

**Patterns of Outpatient Antibiotic Prescribing in Older Adults by Social
Determinants of Health Before and During COVID-19**

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PREFACE

This project used linked and coded population-based administrative health databases at ICES (formerly the Institute for Clinical Evaluative Sciences). Ethics review was not required as ICES is a prescribed entity under section 45 of the Personal Health Information Protection Act (PHIPA) in Ontario. Projects conducted wholly under section 45 of PHIPA, by definition, do not require review or approval by a research ethics board (REB).

This project represents original work. Mia Sapin was responsible for data cleaning, performing the data analysis, interpreting the results, and drafting and editing the thesis monograph. Derek MacFadden, Curtis Cooper, and Colleen Maxwell provided guidance and support throughout the completion of the project, from conceptualization to review and editing of the monograph.

ABSTRACT

Background: Identifying patterns and predictors of antibiotic prescribing can begin to inform interventions aimed at improving antibiotic use and slowing the emergence of antimicrobial resistance. As it stands, patterns of prescribing among older adults by social determinants of health (SDOH) remain poorly described. We sought to examine associations between SDOH variables and antibiotic prescribing among older community-dwelling adults over time and identify variations in these associations before and during the COVID-19 pandemic.

Methods: We conducted a retrospective, population-based cohort study of community-dwelling older adults (≥ 66 years of age) in Ontario between March 2018-March 2020 (pre-pandemic period) and March 2020-March 2022 (pandemic period). We used multivariable Fine-Gray subdistribution hazard models to evaluate associations between SDOH variables (neighbourhood income, neighbourhood proportion of racially minoritized groups, and immigration status) and incident antibiotic prescriptions (overall and for respiratory infections), accounting for mortality as a competing risk. We used interaction terms and stratification to assess for potential effect modification by the COVID-19 pandemic period.

Results: After exclusions, 2,567,382 outpatients were identified in the pre-pandemic period, and 2,744,337 in the pandemic period. In both study periods, antibiotic prescribing was higher among residents in highest income neighbourhoods (vs. lowest) overall (subdistribution hazard ratio [sHR] 1.03, 95% CI 1.02-1.04 and sHR 1.02, 95% CI 1.01-1.03, respectively), with a similar pattern for prescriptions for respiratory infections (sHR 1.06, 95% CI 1.05-1.07 and sHR 1.05, 1.04-1.06, respectively). Antibiotic prescribing was higher among recent immigrants (vs. long-term residents) in both periods, with a more pronounced increase during the pandemic than pre-pandemic period in overall prescriptions (sHR 1.21, 95% CI 1.18-1.25 vs. sHR 1.12, 95% CI

1.09-1.16, $p=0.049$) and in prescriptions for respiratory infections (sHR 1.27, 95% CI 1.23-1.32 vs. sHR 1.15, 95% CI 1.11-1.18, $p<0.001$). Overall antibiotic prescribing was lower among residents in neighbourhoods with the highest proportion racially minoritized (vs. lowest) in both periods, with a more pronounced decrease during the pandemic than pre-pandemic period (sHR 0.81, 95% CI 0.80-0.82 vs. sHR 0.92, 95% CI 0.91-0.93, $p<0.001$); similarly, there was a more pronounced decrease in prescriptions for respiratory infections during the pandemic than pre-pandemic period (sHR 0.93, 95% CI 0.92-0.94 vs. sHR 1.07, 95% CI 1.05-1.08, $p<0.001$).

Conclusion: In this cohort of older outpatients, SDOH variables were associated with outpatient antibiotic prescribing during the two years before and the first two years of the COVID-19 pandemic, with some of these associations being modified during the COVID-19 pandemic period. These findings suggest that patient sociodemographic characteristics are important for identifying populations who could be at risk of disproportionate antibiotic use in the outpatient setting.

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LIST OF ABBREVIATIONS

| | |
|---------|--|
| AMR | Antimicrobial resistance |
| CAPE | Client Agency Program Enrolment |
| CCRS | Continuing Care Reporting System |
| CI | Confidence interval |
| CIF | Cumulative incidence function |
| CIHI | Canadian Institute for Health Information |
| CENSUS | Ontario Census Area Profiles |
| COVAXON | Ontario COVID-19 Vaccine Data |
| DA | Dissemination area |
| DAD | Discharge Abstract Database |
| DIN | Drug identification number |
| ESTSOB | Estimated Schedule of Benefits |
| ICD | International Classification of Diseases |
| IKN | ICES Key Number |
| IRCC | Immigration, Refugees and Citizenship Canada |
| IPDB | ICES Physicians Database |
| IQR | Interquartile range |
| NACRS | National Ambulatory Care Reporting System |
| ODB | Ontario Drug Benefit |
| OHIP | Ontario Health Insurance Plan |
| OMHRS | Ontario Mental Health Reporting System |
| OR | Odds ratio |
| PCCF | Postal Code Conversion File |
| PHU | Public Health Unit |
| RPDB | Registered Persons Database |
| RTI | Respiratory tract infection |

| | |
|------|-------------------------------|
| SD | Standard deviation |
| SDOH | Social determinants of health |
| SDS | Same Day Surgery |
| sHR | Subdistribution hazard ratio |
| UTI | Urinary tract infection |
| WHO | World Health Organization |

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Chapter 1: INTRODUCTION

1.1 Background and rationale

Antimicrobial resistance (AMR) is an important global public health threat that imposes a substantial burden on human health and the healthcare system. Without intervention, estimates suggest that AMR could cause as many as 10 million deaths globally per year by 2050.¹ To date, several healthcare strategies to combat AMR have focused on improving antibiotic use by identifying patterns and predictors of antibiotic prescribing. Many of these strategies have targeted the outpatient setting, where over 90% of antibiotics are prescribed in Canada.² While previous research has identified several provider and patient factors associated with outpatient antibiotic prescribing, there has been a notable gap in studies exploring the impact of social and economic factors on prescribing practices. Collectively known as social determinants of health (SDOH), these non-medical factors are recognized contributors to health inequities and disparities in healthcare access among populations with the potential for marginalization, potentially influencing patterns of antibiotic use in these populations as a result. For example, in Canada, while universal publicly funded health coverage is available to any Canadian citizen or permanent resident, outpatient pharmaceutical benefits are not universal, and cost can be a barrier to obtaining prescription medications, resulting in possible disparities in access to prescription drugs.³ Further, some populations may experience challenges in accessing healthcare or receiving quality healthcare, which could produce differences in prescribed medication use.^{4,5} However, as it stands, the influence of several SDOH variables, including income, recent immigration status, and race and/or ethnicity, on outpatient antibiotic prescribing patterns remains poorly described in Canada.

Moreover, evidence suggests that the recent COVID-19 pandemic drastically influenced the healthcare system and disproportionately impacted marginalized populations. However, whether changes in healthcare delivery and disproportionate rates of SARS-CoV-2 infections among populations with the potential for marginalization influenced patterns of outpatient antibiotic prescribing during the COVID-19 pandemic has yet to be thoroughly investigated.

1.2 Research objectives

The overall goal of this thesis project was to evaluate how, and to what extent, SDOH variables influenced antibiotic prescribing patterns over time among community-dwelling older adults (≥ 66 years of age) in Canada. This study sought to: 1) determine whether SDOH variables (namely, immigration status, and neighbourhood-based measures of both income and proportion racially minoritized) are associated with outpatient antibiotic prescriptions among older adults; and 2) assess whether existing associations between SDOH variables and antibiotic prescribing were modified by the COVID-19 pandemic.

1.3 Thesis outline

This thesis has five chapters including this Introduction. Chapter 2 provides a summary of the literature on antimicrobial resistance, drivers of antibiotic resistance, and predictors of antibiotic prescribing, including both provider and patient characteristics. Chapter 3 describes the data sources and methods used in the study, and Chapter 4 presents the results. Lastly, Chapter 5 discusses key findings and their interpretation, outlines study strengths and limitations, and considers future directions of research on this topic.

Chapter 2: LITERATURE REVIEW

2.1 Antimicrobial resistance (AMR)

2.1.1 AMR prevalence

Antimicrobial resistance (AMR) is a major global public health threat of the 21st century that increasingly jeopardizes the treatment of common infections.^{6,7} AMR is characterized by the ability of microorganisms, including bacteria, parasites, viruses, and fungi, to evolve and grow in the presence of antimicrobial drugs, thereby rendering these drugs ineffective.⁷ The issue is of particular concern regarding antibiotic resistance in bacteria. In 2019, bacterial AMR was directly responsible for over 1.27 million deaths globally and associated with an estimated 4.95 million deaths.⁸ These estimates place AMR on par with other major health problems such as tuberculosis, HIV/AIDS, and malaria.^{8,9} As it stands in Canada, over 1 in 4 bacterial infections are resistant to first-line antimicrobials, where nearly 15 deaths a day can be directly attributable to AMR.¹⁰ Without intervention, estimates suggest that drug-resistant diseases could cause up to 10 million deaths globally each year by 2050.¹

2.1.2 Drivers of AMR

AMR is a natural process that occurs over time, but several factors can accelerate the rate at which resistance develops. Antibiotic overuse and misuse have both been implicated as key modifiable drivers of AMR, which fuel resistance by exerting selective pressure for the development of drug-resistant bacteria.^{11,12} The direct correlation between antibiotic use and antibiotic resistance is well-established in the literature at both individual¹³ and population levels in different settings.¹⁴⁻¹⁹ For example, a large multicenter study using data from 32 centers across 18 different European countries along with information collected on community antibiotic consumption identified a highly significant association between community quinolone use in

2005 and the proportion of levofloxacin-resistant *H. pylori* strains between 2008-2009.¹⁶

Moreover, in a 2010 systematic review evaluating the relationship between outpatient antibiotic prescribing and prevalence of resistance at the individual-level, individuals prescribed an antibiotic for a urinary tract infection (UTI) or a respiratory tract infection (RTI) were found to have up to 2.5 times the odds of developing an antibiotic-resistant infection within two months of treatment (pooled odds ratio [OR] 2.5, 95% CI 2.1-2.9 for urinary infections and pooled OR 2.4, 95% CI 1.4-3.9 for respiratory infections).¹³

Lack of access to existing antibiotics when medically indicated, although less researched compared to antibiotic overuse and misuse, is also problematic. Research has shown that missed or delayed treatment in the case of antibiotic-requiring diagnoses could result in additional medical care and worse clinical outcomes, including increased mortality.²⁰ In a recent systematic review exploring the effects of delayed appropriate antibiotic therapy on the outcomes of patients with severe bacterial infections, the odds of mortality were found to be 43% lower in those who received appropriate therapy without delay compared to those who experienced a delay (pooled OR 0.57, 95% CI 0.45-0.72).²⁰ Inadequate antibiotic access also has the potential to contribute to AMR by promoting the use of alternative antibiotic treatments (suboptimal antibiotic use),²¹ which may fail to effectively treat the bacteria, allowing it to evolve and potentially develop drug resistance.

The critical shortage of new and innovative antibiotics has also added to the problem of AMR. In the last three decades, very few antibiotics have been developed and/or approved that offer clinically significant added antimicrobial spectrum over current drugs.²²⁻²⁴ In a recent analysis of the clinical antibacterial pipeline by the World Health Organization (WHO), out of 11 antibiotics approved since 2017, 9 of these were found to be derivatives of existing antibacterial drugs, with

only 2 representing a novel class of antibiotic.²⁴ These newly approved antibiotics are considered by the WHO to be insufficient to combat increasing rates of resistance.²⁴ In light of the shortage of new antibacterial agents, optimizing the use of these drugs is imperative to maintaining drug effectiveness and slowing the emergence of AMR.

2.2 Antibiotic prescribing and AMR

Several different metrics have been developed to assess antibiotic use and prescribing, with the choice of which metric to use hinging on factors such as the study population, setting, and data availability.²⁵ In long-term care and inpatient settings, antibiotic consumption is often documented directly using medication administration records; however, in the outpatient setting, there is no equivalent system in place to gather this information, and antibiotic use is often estimated from prescription and/or drug dispensing data.²⁵

In Canada, over 90% of antibiotics are prescribed in the outpatient setting,² with substantial amounts of inappropriate prescribing, defined as either prescription of an antibiotic when none is needed (overuse) or prescription of the wrong antibiotic (inappropriate selection), dosing, and duration.²⁶ From 2011 to 2016, nearly 12% of all antibiotics dispensed in a Canadian primary care setting were found to be prescribed for conditions for which they are not indicated, including asthma and influenza.²⁷ Another 12.3% of antibiotics were inappropriately prescribed for conditions for which they are rarely indicated, such as acute respiratory tract infections including bronchitis and sinusitis.²⁷ Similarly, close to 25% of the outpatient antibiotic prescriptions filled in 2016 by over 19 million privately insured children and middle-aged adults in the United States were deemed inappropriate.²⁸ Considering the substantial proportion of antibiotics prescribed in the outpatient setting, along with the notable amounts of inappropriate prescribing, this setting represents a crucial area to implement antimicrobial stewardship

activities aimed at optimizing antibiotic use. Identifying patterns and predictors of antibiotic prescribing in the outpatient setting can begin to provide insight into antibiotic use within specific populations in the community, information that can then be used to inform tailored stewardship interventions.

2.3 Predictors of antibiotic prescribing

The decision to prescribe an antibiotic is complex and requires a balance between addressing the immediate health needs of a patient while considering the potential risks of inappropriate antibiotic use or adverse events and outcomes. This decision can often be influenced by a multitude of interconnected factors, many of which have been identified in previous research, encompassing attributes of both prescribers and patients.

