *J. Antimicrob. Chemother.* 2010;65(12):2650–2657.

74. Statistics Canada. Health Profile, December 2013. Catalogue no. 82-228-XWE. 2013; (http://www12.statcan.gc.ca/health-sante/82-228/index.cfm?Lang=E). (Accessed May 7, 2018)

75. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard—Twelfth Edition. CLSI document M02-A12. Wayne, PA: Committee for Clinical Laboratory Standards; 2015.

76. CDC. Catheter-Associated Urinary Tract Infection (CAUTI) Event; National Healthcare Safety Network Patient Safety Component Manual. Centers for Disease Control and Prevention; 2012.

77. Girard R, Perraud M, Herriot HE, et al. Prevention of hospital-acquired infections: A Practical Guide, 2nd Edition. World Health Organization; 2002.

78. Jeon K, Kwon OJ, Lee NY, et al. Antibiotic Treatment of *Mycobacterium abscessus* Lung Disease: A Retrospective Analysis of 65 Patients. *Am. J. Respir. Crit. Care Med.* 2009;180(9):896–902.

79. Benedict KM, Gow SP, Checkley S, et al. Methodological comparisons for antimicrobial resistance surveillance in feedlot cattle. *BMC Vet. Res.* 2013;9(1):216.

80. Amari EBE, Chamot E, Auckenthaler R, et al. Influence of Previous Exposure to Antibiotic Therapy on the Susceptibility Pattern of *Pseudomonas aeruginosa* Bacteremic Isolates. *Clin. Infect. Dis.* 2001;33(11):1859–1864.

81. Shaban-Nejad A, Lavigne M, Okhmatovskaia A, et al. PopHR: a knowledge-based platform to support integration, analysis, and visualization of population health data: The Population Health Record (PopHR). *Ann. N. Y. Acad. Sci.* 2017;1387(1):44–53.

82. Régie de l'assurance maladie du Québec. Data and statistics. 2018; (http://www.ramq.gouv.qc.ca/en/data-statistics/pages/data-statistics.aspx). (Accessed January 22, 2018)

83. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2018. Oslo: 2017.

84. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.(https://www.R-project.org/)

85. Gelman A, Hill J. Data Analysis Using Regression and Multilevel/Hierarchical Models. Cambridge: Cambridge University Press; 2006.

86. Gelman A. Prior distributions for variance parameters in hierarchical models (Comment on Article by Browne and Draper). *Bayesian Anal.* 2006;1(3):515–534.

87. de Valpine P, Turek D, Paciorek CJ, et al. Programming With Models: Writing Statistical Algorithms for General Model Structures With NIMBLE. *J. Comput. Graph. Stat.* 2017;26(2):403–413.

88. Durbin J, Koopman SJ. Linear state space models. In: *Time Series Analysis by State Space Methods: Second Edition*. Oxford: Oxford University Press; 2012:43–75.

89. West M, Harrison J. Bayesian forecasting and dynamic models. 2nd ed. New York: Springer; 1997.

90. Petris G, Petrone S, Campagnoli P. Dynamic linear models With R. New York: Springer; 2009.

91. Alves MB, Gamerman D, Ferreira MA. Transfer functions in dynamic generalized linear models. *Stat. Model.* 2010;10(1):03–40.

92. Ravines RR, Schmidt AM, Migon HS. Revisiting distributed lag models through a Bayesian perspective. *Appl. Stoch. Models Bus. Ind.* 2006;22(2):193–210.

93. Almon S. The Distributed Lag Between Capital Appropriations and Expenditures. *Econometrica*. 1965;33(1):178.

94. Koyck LM. Distributed Lags Models and Investment Analysis. Amsterdam: North-Holland; 1954.

95. Watanabe S. Asymptotic Equivalence of Bayes Cross Validation and Widely Applicable Information Criterion in Singular Learning Theory. *J. Mach. Learn. Res.* 2010;11:3571–3594.

96. Tibbits MM, Groendyke C, Haran M, et al. Automated Factor Slice Sampling. *J. Comput. Graph. Stat.* 2014;23(2):543–563.

97. Turek D, de Valpine P, Paciorek CJ, et al. Automated Parameter Blocking for Efficient Markov Chain Monte Carlo Sampling. *Bayesian Anal.* 2017;12(2):465–490.