2.3.1 Physician characteristics

Studies examining physician factors associated with prescribing have found that patients may be more likely to receive antibiotics from late-career and older physicians,^{29–32} providers trained outside of Canada,^{30,31,33} and providers with higher patient volumes.^{30,31,34} Physician attitudes, such as fear of more serious complications developing, have also been associated with higher prescribing.^{35,36} Of note, it has previously been suggested that provider characteristics may influence antibiotic prescribing regardless of patient characteristics. In a recent 5-year cohort study including approximately 4 million physician-patient encounters, over 300 thousand unique patients, and 313 physicians from 41 family medicine clinics, the odds of a patient receiving an antibiotic from a family physician were found to vary by 1.7 times simply by encountering different physicians.³⁴

2.3.2 Patient characteristics

In terms of patient characteristics, signs and symptoms,³⁷⁻⁴⁰ female sex,⁴¹⁻⁴⁵ presence of chronic conditions,^{38,42,44,46,47} and rural residence^{42,47-49} have often been associated in the literature with either higher antibiotic prescribing or higher inappropriate prescribing. Differences in infection susceptibility and infection outcomes among various patient groups could also influence the probability of receiving an antibiotic prescription.^{50,51} Further, differences in the number of physician visits and utilization of healthcare services among specific populations may influence the probability of receiving an antibiotic prescription by increasing the number of opportunities for antibiotics to be prescribed.^{4,52,53} Patient attitudes and behaviours, such as expectations, pressure, and knowledge of antibiotic use have also been identified as contributors to prescription patterns in different settings and countries.^{37,40,54-56} For example, one study conducted across 13 European countries revealed that patients expecting or hoping for an antibiotic prescription were more likely to be prescribed an antibiotic compared to patients with no expectations or hopes (OR 2.08, 95% CI 1.48-2.93 and OR 2.48, 95% CI 1.73-3.55, respectively).⁵⁵

2.3.3 Antibiotic prescribing among older adults

Older adults represent a key population at risk for excessive and inappropriate prescribing due in part to their increased susceptibility to infections, particularly RTIs and UTIs, and increased risk of severe disease.⁵⁰ Several studies have identified elevated rates of antibiotic prescribing among older adults.^{27,31,43,50,57-60} Notably, out of a population of over 185,000 older Ontarians (65+ years of age), approximately 46% inappropriately received a prescription from a primary care physician practice for a likely viral respiratory infection in 2012.³¹ Another study in the United States demonstrated a 30% increase in outpatient antibiotic prescriptions for older adults between

2000 and 2010, while prescribing either decreased or remained unchanged among children and younger adult populations.⁵⁷ When specifically examining antibiotic prescriptions for acute RTIs during the same period, comparable findings emerged, with prescribing decreasing among both children and younger adults but remaining constant for older adults.⁵⁷

2.3.4 Seasonal trends in outpatient antibiotic prescriptions

Aside from patient and provider characteristics, seasonal variations exist in antibiotic prescribing and use, which largely result from increased incidence of RTIs during the winter months.⁶¹⁻⁶³

Over a 5-year period in the United States, almost 25% more antibiotic prescriptions were dispensed during the winter compared to the summer months, with drastic increases observed in prescriptions of antibiotics indicated for respiratory infections during the winter months, including macrolides and penicillins.⁶¹

2.4 Social determinants of health and antibiotic prescribing

While several patient characteristics have been consistently implicated as risk factors for antibiotic prescribing, various social and economic factors that contribute to health inequities across a wide range of health indicators and populations have been less researched.

Accumulating evidence indicates that these non-medical factors, otherwise known as social determinants of health (SDOH), produce disparities in access to healthcare, quality of care, infection susceptibility, and infection outcomes among populations with the potential for marginalization, including recent immigrants, racially minoritized persons, and low-income individuals. For example, disparities in healthcare utilization have previously been identified among low versus high-income neighbourhoods in Canada^{64,65} and racially minoritized persons in the United States.^{4,52,66,67} Lower income and race and/or ethnicity have also previously been identified as risk factors for bacteremic pneumococcal pneumonia infection,⁶⁸ and higher rates of

vaccine-preventable disease-related hospitalizations have been reported among immigrant populations compared to Canadian-born counterparts.⁵¹ Further, evidence suggests that immigrant populations face unique challenges when accessing healthcare or interacting with the health system due to language barriers, economic barriers, and cultural differences.^{5,69,70} Many of these SDOH-related disparities have also been found to persist for older adults living in the community.^{71,72}

Baseline SDOH-related disparities in healthcare access and infection susceptibility and outcomes among populations with the potential for marginalization may have implications for antibiotic use and could lead to potential variations in prescribing patterns among those populations. However, to date, literature describing the influence of social and/or economic factors, such as immigration status, income, and visible minority status, on antibiotic prescribing remains poorly described – particularly in Canada.

2.4.1 Immigration status and antibiotic prescribing

Research exploring the association between immigration status and antibiotic prescribing yields conflicting results and is largely limited to European populations. In a recent scoping review performed by the WHO, evidence on access to antibiotics in various refugee and migrant populations was captured across different settings.⁷³ Overall, seven relevant studies were identified comparing antibiotic prescription rates between foreign-born and host populations,^{44,74–79} and two studies were identified which used information on dispensed antibiotics or reimbursement rates to assess prescribing patterns.^{80,81}

Of the seven studies comparing antibiotic prescribing rates, four suggested that foreign-born populations were significantly more likely to receive an antibiotic prescription compared to host

populations in Europe.^{44,74-76} Notably, in a 2010 cross-sectional study including 1,015 non-western immigrants and 995 native Dutch individuals selected from the Utrecht Health Project database, first-generation immigrants had 1.3 times the odds (OR 1.31, 95% CI 1.04-1.65) of receiving a prescription for antibiotics most often used in Dutch primary care.⁴⁴ Another study using information from 17,450 non-institutionalized children and adolescents (0-17 years) in Germany collected from the longitudinal KiGGS survey (German Health Interview and Examination Survey for Children and Adolescents) found that individuals with an immigration background had 2.4 times the odds (OR 2.37; 95% CI 1.51, 3.73) of prescribed antibiotic use compared to those with no immigration background.⁷⁵ Two of the seven studies identified suggested comparable rates of antibiotic prescribing between foreign-born and host populations in Europe, although both of these studies were conducted exclusively in children and adolescent (0-13 years of age) populations.^{77,78} In the only study identified from the United States, prescription rates between American and foreign-born populations were compared using data collected from 129 patients across six community health centers in New York with skin and soft tissue infections compatible with *S. aureus* infections.⁷⁹ Among the included patients, 40 were immigrants born outside of the United States, and it was observed that these patients were less likely to receive an antibiotic prescription for a lesion compared to native-born patients, although this difference was not statistically significant ($p=0.10$).⁷⁹ It should also be noted that the observed differences in antibiotic use between the two groups may in part be attributable to differences in infection profiles between immigrant and native-born patients. Notably, immigrant patients were more likely to have methicillin-susceptible *S. aureus* infection compared to individuals born in the United States, and potentially appropriately needed fewer antibiotics as a result.⁷⁹

The two studies focusing on dispensed antibiotic or reimbursement rates also provide conflicting results, with one study finding lower antibiotic utilization rates among migrants compared to host populations in Europe,⁸⁰ and one study finding mixed results depending on the country of origin of foreign-born individuals.⁸¹ Notably, in a cross-sectional study examining all purchased drug prescriptions classified according to the Anatomical Therapeutic Chemical system for one calendar year in both Norway and Aragon (Spain), a lower proportion of immigrant groups from Poland, China, Columbia, and Morocco purchased Beta-Lactam Antibacterials, Penicillins, and Macrolides, Lincosamides, and Streptogramins compared to the host population.⁸⁰ In contrast, out of over 20,000 individuals included in the HELIUS study (Healthy Life in an Urban Setting) in Amsterdam, only first and second generation Ghanaian and first-generation Moroccan migrants had higher odds of receiving more than one antibiotic prescription in the 12 months prior to the study compared to individuals of Dutch origin.⁸¹ No differences were observed for first or second generation South-Asia Surinamese, African Surinamese, or Turkish migrants.⁸¹

2.4.2 Income and antibiotic prescribing

The influence of income on antibiotic prescribing is also not uniform across studies from North America,^{34,82-84} New Zealand,⁶⁰ Australia,⁵³ and Europe.^{45,85,86} In a five-year cohort study in Ontario, Canada, information from 3,956,921 physician-patient encounters, with 322,129 unique patients, revealed that increasing neighbourhood income quintile (from Canada Census) was associated with small but statistically significant increases in antibiotic prescribing among residents of neighbourhoods with the highest income compared to the lowest (OR 1.09, 95% CI 1.07-1.10).³⁴ Similarly, a Swedish study that analyzed dispensed antibiotics over a two-year period (from 2016-2017) in the entire population and used information on family income for the years 2000, 2005, and 2010 (categorized into high, middle, and low income) found that low-

income earners were dispensed slightly fewer antibiotics than high-income earners (prevalence ratio 0.97, 99% CI 0.97-0.97).⁴⁵ In contrast, a study from the United States investigating the correlation between antibiotic prescribing rate and county income analysed over 50 million antibiotic prescriptions across 807 counties to discover that increasing household income was associated with decreasing rates of antibiotic prescriptions.⁸² Specifically, as the proportion of individuals in a county with an income of at least \$65,000 increased, antibiotic prescribing decreased.⁸² Another Canadian study showed similar results, with a higher proportion of respondents having a household income below \$60,000 reporting more frequent use of antibiotics (more than twice in the last 12 months) compared to those with a higher income out of a population of over 1,500 survey respondents.⁸⁴

2.4.3 Race and/or ethnicity and antibiotic prescribing

Several studies in the United States and a few in New Zealand have reported on variations in antibiotic prescribing by race and/or ethnicity.^{4,29,43,49,60,82,87-92} Although differences exist in study design, setting, population, and definitions of race and/or ethnicity, results of these studies generally demonstrate lower antibiotic prescribing among racially minoritized groups. In a cross-sectional study using data from the National Health Interview Survey (2007-2018) linked with Medicare claims data on 13,672 individuals aged 65 years or older in the United States, Non-Hispanic Black adults (OR 0.61, 95% CI, 0.51–0.87) and non-Hispanic Asian adults (OR 0.65, 95% CI, 0.49–0.87) were found to be less likely to receive an outpatient antibiotic prescription compared to non-Hispanic White adults.⁹² Similarly, another study in the United States using information from 448,990 outpatient visits in North Carolina for common upper RTIs between 2014-2016 found that White patients received more antibiotic prescriptions than African American (incident risk ratio [IRR] 0.85, 95% CI 0.82-0.89), Asian (IRR 0.85, 95% CI 0.79-

0.92), and persons of other races (IRR 0.95, 95% CI 0.93-0.97).²⁹ In one study from New Zealand, approximately 36 million government-subsidized systemic outpatient antibiotic claims between 2006-2014 were analyzed to reveal that antibiotic consumption was lower among Māori (21.4 defined daily dose per 1000 population per day [DID]) and Asian persons (17.9 DID) compared to Pacific peoples (30.0 DID). In the one study identified from Canada, information from respondents in British Columbia was collected from three cycles of the Canadian Community Health survey from 2001-2005 along with dispensing data from the British Columbia PharmaNet database for all prescriptions filled during 2005 to determine whether variations exist in the use of prescription drugs among individuals of different ethnic groups.⁹³ Overall, information from 19,730 individuals was included in the analysis and results indicated that compared to White women, Chinese women (OR 0.71, 95% CI 0.57-0.89), and Non-Asian, non-white women (OR 0.60, 95% CI 0.42-0.87) were less likely to fill an antibiotic prescription, whereas South Asian men were more likely to fill a prescription (OR 1.57, 95% CI 1.16-2.12) compared to White men.⁹³

2.5 Summary of existing literature

While the existing literature begins to provide valuable insight into the associations between various SDOH variables and antibiotic prescribing, few of the identified studies have had a pre-specified health equity focus. In addition, almost all previous studies have focused on children and adolescent populations, or have included patients of all ages, and few have focused exclusively on older (65+ years of age) adults. Further, in exploring the impact of SDOH variables on antibiotic prescribing, it is evident that the available literature is predominately derived from the United States and various European countries. Only a limited number of studies were identified in Canada, and the influence of several sociodemographic factors on prescribing

patterns remains poorly described in this context. It is important to recognize that the results from international studies may not be easily generalizable to other regions with different healthcare systems or different barriers to healthcare access and utilization. Finally, out of the identified studies, none have evaluated the impact of SDOH variables on the cumulative incidence of receiving an antibiotic prescription over time. Therefore, this thesis aimed to add to the existing literature on SDOH and antibiotic prescribing and address evidence gaps about the influence of SDOH variables on prescribing patterns over time within specific older populations with the potential for marginalization in Canada.

2.6 Impacts of the COVID-19 pandemic

The recent COVID-19 pandemic caused by the SARS-CoV-2 virus has inflicted a staggering toll worldwide, resulting in millions of deaths and profoundly impacting healthcare systems and delivery.^{94,95} The rapid spread of the novel coronavirus strained medical infrastructure and overwhelmed hospitals and healthcare professionals, resulting in significant barriers for individuals seeking healthcare services. As with past infectious disease outbreaks, however, evidence suggests that marginalized individuals or underserved communities were disproportionately affected by the pandemic and associated healthcare disruptions.⁹⁶⁻⁹⁸ For example, in addition to identifying variations in SARS-CoV-2 infection rates and mortality among marginalized individuals, research has also identified differences in the use of telemedicine during the COVID-19 pandemic by patient sociodemographic characteristics. Notably, younger individuals were more likely to use the service compared to older adults,^{99,100} and patients living in neighbourhoods of lower socioeconomic status or non-native English speaking patients were less likely to choose the service.⁹⁹ Racial/ethnic differences in the use of

the service have also been identified in the United States, with Hispanic individuals being less likely to choose and use the service compared to non-Hispanic White individuals.^{99,100}

The healthcare access disruptions experienced during the COVID-19 pandemic are partly attributable to the various social distancing measures implemented to curb the spread of the SARS-CoV-2 virus.^{101,102} Amidst these disruptions, however, emerged many positive health outcomes, including enhanced hygiene practices in the community and reduced transmission of other seasonal communicable diseases such as influenza and respiratory syncytial virus.^{103–106} Changes in healthcare delivery coupled with the altered transmission of other respiratory pathogens have resulted in reductions in outpatient antibiotic prescribing following the start of the COVID-19 pandemic.^{62,101,102,107} Whether marginalized populations with pre-existing health inequities were at risk of disproportionate antibiotic prescribing during the pandemic period remains largely under-researched.

Chapter 3: METHODS

3.1 Study design and setting

This population-based retrospective cohort study used linked and coded administrative health databases at ICES (formerly the Institute for Clinical Evaluative Sciences) – an independent, non-profit research organization that collects and analyzes health-related data in Ontario (<https://www.ices.on.ca/>). The study sample included community-dwelling older (≥ 66 years of age) adults in Ontario not residing in long-term care from March 11th, 2018, to March 10th, 2020, which we defined as the pre-pandemic period, and from March 11th, 2020, to March 11th, 2022, which we defined as the pandemic period. These two-year periods were chosen to allow sufficient time to examine prescribing patterns in this population over time and were determined according to when the WHO officially declared the SARS-CoV-2 outbreak a pandemic (March 11th, 2020). Eligible individuals in each study period were randomly assigned an index date during accrual (more details below) and followed until either outpatient antibiotic prescription, a censoring or competing risk event, or until the end of the study period, whichever occurred first.

3.2 Study population

Information in the registered persons database (RPDB) at ICES was used to identify eligible older adults in each period. The RPDB is an electronic registry that provides basic demographic and vital status information on all Ontario residents who have received an Ontario Health Insurance Plan (OHIP) card.¹⁰⁸ The pre-pandemic and pandemic cohorts were further defined by linking data for persons in the RPDB to the Continuing Care Reporting System (CCRS) and the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) to obtain information on long-term care admissions and hospitalizations, respectively, which was used to exclude certain individuals. Datasets were linked using unique encoded identifiers at ICES.

3.2.1 Randomly assigned index process

To prevent seasonality from influencing measures of antibiotic use during the winter months,^{61–63} eligible individuals in both periods were assigned a random index date during accrual. Analysts at ICES assigned index dates by first generating a random number between 0 and 1 using a uniform distribution and multiplying this value by the total number of days an individual was alive and eligible (≥ 66 years of age) during the accrual window for each study period. This number of days was then added to the start date of the eligibility window for each study period, which was either the first day of accrual if the individual was already 66 or the date the individual turned 66 during accrual. This process was applied separately to each cohort, and community-dwelling older adults included into the pre-pandemic cohort were not excluded from the pandemic cohort. Instead, these individuals were considered as a repeated measure where applicable during analyses.

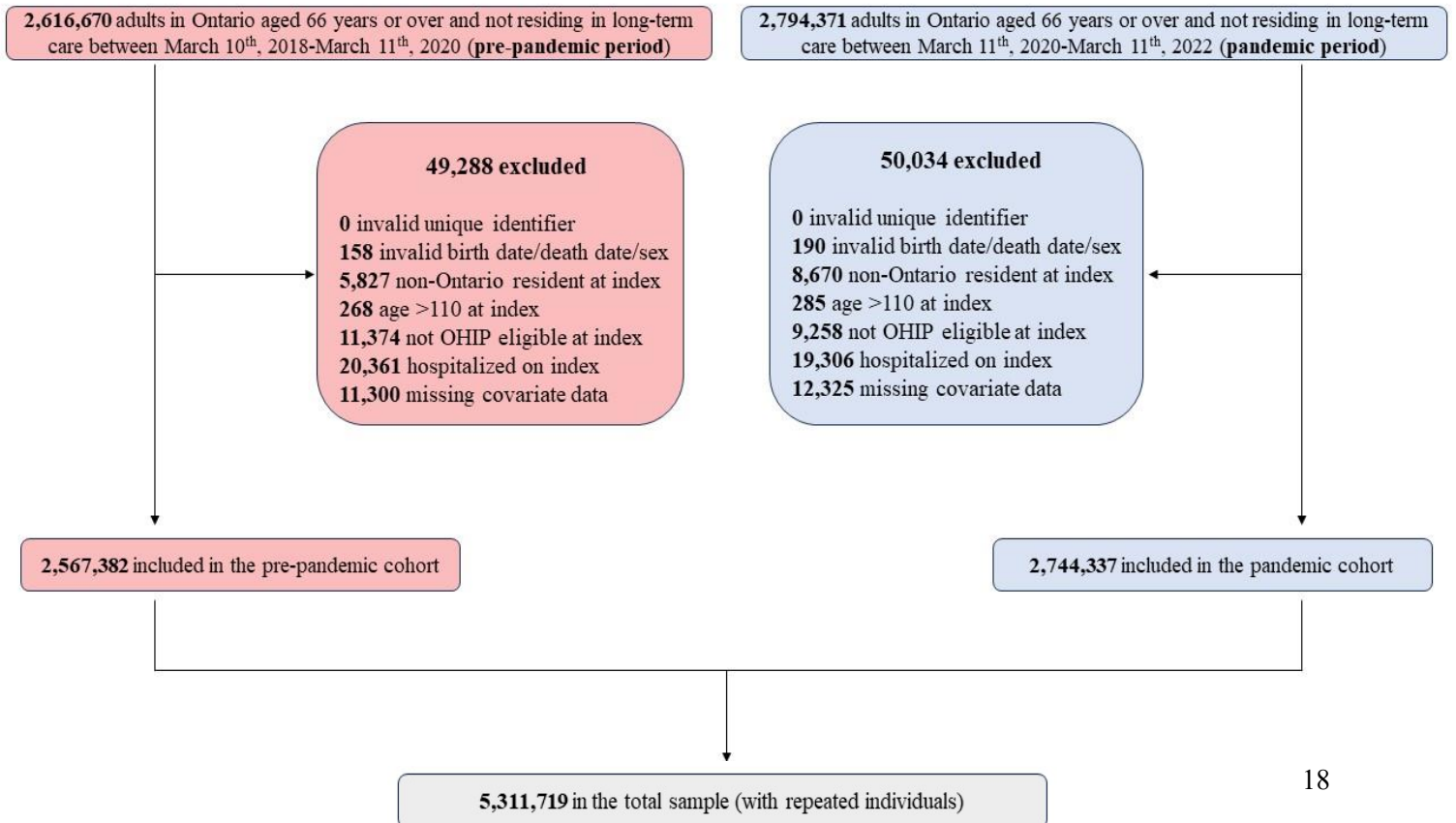
As there are strong seasonal variations in antibiotic prescribing practices, randomly assigning an index date to eligible individuals was done to ensure that the risk of receiving an antibiotic prescription was distributed over time. This approach prevented potential biases that could arise from enrolling individuals during specific seasons, which might inflate or deflate antibiotic prescribing hazards. As the process of assigning random index dates depended on time in the cohort (time alive and eligible), selection bias may have been introduced if this random index process was applied to the entire cohort of individuals over the 4-year period from March 2018–March 2022. This is because individuals ageing into the cohort later in time (during the pandemic period) would have fewer days to choose from to assign the random index, therefore bringing down the mean/median age in the pandemic period, and potentially biasing the results. At the same time, a greater proportion of older individuals would be included earlier at the start

of the study period (during the pre-pandemic period), increasing the mean/median age in the pre-pandemic period. The simplest solution to address this issue involved dividing the population into two distinct cohorts before assigning random index dates, therefore ensuring that while survival bias might persist, it would affect both groups equally, thereby increasing comparability between the two cohorts.

3.2.2 Exclusion criteria

Older outpatients not residing in long-term care (identified through CCRS) at randomly assigned index were excluded from both cohorts for the following reasons: (1) invalid unique identification numbers; (2) invalid birth dates, death dates, or invalid sex; (3) non-Ontario resident at index; (4) non-OHIP eligible at index (with a 93-day grace period to account for the 3-month waiting period for OHIP coverage); (5) age >110 at index; (6) hospitalized at index (identified through CIHI-DAD); and (7) missing covariate data (Figure 1).

Figure 1. Study flow diagram



3.3 Data linkage and access

ICES collects information from health services records for all Ontario residents with an OHIP card. While the information provided to ICES initially arrives in identifiable form, individuals are assigned a unique encoded ICES Key Number (IKN) based on personal identifiers, including health card number, name, birth date, sex, and postal code.¹⁰⁹ Identifying information is then stripped from the data, and the IKN allows records to be deterministically linked across different ICES databases.¹⁰⁹ This study used health administrative data from 15 different linked databases at ICES (see Appendix A for a list of databases and Appendix B for additional database descriptions). We used the IKN for individuals in the RPDB to link our cohorts to additional datasets and obtain information on demographic characteristics, healthcare utilization measures, and vaccination status. These coded data were stored and analyzed at ICES and accessed within a secure research analytic environment.

3.4 Main data sources

3.4.1 Registered Persons Database (RPDB)

The RPDB is a population-based database that provides demographic and vital status information, including age, sex, postal code, and date of birth and death, on all individuals who have ever been issued an Ontario health card number.¹⁰⁸ These data are received directly from the Ontario Ministry of Health and Long-Term Care and are further enriched with information from in-house datasets at ICES, ensuring that information in the RPDB is accurate and up-to-date.¹⁰⁸ The database can also be used to track changes in healthcare eligibility over time and to obtain additional information related to location of residence (via linkage with the Postal Code Conversion File [PCCF] and Ontario Census Area Profiles [CENSUS]), such as income quintile (provided by Statistics Canada) and public health unit (PHU).¹⁰⁸

3.4.2 Ontario Drug Benefit (ODB) Database

The ODB database accurately captures all outpatient claims for prescription drugs received under the Ontario Drug Benefit program, with an error rate of less than 1%.^{110,111} This program provides prescription drug coverage for over 5,000 drug products to all individuals 65 years of age and older, as well as to a few other eligible groups with a valid OHIP card.¹¹² Each record in the dataset represents a dispensed prescription paid for by the Ontario Ministry of Health and contains information on the date the prescription was dispensed, the drug identification number (DIN), drug dosage, and the drug name.¹¹⁰ Information in this database is updated monthly.

3.4.3 Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)

The CIHI-DAD captures administrative and patient-level information on hospital discharges from various institutions in Ontario, including day surgery clinics, and rehabilitation, acute-care, and chronic-care hospitals.¹¹³ This information is received directly from the Ontario Hospital Medical Records departments of participating hospitals (around 85% of all hospital inpatient discharges in Canada).¹¹³ Each record in the database represents a single hospital discharge and includes information on the date of admission and discharge, diagnoses received, and procedures performed during hospitalization.

3.4.4 Continuing Care Reporting System (CCRS)

The CCRS is a cumulative dataset that collects clinical and demographic information from assessments of individuals who receive facility-based continuing care services.¹¹⁴ This information is collected using a standardized assessment (RAI-MDS) which is designed to gather data that will inform care planning and monitoring for individuals in long-term care settings.¹¹⁵ Such data include the admission date, admission reason, and reason for assessment.

3.4.5 Ontario Census Area Profiles (CENSUS)

The CENSUS database contains information provided by Statistics Canada (e.g., proportion of racially minoritized persons, and income quintile) from the past seven Canadian censuses of the population.¹¹⁶ This study used information from the 2016 Census as 2021 data were not yet available.

3.4.6 IRCC Permanent Residents Database (CIC)

The Immigration, Refugees, and Citizenship Canada (IRCC) database is a federal database that captures information about individuals who immigrated to Canada and were granted permanent resident status.¹¹⁷ Records of all new immigrants who landed in Ontario and were subsequently issued an Ontario health card are available at ICES. This dataset does not include information on new immigrants who originally landed in another province or who landed in Ontario and did not stay long enough to be issued a health card.¹¹⁸ Information provided by the dataset includes permanent residents' country of citizenship, mother tongue, and landing date in Canada.

3.5 Exposures

The primary exposures of interest in this study included various neighbourhood- and individual-level SDOH variables – namely, neighbourhood income, neighbourhood proportion of racially minoritized groups, and recent immigration status.

Neighbourhood quintiles of income were obtained from 2016 Canada Census data at the level of dissemination areas (DAs), the smallest geographic unit (400-700 residents) for which census data are disseminated.¹¹⁹ This variable, which is provided to ICES by Statistics Canada, is a common ecological measure of socioeconomic status used in ICES studies.^{120,121} For each DA, the average after-tax income per single-person equivalent is first calculated to adjust for

household size. After-tax income is used to account for income redistribution. To adjust for differences in cost of living, DAs are then ordered by average income and split into income quintiles ranging from 1 (20% lowest income) to 5 (20% highest income) within each census metropolitan area or census agglomeration (one or more adjacent municipalities centered on a densely populated core).^{122,123} These quintiles are then assigned to IKNs using the relevant version of the PCCF (PCCF 2016 in this case) at ICES.

Neighbourhood levels of the proportion of the population who self-identify as a visible minority were also calculated at the DA level using data from the 2016 Canada Census.^{124,125} The Census of Population provides benchmark data on the visible minority population by asking respondents to indicate whether they belong to one or more of the following response categories (wording from the 2016 Census): “South Asian (e.g., East Indian, Pakistani, Sri Lankan, etc.), Chinese, Black, Filipino, Latin American, Arab, Southeast Asian (e.g., Vietnamese, Cambodian, Laotian, Thai, etc.), West Asian (e.g., Iranian, Afghan, etc.), Korean, Japanese, or Other—specify.”¹²⁶ DAs across the province are then ranked by these percentages into quintiles, ranging from 1 (20% lowest proportion of racially minoritized groups) to 5 (20% highest proportion of racially minoritized groups). This variable is part of one of the dimensions included in the Ontario Marginalization (ON-Marg) index, a validated tool developed to measure marginalization among populations in Ontario.¹²⁷

Immigration status was determined at the individual level using landing date information in the IRCC CIC database at ICES.¹²⁸ Information on landing date is available at ICES up until September 2020 for all individuals who immigrated to Ontario and were subsequently issued a health card number. In this study, individuals were categorized as recent immigrants if they had

landed in Ontario within the last 5 years, a length of time commonly used to define recent immigration status in Canada.¹²⁹

3.6 Outcome

The outcome of interest was incident antibiotic prescriptions, captured as drug claims in the ODB database, and determined by the earliest date of an outpatient systemic antibiotic prescription claim in the ODB database in relation to the randomly assigned index date. DINs and drug names from records in the ODB were used to identify antibiotic prescription claims and group these claims by antibiotic type, including those commonly prescribed for respiratory and non-respiratory infections, following methods used in other studies.¹³⁰

Antibiotics commonly prescribed for respiratory infections included penicillins, macrolides, respiratory fluoroquinolones, doxycycline, and second- and third-generation cephalosporins. Antibiotics prescribed for non-respiratory infections included lincosamides, oxazolidinones, trimethoprim, nitrofurantoin, fosfomycin, imidazole, first-generation cephalosporins, ciprofloxacin, norfloxacin, ofloxacin, minocycline, and tetracycline (see Appendix C for a full list of antibiotic names and classes).

For our first analysis, we considered incident antibiotic prescriptions of any antibiotic type (respiratory or non-respiratory indication) as the outcome of interest, whereas only incident prescriptions of antibiotics indicated for respiratory infections were considered for our second analysis (respiratory analysis). Information on antibiotic type was also used in an additional analysis to evaluate whether there were discernible differences in the prescription patterns of antibiotics for respiratory infections compared to antibiotics for non-respiratory infections.

3.7 Covariates

Statistical models were adjusted for covariates suspected to influence the probability of receiving an antibiotic prescription. These included demographic characteristics (age, sex, rural vs. urban living status), health and healthcare utilization measures (multimorbidity, primary care provider, number of physician visits in the prior 12 months), and vaccination status for influenza, pneumococcal disease, and COVID-19 (see Appendix A for data sources of covariates).

Demographic characteristics and whether individuals had a designated primary care provider were assessed at each individual's random index, whereas the number of physician visits was assessed 12 months prior to the random index date.

COVID-19 vaccination status was determined using the COVAXON database (see Appendix B for further details). Individuals were considered as vaccinated (completed primary series vaccination) if they received 2 or more doses of a Health Canada approved vaccine up to 14 days prior to their random index date. Influenza vaccination status and pneumococcal vaccination status were determined using OHIP billing with specific fee codes and ODB billing with certain DINs from one year up to 14 days before each individual's random index date (see Appendix D for fee codes and DINs).¹²⁴

Multimorbidity level was determined for eligible individuals in each cohort based on the number of prevalent conditions at random index (5-year lookback period). The following 17 chronic conditions were considered: acute myocardial infarction, asthma, cancer, cardiac arrhythmia, chronic coronary syndrome, chronic obstructive pulmonary disease, congestive heart failure, dementia, diabetes, hypertension, mood and anxiety disorders, other mental illnesses (schizophrenia, delusions and other psychoses, personality disorders and substance abuse), osteoarthritis, osteoporosis, renal failure, rheumatoid arthritis and stroke (excluding transient

ischemic attack). These conditions were identified through the International Classification of Diseases, ninth and tenth revisions (ICD-9 and ICD-10), and OHIP codes using multiple ICES data sources including, OHIP, DAD, ODB, RPDB, DIN, NACRS, OMHRS, SDS, and IPDB (see Appendix E for further details). The conditions were selected based on inclusion in previous multimorbidity research in Ontario.¹³¹⁻¹³⁸ Validated case ascertainment algorithms were used where available. The number of chronic conditions was defined as a count of diagnosed conditions among the 17 considered, coded as zero, one, two, three, four, or five-plus conditions.

3.8 Statistical Analysis

3.8.1 Descriptive statistics and cumulative incidence estimates

Descriptive statistics were presented for the pre-pandemic and pandemic cohorts using mean and standard deviation (SD) for normally distributed continuous variables; median and interquartile range (IQR) for non-normally distributed continuous variables; and frequency and proportion for categorical variables. The cumulative incidence of antibiotic prescribing for the average follow-up time was calculated during each two-year period (pre-pandemic and pandemic) and over the entire four-year study period (March 2018-March 2022) according to study variables and by antibiotic class. For each period, we calculated the incidence of prescribing considering incident antibiotic prescriptions of any type as the outcome of interest (overall prescribing) and separately considering incident prescriptions of antibiotics typically indicated for respiratory infections (respiratory prescribing) as the outcome. The 95% confidence intervals (CI) were constructed for each estimate using bootstrapping methods, a statistical resampling procedure that involves random sampling with replacement.

3.8.2 *Fine-Gray subdistribution hazard models*

In survival analysis, a competing risk is an event that occurs before the primary event of interest, thereby preventing the occurrence of this event.^{139,140} Ignoring the possibility of competing risks when using the conventional Cox proportional hazards model can produce biased estimates of the absolute risk of an event of interest.^{140,141} Two different regression models are instead used in the presence of competing risks – the Fine-Gray subdistribution hazard model and the cause-specific hazard model.^{139,140} The former models the effect of covariates on the subdistribution hazard function, which is defined as the probability of an event of interest given that an individual has not yet experienced this event.^{141,142} Therefore, the risk set for the subdistribution hazard model includes individuals who are event-free as well as those who have previously experienced a competing event.¹⁴¹ This contrasts with the cause-specific hazard model, which removes individuals from the risk set when any type of event occurs.¹⁴¹ This property of the subdistribution hazard model is necessary to establish a direct relation with the cumulative incidence function (CIF), which makes the model useful in predicting an individual's risk.^{141,142} Cause-specific models, on the other hand, are better suited for studying disease etiology.¹⁴¹

In this study, we used Fine-Gray subdistribution hazard models to evaluate the influence of SDOH variables on incident antibiotic prescribing in the pre-pandemic and pandemic periods, with all-cause mortality as a competing risk. Follow-up time in each period was calculated as the number of days from the randomly assigned index date for each individual until the earliest outpatient antibiotic claim date, death date, censoring date, or end of study date (maximum 2 years follow-up). Individuals were censored in the case of admission to long-term care, hospitalization, or loss of OHIP eligibility (with a 93-day grace period). In the respiratory analysis, follow-up was calculated from random index date until the earliest date of an outpatient

claim of an antibiotic indicated for respiratory infections. Models were adjusted for relevant covariates (i.e., age, sex, rural vs. urban living status, multimorbidity level, primary care provider, prior physician visits, and vaccination status for influenza, pneumococcal disease, and COVID-19). Unadjusted CIFs were generated from subdistribution hazard models to visualize associations between SDOH and antibiotic prescribing over each two-year study period.

3.8.3 Effect modification assessment

To determine whether associations between social determinants and antibiotic prescribing were modified by the COVID-19 pandemic, we examined interaction terms between each SDOH variable (recent immigration status, neighbourhood income, and neighbourhood proportion racially minoritized) and a binary study period variable (pandemic vs. pre-pandemic) in multivariable Fine-Gray models that included the total study sample (combined pre-pandemic and pandemic cohorts). Robust sandwich estimators with unique encoded identifiers as the cluster level were used to account for repeated individuals in the total sample. Analyses were performed using SAS Enterprise Guide Version 7.1.

3.8.4 Additional analyses

Three additional analyses were conducted to evaluate whether differences in antibiotic prescribing could be attributed to differences in healthcare access, to determine the influence of the different waves of the pandemic on the hazard of incident antibiotic use, and to assess whether geographically restricting the study population to an urban area would influence the associations between recent immigration status and antibiotic prescribing.

For the first additional analysis, results from adjusted Fine-Gray subdistribution hazard models considering incident antibiotic prescriptions of any type as the outcome of interest were stratified by antibiotic type (non-respiratory vs. respiratory). This was done to determine whether

inequities in prescribing could be attributed to differences in healthcare utilization among different groups. Observed changes in the hazard of prescribing for both antibiotic types among populations experiencing marginalization may provide evidence for potential healthcare access issues. In contrast, changes in the hazard of prescribing of only one type of antibiotic and not the other could help rule out inequities in access. For this analysis, if individuals were prescribed a respiratory and non-respiratory prescription on the same day, only one prescription was considered. Given the low proportion of individuals who were prescribed both types of antibiotics as their first prescription in the pre-pandemic (n=7,763) and pandemic periods (n=6,576), not considering multiple prescriptions is unlikely to have influenced the results.

Information from Public Health Ontario was used for the second analysis to define the different waves of the COVID-19 pandemic between the study period from March 2020-March 2022 (pandemic period). This sensitivity analysis was motivated by previously reported changes in the types of antibiotics prescribed over time during the pandemic in Ontario and accumulating evidence not supporting the use of antibiotics for the treatment of SARS-CoV-2 or treatment of associated coinfections.^{101,143,144} To account for the effect of the different pandemic waves in this study, we included a categorical wave predictor variable in adjusted Fine-Gray subdistribution hazard models. The different waves of the pandemic were defined as follows:¹⁴⁵

1. March 11, 2020-August 31, 2020 (wave began February 26, 2020)
2. September 1, 2020-February 28, 2021
3. March 1, 2021-July 31, 2021
4. August 1, 2021-December 14, 2021
5. December 15, 2021-February 28, 2022
6. March 1, 2022-March 11, 2022 (wave ended June 18, 2022)

For the last analysis, we geographically restricted our study population to individuals living in the Toronto PHU (PHU 3895). Given the small proportion of recent immigrants in our study population and the fact that most immigrants tend to settle in large urban areas in Canada,¹⁴⁶ we wanted to investigate whether restricting the study sample to an urban area with a potentially higher proportion of recent immigrants would influence the associations between immigration status and antibiotic prescribing. PHU information was obtained from the RPDB.

3.8.5 Missing data

Approximately 0.44% (n=11,300) and 0.45% (n=12,325) of older outpatients had missing covariate data on income, visible minority status, and rural vs. urban residence in the pre-pandemic and pandemic cohort, respectively. These individuals were excluded from all analyses.

Chapter 4: RESULTS

4.1 Descriptive characteristics

Between March 11, 2018, and March 11, 2022, we identified 5,411,041 community-dwelling older adults (≥ 66 years of age) in Ontario not residing in long-term care, 2,616,670 of which were identified in the pre-pandemic period, and 2,794,371 in the pandemic period. After exclusions, 2,567,382 (98.1%) individuals remained in the pre-pandemic cohort, and 2,744,337 (98.2%) in the pandemic cohort (Figure 1), with average follow-up periods of 240 (median 186 [IQR 70-374]) days and 260 days (median 211 [IQR 81-410]), respectively. Most records in both cohorts were excluded due to individuals being hospitalized on index, ineligible for OHIP coverage, or missing covariate data. Approximately 89% of individuals in the total study sample were included in both the pre-pandemic and pandemic cohorts.

Baseline characteristics for the two cohorts overall and by receipt of an antibiotic prescription are presented in Table 1. Overall, the two cohorts were similar in mean age (75 years), female sex (54%), and the majority had a primary care provider (82%). Just under half of the individuals in the pre-pandemic period received an influenza vaccination in the prior 12 months (48%), whereas 41% of individuals in the pandemic period received an influenza vaccination, and 33% received two or more doses of a Health Canada approved COVID-19 vaccine in the prior 12 months. In each period, over one third of individuals had 5 or more comorbidities (range 36-37%), around 1% were recent immigrants, and 23% lived in neighbourhoods with the highest proportion of racially minoritized groups. Residence in both cohorts was more evenly distributed among neighbourhood income quintile (range 19%-21%).

Table 1. Baseline characteristics of older outpatients between March 2018-March 2020 (pre-pandemic period) and March 2020-March 2022 (pandemic period) in Ontario, Canada

| Variable | Pre-Pandemic Period | | | Pandemic Period | | |
|--|---------------------|-------------------|-----------------|-------------------|-------------------|-----------------|
| | Total | No Antibiotics | Antibiotics | Total | No Antibiotics | Antibiotics |
| Sample Size - n | 2,567,382 | 1,750,682 (68%) | 816,700 (32%) | 2,744,337 | 2,050,037 (75%) | 694,300 (25%) |
| Demographics | | | | | | |
| Age (years) - mean (SD) | 74.8 (7.6) | 74.5 (7.6) | 75.4 (7.5) | 74.8 (7.6) | 74.5 (7.6) | 75.7 (7.6) |
| Female sex | 1,377,263 (53.6%) | 914,855 (52.3%) | 462,408 (56.6%) | 1,472,035 (53.6%) | 1,077,765 (52.6%) | 394,270 (56.8%) |
| Rural resident | 316,400 (12.3%) | 220,555 (12.6%) | 95,845 (11.7%) | 341,039 (12.4%) | 255,598 (12.5%) | 85,441 (12.3%) |
| Social Determinants of Health | | | | | | |
| Recent immigrant | 30,450 (1.2%) | 23,922 (1.4%) | 6,528 (0.8%) | 28,584 (1.0%) | 23,468 (1.1%) | 5,116 (0.7%) |
| Neighbourhood income quintile | | | | | | |
| 1 (lowest) | 512,597 (20.0%) | 350,455 (20.0%) | 162,142 (19.9%) | 533,814 (19.5%) | 399,433 (19.5%) | 134,381 (19.4%) |
| 2 | 536,617 (20.9%) | 366,104 (20.9%) | 170,513 (20.9%) | 566,857 (20.7%) | 423,333 (20.7%) | 143,524 (20.7%) |
| 3 | 512,719 (20.0%) | 349,358 (20.0%) | 163,361 (20.0%) | 550,834 (20.1%) | 411,364 (20.1%) | 139,470 (20.1%) |
| 4 | 485,837 (18.9%) | 330,629 (18.9%) | 155,208 (19.0%) | 528,337 (19.3%) | 394,747 (19.3%) | 133,590 (19.2%) |
| 5 (highest) | 519,612 (20.2%) | 354,136 (20.2%) | 165,476 (20.3%) | 564,495 (20.6%) | 421,160 (20.5%) | 143,335 (20.6%) |
| Neighbourhood proportion of racially minoritized groups quintile | | | | | | |
| 1 (lowest) | 487,519 (19.0%) | 333,862 (19.1%) | 153,657 (18.8%) | 522,606 (19.0%) | 387,192 (18.9%) | 135,414 (19.5%) |
| 2 | 497,991 (19.4%) | 334,245 (19.1%) | 163,746 (20.0%) | 531,449 (19.4%) | 388,807 (19.0%) | 142,642 (20.5%) |
| 3 | 490,981 (19.1%) | 327,464 (18.7%) | 163,517 (20.0%) | 520,767 (19.0%) | 381,285 (18.6%) | 139,482 (20.1%) |
| 4 | 502,913 (19.6%) | 341,292 (19.5%) | 161,621 (19.8%) | 535,418 (19.5%) | 399,331 (19.5%) | 136,087 (19.6%) |
| 5 (highest) | 587,978 (22.9%) | 413,819 (23.6%) | 174,159 (21.3%) | 634,097 (23.1%) | 493,422 (24.1%) | 140,675 (20.3%) |
| Health and Healthcare Use | | | | | | |
| Multimorbidity level | | | | | | |
| 0 conditions | 136,277 (5.3%) | 123,077 (7.0%) | 13,200 (1.6%) | 142,169 (5.2%) | 130,860 (6.4%) | 11,309 (1.6%) |
| 1 condition | 225,714 (8.8%) | 184,695 (10.5%) | 41,019 (5.0%) | 245,856 (9.0%) | 211,499 (10.3%) | 34,357 (4.9%) |
| 2 conditions | 359,550 (14.0%) | 273,395 (15.6%) | 86,155 (10.5%) | 389,543 (14.2%) | 317,990 (15.5%) | 71,553 (10.3%) |
| 3 conditions | 452,634 (17.6%) | 321,915 (18.4%) | 130,719 (16.0%) | 486,252 (17.7%) | 377,650 (18.4%) | 108,602 (15.6%) |
| 4 conditions | 449,633 (17.5%) | 300,205 (17.1%) | 149,428 (18.3%) | 481,158 (17.5%) | 355,739 (17.4%) | 125,419 (18.1%) |
| 5+ conditions | 943,574 (36.8%) | 547,395 (31.3%) | 396,179 (48.5%) | 999,359 (36.4%) | 656,299 (32.0%) | 343,060 (49.4%) |
| Primary care provider | 2,103,212 (81.9%) | 1,396,914 (79.8%) | 706,298 (86.5%) | 2,250,163 (82.0%) | 1,652,521 (80.6%) | 597,642 (86.1%) |
| Physician visits prior (12 mo) - median (IQR) | 6 (3-11) | 5 (2-9) | 8 (5-14) | 5 (2-10) | 5 (1-9) | 8 (4-14) |
| Vaccination Status | | | | | | |
| Pneumococcal vaccinated | 58,599 (2.3%) | 37,299 (2.1%) | 21,300 (2.6%) | 43,242 (1.6%) | 29,856 (1.5%) | 13,386 (1.9%) |
| Influenza vaccinated | 1,220,874 (47.6%) | 770,962 (44.0%) | 449,912 (55.1%) | 1,126,357 (41.0%) | 781,413 (38.1%) | 344,944 (49.7%) |
| COVID-19 Vaccinated (>=2 doses) | — | — | — | 892,190 (32.5%) | 771,331 (37.6%) | 120,859 (17.4%) |

Abbreviations: SD, standard deviation; IQR, interquartile range.
Table shows number (column %) unless otherwise indicated.

4.2 Cumulative incidence of antibiotic prescribing

4.2.1 Cumulative incidence of antibiotic prescribing by SDOH

The unadjusted cumulative incidence of overall antibiotic prescribing for the pre-pandemic, pandemic, and total study periods by study variables is presented in Table 2. Of the individuals in the pre-pandemic cohort, 28.6% (95% CI 28.5-28.6) filled at least one outpatient antibiotic prescription during average follow-up (240 days), whereas 22.5% (95% CI 22.5-22.6) of individuals in the pandemic period filled at least one prescription during average follow-up (260 days). The cumulative incidence of antibiotic prescribing was lower among recent immigrants compared to long-term residents over average follow-up in the pre-pandemic (19.6, 95% CI 19.2-20.1 vs. 28.7, 95% CI 28.6-28.7) and pandemic periods (16.4, 95% CI 16.0-16.8 vs. 22.6, 95% CI 22.6-22.7). Similarly, in both periods, the cumulative incidence of prescribing was slightly lower among residents of neighbourhoods with the highest proportion of racially minoritized groups compared to the lowest (27.1, 95% CI 27.0-27.2 vs. 27.8, 95% CI 27.7-28.0 pre-pandemic; and 20.1, 95% CI 20.0-20.2 vs. 22.8, 95% CI 22.7-22.9 pandemic). Residents in neighbourhoods with the highest income had a slightly higher crude cumulative incidence of antibiotic prescribing over average follow-up compared to residents in neighbourhoods with the lowest income both pre-pandemic (29.0, 95% CI 28.8-29.1 vs. 27.9, 95% CI 27.2-28.0) and during the pandemic period (22.9, 95% CI 22.8-23.0 vs. 22.0, 95% CI 21.9-22.2).

4.2.2 Cumulative incidence of antibiotic prescribing by study covariates

In both pre-pandemic and pandemic periods, the cumulative incidence of antibiotic prescribing was slightly higher among urban vs. rural residents, higher among females compared to males, individuals with a primary care provider compared to those with no provider, individuals with physician visits in the prior 12 months compared to those with no prior visits, and individuals

vaccinated against pneumococcal disease and influenza compared to unvaccinated individuals, whereas individuals vaccinated against COVID-19 had a lower crude cumulative incidence of prescribing compared to unvaccinated individuals (Table 2). The cumulative incidence of prescribing was highest among those with 5 or more chronic conditions in both periods and highest among individuals between the ages of 75-84 years compared to younger (66-74 years) and older individuals (85+ years).

Table 2. Unadjusted cumulative incidence of antibiotic prescribing among older outpatients over average follow-up for the pre-pandemic, pandemic, and total study periods in Ontario, Canada

| Variable | Pre-Pandemic Period | Pandemic Period | Total Study Period |
|--|----------------------------|------------------------|---------------------------|
| | CI (95% CI) | CI (95% CI) | CI (95% CI) |
| <i>All</i> | 28.6 (28.5-28.6) | 22.5 (22.5-22.6) | 25.4 (25.4-25.5) |
| Demographics | | | |
| Age 66-74 (years) | 27.6 (27.5-27.7) | 21.2 (21.2-21.3) | 24.3 (24.3-24.4) |
| Age 75-84 (years) | 30.4 (30.3-30.5) | 24.3 (24.2-24.4) | 27.2 (27.2-27.3) |
| Age 85+ (years) | 28.5 (28.3-28.6) | 24.2 (24.0-24.3) | 26.3 (26.2-26.4) |
| Female sex | 30.5 (30.4-30.6) | 24.2 (24.1-24.3) | 27.3 (27.2-27.3) |
| Male sex | 26.3 (26.2-26.4) | 20.6 (20.5-20.7) | 23.4 (23.3-23.4) |
| Rural resident | 26.7 (26.5-26.8) | 22.0 (21.9-22.2) | 24.3 (24.1-24.4) |
| Urban resident | 28.8 (28.8-28.9) | 22.6 (22.6-22.7) | 25.6 (25.6-25.7) |
| Social Determinants of Health | | | |
| Recent immigrant | 19.6 (19.2-20.1) | 16.4 (16.0-16.8) | 18.1 (17.7-18.4) |
| Long-term resident | 28.7 (28.6-28.7) | 22.6 (22.6-22.7) | 25.5 (25.5-25.6) |
| Income Q1 (lowest neighbourhood income quintile) | 27.9 (27.8-28.0) | 22.0 (21.9-22.2) | 24.9 (24.8-25.0) |
| Income Q2 | 28.4 (28.3-28.6) | 22.5 (22.4-22.6) | 25.4 (25.3-25.5) |
| Income Q3 | 28.7 (28.5-28.8) | 22.6 (22.5-22.7) | 25.5 (25.4-25.6) |
| Income Q4 | 28.8 (28.7-28.9) | 22.7 (22.6-22.8) | 25.6 (25.5-25.7) |
| Income Q5 (highest neighbourhood income quintile) | 29.0 (28.8-29.1) | 22.9 (22.8-23.0) | 25.8 (25.7-25.9) |
| Racialized Q1 (lowest neighbourhood proportion of racially minoritized groups quintile) | 27.8 (27.7-28.0) | 22.8 (22.7-22.9) | 25.2 (25.1-25.3) |
| Racialized Q2 | 29.2 (29.1-29.3) | 23.8 (23.6-23.9) | 26.4 (26.3-26.5) |
| Racialized Q3 | 29.9 (29.8-30.0) | 23.9 (23.7-24.0) | 26.8 (26.7-26.9) |
| Racialized Q4 | 29.0 (28.9-29.2) | 22.8 (22.6-22.9) | 25.8 (25.7-25.9) |
| Racialized Q5 (highest neighbourhood proportion of racially minoritized groups quintile) | 27.1 (27.0-27.2) | 20.1 (20.0-20.2) | 23.4 (23.4-23.5) |
| Health and Healthcare Use | | | |
| Multimorbidity level | | | |
| 0 conditions | 9.0 (8.8-9.2) | 7.3 (7.2-7.5) | 8.1 (8.0-8.3) |
| 1 condition | 16.9 (16.8-17.1) | 12.9 (12.8-13.1) | 14.8 (14.7-15.0) |
| 2 conditions | 22.3 (22.1-22.4) | 16.9 (16.8-17.1) | 19.5 (19.4-19.6) |
| 3 conditions | 26.5 (26.4-26.7) | 20.4 (20.3-20.5) | 23.4 (23.3-23.4) |
| 4 conditions | 30.3 (30.2-30.4) | 23.6 (23.5-23.7) | 26.8 (26.7-26.9) |
| 5+ conditions | 36.7 (36.6-36.8) | 29.8 (29.7-29.9) | 33.1 (33.1-33.2) |
| Primary care provider | 30.2 (30.1-30.3) | 23.7 (23.6-23.8) | 26.8 (26.8-26.9) |
| No primary care provider | 21.1 (21.0-21.2) | 17.3 (17.2-17.4) | 19.1 (19.1-19.2) |
| Physician visits prior (12 mo) | 31.5 (31.5-31.6) | 25.3 (25.3-25.4) | 28.4 (28.3-28.4) |
| No physician visits prior (12 mo) | 7.2 (7.1-7.3) | 7.1 (7.0-7.2) | 7.1 (7.1-7.2) |
| Vaccination Status | | | |
| Pneumococcal vaccinated | 33.2 (32.8-33.6) | 27.8 (27.4-28.2) | 30.9 (30.6-31.2) |
| Pneumococcal unvaccinated | 28.4 (28.4-28.5) | 22.5 (22.4-22.5) | 25.3 (25.3-25.4) |
| Influenza vaccinated | 33.2 (33.1-33.3) | 27.3 (27.2-27.4) | 30.4 (30.3-30.4) |
| Influenza unvaccinated | 24.4 (24.3-24.4) | 19.2 (19.1-19.3) | 21.6 (21.5-21.6) |
| COVID-19 vaccinated | — | 12.5 (12.5-12.6) | 12.5 (12.5-12.6) |
| COVID-19 unvaccinated | — | 27.4 (27.3-27.4) | 28.1 (28.0-28.1) |

Abbreviations : CI, cumulative incidence; 95% CI, 95% confidence intervals.

4.3 Cumulative incidence of respiratory antibiotic prescribing

4.3.1 Cumulative incidence of respiratory antibiotic prescribing by SDOH

Of the eligible individuals in the pre-pandemic period, 19.7% (95% CI 19.6-19.7) filled at least one outpatient prescription of an antibiotic indicated for a respiratory infection during average follow-up (260 days, median 215 [IQR 85-410] days), and 13.7% (95% CI 13.6-13.7) of the individuals in the pandemic period filled at least one prescription during average follow-up (280 days, median 242 [IQR 97-444] days; Table 3). Recent immigrants had a lower cumulative incidence of respiratory antibiotic prescribing compared to long-term residents over average follow-up in the pre-pandemic (14.5, 95% CI 14.1-14.9 vs. 19.8, 95% CI 19.7-19.8) and pandemic periods (11.1, 95% CI 10.8-11.4 vs. 13.7, 95% CI 13.6-13.7). Residents of neighbourhoods with the highest proportion of racially minoritized groups compared to the lowest proportion initially had a higher cumulative incidence of respiratory antibiotic prescribing over follow-up pre-pandemic (20.2, 95% CI 20.1-20.2 vs. 18.2, 95% CI 18.1-18.3), but a similar cumulative incidence in the pandemic period (13.1, 95% CI 13.0-13.1 vs. 13.3 95% CI 13.2-13.4). Lastly, residents in the highest income neighbourhoods had a higher cumulative incidence of respiratory antibiotic prescribing over average follow-up compared to residents in neighbourhoods with the lowest income pre-pandemic (20.1, 95% CI 20.0-20.2 vs. 19.1, 95% CI 19.0-19.2) and during the pandemic period (14.0, 95% CI 13.9-14.1 vs. 13.2, 95% CI 13.1-13.3).

4.3.2 Cumulative incidence of respiratory antibiotic prescribing by study covariates

Similar to the results for overall antibiotic prescribing, in both pre-pandemic and pandemic periods, the cumulative incidence of prescribing of antibiotics indicated for respiratory infections was slightly higher among urban vs. rural residents, higher among individuals with a primary care provider compared to those with no provider, individuals with physician visits in the prior

12 months compared to those with no prior visits, and individuals vaccinated against pneumococcal disease and influenza compared to unvaccinated individuals, whereas individuals vaccinated against COVID-19 had a lower crude cumulative incidence of prescribing compared to unvaccinated individuals (Table 3). The cumulative incidence of prescribing of antibiotics indicated for respiratory infections was highest among those with 5 or more chronic conditions in both periods and slightly higher among individuals between the ages of 75-84 years compared to younger (66-74 years) and older individuals (85+ years). Contrary to the results for overall prescribing, the crude cumulative incidence of respiratory antibiotic prescribing was slightly higher among females in the pre-pandemic period, but similar in the pandemic period.

Table 3. Unadjusted cumulative incidence of respiratory antibiotic prescribing among older outpatients over average follow-up for the pre-pandemic, pandemic, and total study periods in Ontario, Canada

| | Pre-Pandemic Period | Pandemic Period | Total Study Period |
|---|----------------------------|------------------------|---------------------------|
| Variable | CI (95% CI) | CI (95% CI) | CI (95% CI) |
| <i>All</i> | 19.7 (19.6-19.7) | 13.7 (13.6-13.7) | 16.6 (16.5-16.6) |
| Demographics | | | |
| Age 66-74 (years) | 19.8 (19.7-19.9) | 13.6 (13.5-13.6) | 16.6 (16.5-16.6) |
| Age 75-84 (years) | 20.5 (20.4-20.6) | 14.3 (14.3-14.4) | 17.3 (17.3-17.4) |
| Age 85+ (years) | 17.3 (17.2-17.5) | 12.5 (12.4-12.6) | 14.8 (14.8-14.9) |
| Female sex | 20.2 (20.1-20.3) | 13.7 (13.6-13.8) | 16.8 (16.8-17.9) |
| Male sex | 19.1 (19.0-19.2) | 13.6 (13.6-13.7) | 16.3 (16.2-16.3) |
| Rural resident | 17.2 (17.1-17.3) | 12.9 (12.7-13.0) | 14.9 (14.8-15.0) |
| Urban resident | 20.0 (20.0-20.1) | 13.8 (13.7-13.8) | 16.8 (16.8-16.8) |
| Social Determinants of Health | | | |
| Recent immigrant | 14.5 (14.1-14.9) | 11.1 (10.8-11.4) | 12.9 (12.6-13.1) |
| Long-term resident | 19.8 (19.7-19.8) | 13.7 (13.6-13.7) | 16.6 (16.6-16.7) |
| Income Q1 (lowest neighbourhood income quintile) | 19.1 (19.0-19.2) | 13.2 (13.1-13.3) | 16.1 (16.0-16.2) |
| Income Q2 | 19.6 (19.5-19.7) | 13.5 (13.5-13.6) | 16.5 (16.4-16.6) |
| Income Q3 | 19.8 (19.7-19.9) | 13.8 (13.7-13.9) | 16.7 (16.6-16.7) |
| Income Q4 | 19.9 (19.8-20.0) | 13.8 (13.7-13.9) | 16.7 (16.7-16.8) |
| Income Q5 (highest neighbourhood income quintile) | 20.1 (20.0-20.2) | 14.0 (13.9-14.1) | 16.9 (16.8-17.0) |
| Racialized Q1 (lowest neighbourhood proportion of racially minoritized groups) | 18.2 (18.1-18.3) | 13.3 (13.2-13.4) | 15.6 (15.6-15.7) |
| Racialized Q2 | 19.4 (19.3-19.5) | 14.0 (13.9-14.0) | 16.6 (16.5-16.7) |
| Racialized Q3 | 20.3 (20.2-20.4) | 14.3 (14.2-14.4) | 17.2 (17.1-17.3) |
| Racialized Q4 | 20.3 (20.1-20.4) | 13.9 (13.8-14.0) | 17.0 (16.9-17.0) |
| Racialized Q5 (highest neighbourhood proportion of racially minoritized groups) | 20.2 (20.1-20.2) | 13.1 (13.0-13.1) | 16.6 (16.4-16.5) |
| Health and Healthcare Use | | | |
| Multimorbidity level | | | |
| 0 conditions | 6.3 (6.1-6.4) | 4.7 (4.6-4.8) | 5.5 (5.4-5.6) |
| 1 condition | 11.7 (11.6-11.8) | 8.1 (8.0-8.2) | 9.8 (9.7-9.9) |
| 2 conditions | 15.3 (15.2-15.4) | 10.4 (10.3-10.5) | 12.8 (12.7-12.8) |
| 3 conditions | 18.1 (18.0-18.3) | 12.4 (12.3-12.5) | 15.1 (15.1-15.2) |
| 4 conditions | 20.8 (20.6-20.9) | 14.1 (14.0-14.2) | 17.3 (17.2-17.4) |
| 5+ conditions | 25.5 (25.4-25.5) | 18.0 (17.9-18.1) | 21.6 (21.5-21.7) |
| Primary care provider | 20.8 (20.7-20.8) | 14.3 (14.3-14.4) | 17.4 (17.4-17.5) |
| No primary care provider | 14.8 (14.7-14.9) | 10.6 (10.5-10.7) | 12.6 (12.6-12.7) |
| Physician visits prior (12 mo) | 21.7 (21.7-21.8) | 15.3 (15.3-15.4) | 18.5 (18.5-18.5) |
| No physician visits prior (12 mo) | 4.8 (4.7-4.9) | 4.3 (4.3-4.4) | 4.5 (4.5-4.6) |
| Vaccination Status | | | |
| Pneumococcal vaccinated | 23.7 (23.4-24.1) | 17.9 (17.5-18.2) | 21.2 (21.0-21.5) |
| Pneumococcal unvaccinated | 19.6 (19.6-19.6) | 13.6 (13.6-13.6) | 16.5 (16.5-16.5) |
| Influenza vaccinated | 23.0 (22.9-23.1) | 16.6 (16.6-16.7) | 19.9 (19.9-20.0) |
| Influenza unvaccinated | 16.7 (16.6-16.7) | 11.6 (11.5-11.6) | 13.9 (13.9-13.9) |
| COVID-19 vaccinated | — | 7.3 (7.3-7.4) | 7.3 (7.3-7.4) |
| COVID-19 unvaccinated | — | 16.7 (16.7-16.8) | 18.4 (18.4-18.5) |

Abbreviations : CI, cumulative incidence; 95% CI, 95% confidence interval.

4.4 Cumulative incidence of antibiotic prescribing by antibiotic class

Overall, the unadjusted cumulative incidence of prescribing of antibiotics indicated for respiratory infections was higher than that of non-respiratory infections over average follow-up during the pre-pandemic (19.7, 95% CI 19.6-19.7 vs. 14.3, 95% CI 14.3-14.3) and the pandemic (13.7, 95% CI 13.6-13.7 vs. 12.6, 95% CI 12.6-12.7) period (Table 4). Penicillins were the most prescribed antibiotic class in both periods. The cumulative incidence of prescribing of all antibiotic classes decreased from the pre-pandemic to the pandemic period. This decrease was most pronounced among antibiotics indicated for respiratory infections compared to non-respiratory infections, and specifically, among macrolides compared to all other respiratory antibiotics.

Table 4. Unadjusted cumulative incidence of antibiotic prescribing by antibiotic class among older outpatients over average follow-up for the pre-pandemic, pandemic, and total study periods in Ontario, Canada

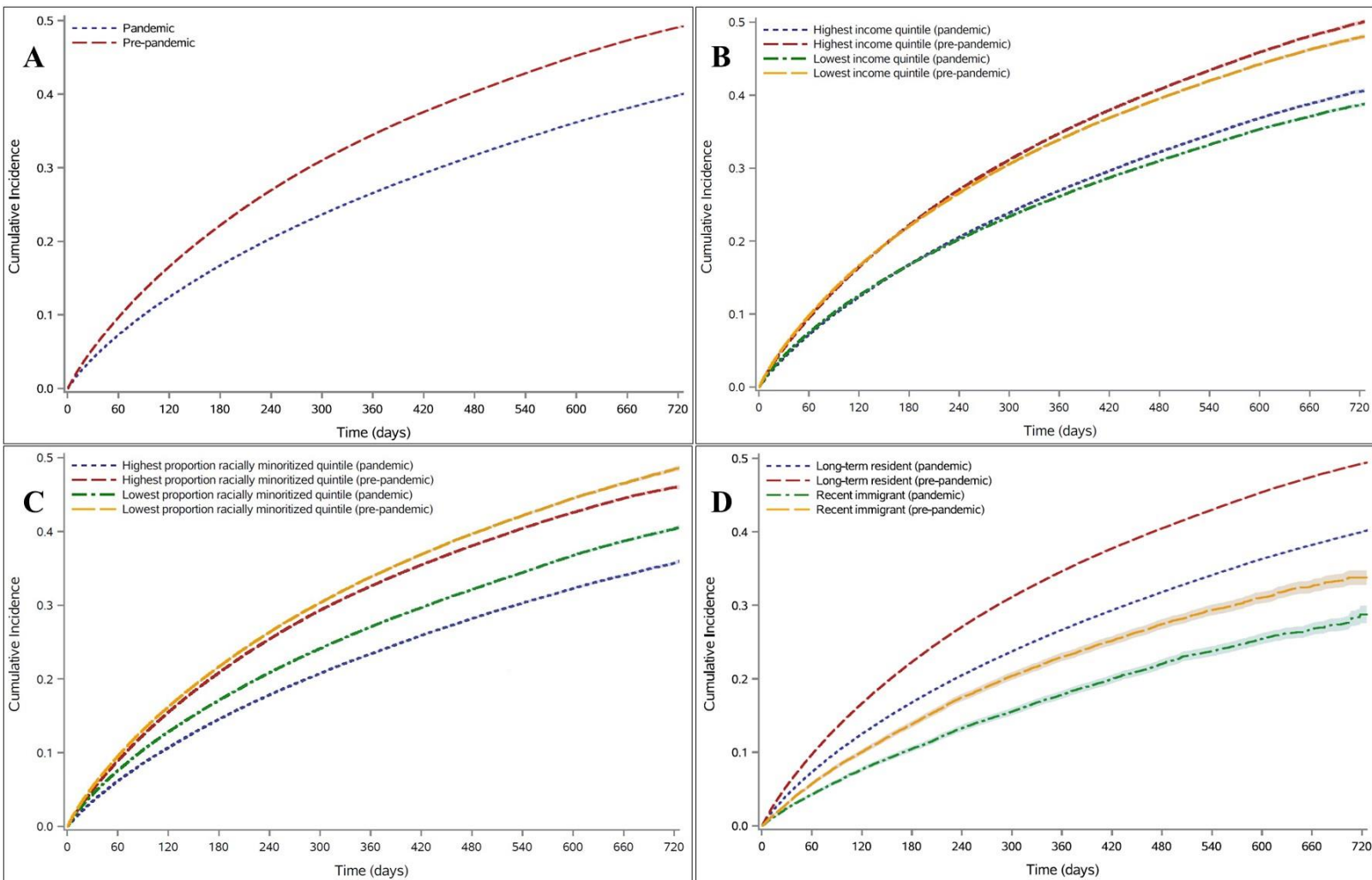
| | Pre-Pandemic Period | Pandemic Period | Total Study Period |
|-------------------------------|----------------------------|------------------------|---------------------------|
| Antibiotic Class | CI (95% CI) | CI (95% CI) | CI (95% CI) |
| All Antibiotics | 28.6 (28.5-28.6) | 22.5 (22.5-22.6) | 25.4 (25.4-25.5) |
| Respiratory antibiotics* | 19.7 (19.6-19.7) | 13.7 (13.6-13.7) | 16.6 (16.5-16.6) |
| Non-respiratory antibiotics | 14.3 (14.3-14.3) | 12.6 (12.6-12.7) | 13.4 (13.4-13.5) |
| Penicillins | 12.8 (12.8-12.8) | 10.4 (10.3-10.4) | 11.5 (11.5-11.6) |
| 1st Generation Cephalosporins | 4.8 (4.8-4.8) | 3.9 (3.9-3.9) | 4.3 (4.3-4.3) |
| 2nd Generation Cephalosporins | 0.9 (0.9-0.9) | 0.4 (0.4-0.4) | 0.6 (0.6-0.6) |
| 3rd Generation Cephalosporins | 0.9 (0.9-0.9) | 0.5 (0.5-0.5) | 0.7 (0.7-0.7) |
| Fluoroquinolones | 6.0 (6.0-6.0) | 4.2 (4.2-4.2) | 5.1 (5.1-5.1) |
| Macrolides | 6.1 (6.0-6.1) | 2.3 (2.3-2.4) | 4.1 (4.1-4.2) |
| Doxycycline/Tetracycline | 1.4 (1.4-1.4) | 1.2 (1.2-1.2) | 1.3 (1.3-1.3) |
| Lincosamides | 1.5 (1.5-1.5) | 1.3 (1.3-1.3) | 1.4 (1.4-1.4) |
| Trimethoprim/sulfamethoxazole | 1.9 (1.8-1.9) | 1.6 (1.6-1.7) | 1.7 (1.7-1.8) |
| Nitrofurantoin | 4.2 (4.2-4.2) | 3.8 (3.8-3.9) | 4.0 (4.0-4.0) |
| Fosfomycin | 1.1 (1.1-1.2) | 1.4 (1.3-1.4) | 1.3 (1.2-1.3) |
| Imidazole | 1.1 (1.1-1.2) | 0.8 (0.8-0.8) | 0.9 (0.9-0.9) |

*Respiratory antibiotics include macrolides, penicillins, respiratory fluoroquinolones, second and third generation cephalosporins, and doxycycline.

4.5 Unadjusted cumulative incidence functions of antibiotic prescribing

Figure 2 shows the unadjusted cumulative incidence functions of overall antibiotic prescribing over the two-year pre-pandemic and pandemic periods: (Panel A) for the entire study population; (Panel B) by highest and lowest quintiles of neighbourhood income; (Panel C) by highest and lowest quintile of the proportion of racially minoritized groups; and (Panel D) by immigration status. After accounting for censoring and the competing risk of death, antibiotic prescribing in this older population over time was lower in the pandemic compared to the pre-pandemic period (unadjusted subdistribution hazard ratio [sHR], 0.74, 95% CI 0.73-0.74), with approximately half of the study population filling an outpatient antibiotic prescription over the two-year pre-pandemic period (50%) and less than half over the two-year pandemic period (40%). In both periods, antibiotic prescribing was slightly higher among residents of neighbourhoods with the highest income compared to the lowest (unadjusted sHR 1.03, 95% CI 1.02-1.03 pre-pandemic, and unadjusted sHR 1.03, 95% CI 1.02-1.04 pandemic). Antibiotic prescribing was lower among residents of neighbourhoods with the highest proportion of racially minoritized groups compared to the lowest in both periods, with a more pronounced decrease during the pandemic than pre-pandemic period (unadjusted sHR 0.84, 95% CI 0.84-0.85 vs. unadjusted sHR 0.95, 95% CI 0.94-0.96). Lastly, unadjusted results show that antibiotic prescribing was lower among recent immigrants compared to long-term residents' pre-pandemic (unadjusted sHR 0.61, 95% CI 0.59-0.62) and during the pandemic period (unadjusted sHR 0.64, 95% CI 0.62-0.66).

Figure 2. Unadjusted cumulative incidence functions of antibiotic prescribing among older outpatients over time and by social determinants of health in Ontario, Canada

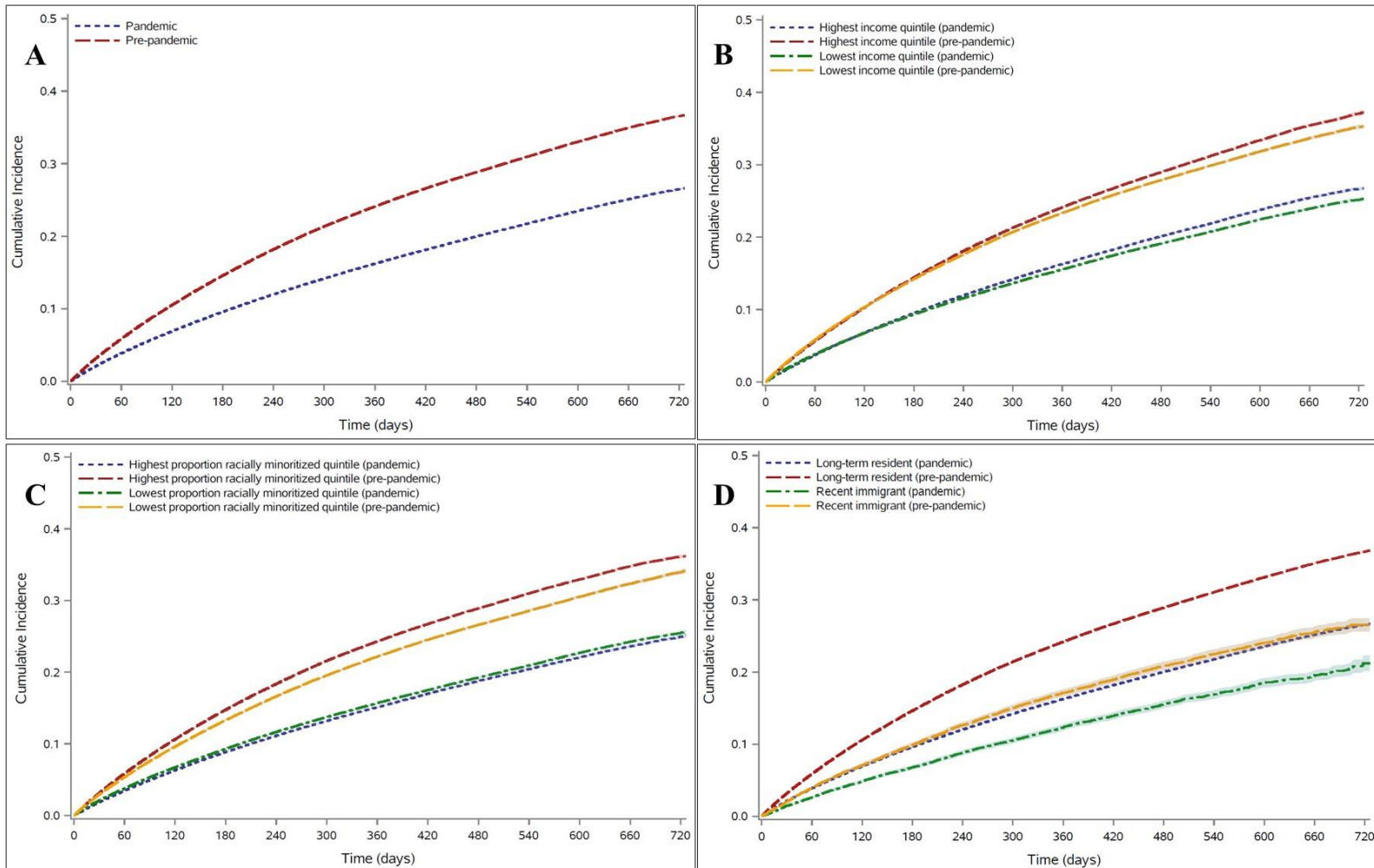


Cumulative incidence functions of antibiotic prescribing among older outpatients by study period (Panel A), highest and lowest neighbourhood income quintiles (Panel B), highest and lowest neighbourhood proportion of racially minoritized groups quintiles (Panel C), and immigration status (Panel D).

4.6 Unadjusted cumulative incidence functions of respiratory antibiotic prescribing

Figure 3 shows the cumulative incidence functions of prescribing of antibiotics indicated for respiratory infections over the two-year pre-pandemic and pandemic periods: (Panel A) for the entire study population; (Panel B) by highest and lowest quintiles of neighbourhood income; (Panel C) by highest and lowest quintile of the proportion of racially minoritized groups; and (Panel D) by immigration status. After accounting for censoring and the competing risk of death, respiratory antibiotic prescribing in this older population during follow-up was lower in the pandemic compared to the pre-pandemic period (unadjusted sHR 0.65, 95% CI 0.65-0.66), with over one-third of older adults filling an outpatient respiratory antibiotic prescription over the two-year pre-pandemic period (35%) and close to one-quarter over the two-year pandemic period (25%). Respiratory antibiotic prescribing was slightly higher among residents of neighbourhoods with the highest income compared to the lowest both pre-pandemic (unadjusted sHR 1.04, 95% CI 1.03-1.05) and during the pandemic period (unadjusted sHR 1.05, 1.04-1.06). While respiratory antibiotic prescribing was slightly higher among residents in neighbourhoods with the highest proportion of racially minoritized groups compared to the lowest in the pre-pandemic period (unadjusted sHR 1.11, 95% CI 1.10-1.12), prescribing was lower among residents of this neighbourhood compared to the reference in the pandemic period (unadjusted sHR 0.96, 95% CI 0.95-0.97). Finally, unadjusted results indicate that respiratory antibiotic prescribing was lower among recent immigrants compared to long-term residents in both the pre-pandemic (unadjusted sHR 0.67, 95% CI 0.65-0.69) and pandemic (unadjusted sHR 0.73, 95% CI 0.71-0.76) periods.

Figure 3. Unadjusted cumulative incidence functions of respiratory antibiotic prescribing among older outpatients over time and by social determinants of health in Ontario, Canada



Cumulative incidence functions of respiratory antibiotic prescribing among older outpatients by study period (Panel A), highest and lowest neighbourhood income quintiles (Panel B), highest and lowest neighbourhood proportion of racially minoritized groups quintiles (Panel C), and immigration status (Panel D).

4.7 Adjusted subdistribution hazard ratios of antibiotic prescribing

4.7.1 Adjusted subdistribution hazard ratios of antibiotic prescribing by SDOH

Results from adjusted Fine-Gray subdistribution hazard models considering incident prescribing of any antibiotic (Table 5 and Figure 4) showed a similar trend as unadjusted results for most SDOH variables. In adjusted models including the entire study sample, overall antibiotic prescribing varied by study period and was lower in the pandemic compared to the pre-pandemic period (sHR 0.73, 95% CI 0.73-0.73). In separate pre-pandemic and pandemic models, overall antibiotic prescribing was slightly higher among residents of the highest income neighbourhoods compared to the lowest in both periods (sHR 1.03, 95% CI 1.02-1.04 pre-pandemic, and sHR 1.02, 95% CI 1.01-1.03 pandemic). Antibiotic prescribing decreased among residents of neighbourhoods with an increasing proportion of racially minoritized groups. This was most evident among residents of neighbourhoods with the highest proportion of racially minoritized groups compared to the lowest pre-pandemic (sHR 0.92, 95% CI 0.91-0.93) and during the pandemic, with a more pronounced decrease evident during the pandemic period (sHR 0.81, 95% CI 0.80-0.82). In contrast to the unadjusted results for the association between recent immigration and antibiotic prescribing, the adjusted subdistribution hazard ratio of overall antibiotic prescribing was higher among recent immigrants compared to long-term resident's both pre-pandemic (sHR 1.12, 95% CI 1.09-1.16) and during the pandemic, with a more pronounced increase during the pandemic period (sHR 1.21, 95% CI 1.18-1.25). The direction of this association was noted to have changed after adjustment for multimorbidity level.

4.7.2 Adjusted subdistribution hazard ratios of respiratory antibiotic prescribing by SDOH

Results from models considering incident prescribing of only antibiotics indicated for respiratory infections are shown in Table 6 and Figure 5. Similar to the results for overall antibiotic

prescribing, prescribing of antibiotics indicated for respiratory infections varied by study period and was lower in the pandemic compared to the pre-pandemic period (sHR 0.64, 95% CI 0.64-0.64). In separate models by study period, prescribing of antibiotics indicated for respiratory infections was higher among residents in the highest income neighbourhoods compared to the lowest both pre-pandemic (sHR 1.06, 95% CI 1.05-1.07) and during the pandemic (sHR 1.05, 95% CI 1.04-1.06) period. Among residents in neighbourhoods with the highest proportion of racially minoritized groups compared to the lowest, prescribing of antibiotics indicated for respiratory infections was initially higher in the pre-pandemic period (sHR 1.07, 95% CI 1.05-1.08), but was lower in the pandemic period (sHR 0.93, 95% CI 0.92-0.94). Lastly, in contrast to unadjusted results, the adjusted subdistribution hazard ratio of prescribing of antibiotics indicated for respiratory infections was higher among recent immigrants compared to long-term residents in both pre-pandemic (sHR 1.15, 95% CI 1.11-1.18) and pandemic periods, with a more pronounced increase during the pandemic period (sHR 1.27, 95% CI 1.23-1.32). The direction of this association changed after multimorbidity level was added to the models.

4.7.3 Impact of COVID-19 on the associations between SDOH and antibiotic prescribing

In separate models with interaction terms, there was evidence of meaningful effect modification by the COVID-19 pandemic period for recent immigrants and neighbourhood-level racially minoritized groups. The association between neighbourhood-level highest proportion of racially minoritized groups and antibiotic prescribing was stronger in the pandemic period versus pre-pandemic period when considering overall antibiotic prescriptions (sHR 0.81 vs. sHR 0.92, interaction term -0.13, $p < 0.001$) and when considering only prescriptions of antibiotics indicated for respiratory infections (sHR 0.93 vs. sHR 1.07, interaction term -0.15, $p < 0.001$). Similarly, the association between recent immigration and antibiotic prescribing was stronger in the

pandemic study period compared to the pre-pandemic period for overall prescriptions (sHR 1.21 vs. sHR 1.12, interaction term 0.04, $p=0.049$) and when considering only antibiotic prescriptions indicated for respiratory infections (sHR 1.27 vs. sHR 1.15, interaction term 0.08, $p<0.001$).

There was no evidence of meaningful effect modification of the COVID-19 pandemic period on neighbourhood income when considering either overall antibiotic prescription (sHR 1.02 vs. sHR 1.03, interaction term 0.00, $p=0.514$) or prescriptions for respiratory infections (sHR 1.05 vs. sHR 1.06, interaction term 0.01, $p=0.080$).

4.7.4 Adjusted subdistribution hazard ratios of antibiotic prescribing by study covariates

Several study covariates were significantly associated with subdistribution hazard ratios of overall antibiotic prescribing in adjusted pre-pandemic and pandemic period models (Table 5). In both periods, overall antibiotic prescribing was higher among females (sHR 1.17, 95% CI 1.16-1.17 pre-pandemic and pandemic), individuals with a primary care provider (sHR 1.17, 95% CI 1.16-1.18 pre-pandemic and sHR 1.14, 95% CI 1.13-1.15 pandemic), and individuals vaccinated against influenza (sHR 1.17, 95% CI 1.16-1.18 pre-pandemic and sHR 1.13, 1.12-1.14 pandemic). Overall antibiotic prescribing was slightly higher among individuals vaccinated against pneumococcal disease in both periods (sHR 1.06, 95% CI 1.04-1.08 pre-pandemic and sHR 1.05, 95% CI 1.03-1.07), and slightly lower among rural residents in the pre-pandemic period (sHR 0.97, 95% CI 0.96-0.97), but this association was not significant in the pandemic period (sHR 1.00, 95% CI 0.99-1.01). COVID-19 vaccination was associated with slightly higher antibiotic prescribing in the pandemic period, with a subdistribution hazard ratio of 1.09 (95% CI 1.08-1.10). The subdistribution hazard ratio of antibiotic prescribing increased with increasing multimorbidity level and was highest among individuals with 5 or more conditions in both pre-pandemic (sHR 3.89, 95% CI 3.76-4.03) and pandemic (sHR 3.66, 95% CI 3.55-3.78)

periods. In both periods, the subdistribution hazard ratio of overall antibiotic prescribing decreased slightly with increasing patient age (sHR 0.99 per 1-year increase, 95% CI 0.99-0.99), and increased slightly with increasing number of prior physician assessments (sHR 1.02 per 1 visit increase, 95% 1.02-1.02).

Results from adjusted models considering prescriptions of antibiotics indicated for respiratory infections showed similar patterns for most study covariates, except for sex and rural residence (Table 6). Female sex was associated with slightly higher respiratory antibiotic prescribing in the pre-pandemic period (sHR 1.03, 95% CI 1.04-1.04), but slightly lower in the pandemic period (sHR 0.97, 95% CI 0.96-0.98). The subdistribution hazard of prescribing of antibiotics indicated for respiratory infections was also slightly lower among rural residents in both the pre-pandemic (sHR 0.94, 95% CI 0.93-0.94) and pandemic (sHR 0.99, 95% CI 0.98-0.99) periods.

Table 5. Adjusted subdistribution hazard ratios of antibiotic prescribing among older outpatients during the pre-pandemic, pandemic, and total study periods in Ontario, Canada

| | Pre-Pandemic Period | Pandemic Period | Total Study Period |
|---|----------------------------|------------------------|---------------------------|
| Variable | sHR (95% CI) | sHR (95% CI) | sHR (95% CI) |
| <i>Demographics</i> | | | |
| Age (years) | 0.99 (0.99-0.99) | 0.99 (0.99-0.99) | 0.99 (0.99-0.99) |
| Female sex | 1.17 (1.16-1.17) | 1.17 (1.16-1.17) | 1.17 (1.16-1.17) |
| Rural resident | 0.97 (0.96-0.97) | 1.00 (0.99-1.01) | 0.98 (0.97-0.99) |
| <i>Social Determinants of Health</i> | | | |
| Recent immigrant | 1.12 (1.09-1.16) | 1.21 (1.18-1.25) | 1.16 (1.14-1.19) |
| Income Q1 (lowest neighbourhood income quintile) | (reference) | (reference) | (reference) |
| Income Q2 | 1.01 (1.00-1.02) | 1.00 (0.99-1.01) | 1.00 (0.99-1.01) |
| Income Q3 | 1.02 (1.02-1.03) | 1.01 (1.01-1.02) | 1.02 (1.01-1.03) |
| Income Q4 | 1.03 (1.03-1.04) | 1.02 (1.01-1.03) | 1.03 (1.02-1.04) |
| Income Q5 (highest neighbourhood income quintile) | 1.03 (1.02-1.04) | 1.02 (1.01-1.03) | 1.03 (1.02-1.03) |
| Racialized Q1 (lowest neighbourhood proportion of racially minoritized groups) | (reference) | (reference) | (reference) |
| Racialized Q2 | 1.01 (0.99-1.02) | 1.00 (0.99-1.01) | 1.00 (0.99-1.01) |
| Racialized Q3 | 0.99 (0.99-1.00) | 0.97 (0.96-0.98) | 0.98 (0.98-0.99) |
| Racialized Q4 | 0.96 (0.95-0.97) | 0.91 (0.90-0.92) | 0.94 (0.93-0.94) |
| Racialized Q5 (highest neighbourhood proportion of racially minoritized groups) | 0.92 (0.91-0.93) | 0.81 (0.80-0.82) | 0.87 (0.86-0.87) |
| <i>Health and Healthcare Use</i> | | | |
| Multimorbidity level | | | |
| 0 conditions | (reference) | (reference) | (reference) |
| 1 condition | 1.73 (1.69-1.77) | 1.64 (1.60-1.68) | 1.69 (1.66-1.72) |
| 2 conditions | 2.20 (2.16-2.25) | 2.07 (2.02-2.12) | 2.14 (2.11-2.18) |
| 3 conditions | 2.64 (2.57-2.70) | 2.46 (2.40-2.52) | 2.56 (2.51-2.61) |
| 4 conditions | 3.03 (2.95-3.11) | 2.81 (2.75-2.88) | 2.93 (2.87-3.00) |
| 5+ conditions | 3.89 (3.76-4.03) | 3.66 (3.55-3.78) | 3.79 (3.69-3.90) |
| Primary care provider | 1.17 (1.16-1.18) | 1.14 (1.13-1.15) | 1.15 (1.14-1.16) |
| Physician visits prior (12 mo) | 1.02 (1.02-1.02) | 1.02 (1.02-1.02) | 1.02 (1.02-1.02) |
| <i>Vaccination Status</i> | | | |
| Pneumococcal vaccinated | 1.06 (1.04-1.08) | 1.05 (1.03-1.07) | 1.06 (1.04-1.07) |
| Influenza vaccinated | 1.17 (1.16-1.18) | 1.13 (1.12-1.14) | 1.15 (1.15-1.16) |
| COVID-19 vaccinated | — | 1.09 (1.08-1.10) | 1.08 (1.07-1.09) |
| <i>Time</i> | | | |
| Pandemic period | — | — | 0.73 (0.73-0.73) |

Abbreviations: sHR, subdistribution hazard ratio, 95% CI, 95% confidence interval.

Models adjusted for all variables listed in the table.

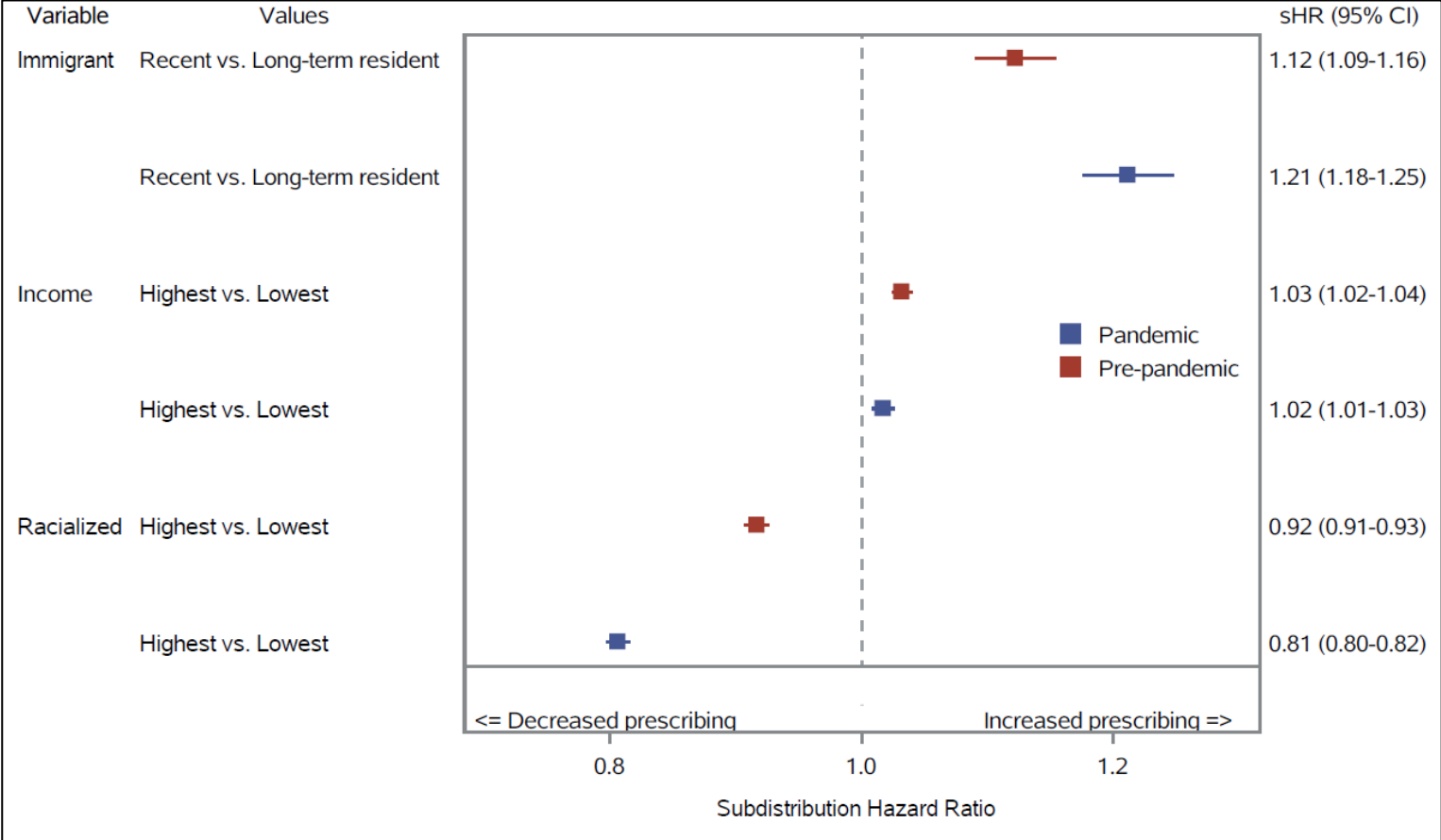
Table 6. Adjusted subdistribution hazard ratios of respiratory antibiotic prescribing among older outpatients during in the pre-pandemic, pandemic, and total study periods in Ontario, Canada

| | Pre-Pandemic Period | Pandemic Period | Total Study Period |
|---|----------------------------|------------------------|---------------------------|
| Variable | sHR (95% CI) | sHR (95% CI) | sHR (95% CI) |
| Demographics | | | |
| Age (years) | 0.99 (0.99-0.99) | 0.99 (0.99-0.99) | 0.99 (0.99-0.99) |
| Female sex | 1.03 (1.02-1.04) | 0.97 (0.96-0.98) | 1.00 (0.99-1.01) |
| Rural resident | 0.94 (0.93-0.95) | 0.99 (0.98-0.99) | 0.96 (0.95-0.97) |
| Social Determinants of Health | | | |
| Recent immigrant | 1.15 (1.11-1.18) | 1.27 (1.23-1.32) | 1.20 (1.17-1.23) |
| Income Q1 (lowest neighbourhood income quintile) | (reference) | (reference) | (reference) |
| Income Q2 | 1.02 (1.01-1.03) | 1.01 (0.99-1.02) | 1.02 (1.01-1.03) |
| Income Q3 | 1.04 (1.03-1.05) | 1.04 (1.02-1.05) | 1.04 (1.03-1.05) |
| Income Q4 | 1.06 (1.05-1.07) | 1.04 (1.03-1.05) | 1.05 (1.04-1.06) |
| Income Q5 (highest neighbourhood income quintile) | 1.06 (1.05-1.07) | 1.05 (1.04-1.06) | 1.06 (1.05-1.06) |
| Racialized Q1 (lowest neighbourhood proportion of racially minoritized groups) | (reference) | (reference) | (reference) |
| Racialized Q2 | 1.02 (1.01-1.03) | 1.01 (0.99-1.02) | 1.02 (1.01-1.03) |
| Racialized Q3 | 1.03 (1.02-1.04) | 1.00 (0.99-1.01) | 1.02 (1.01-1.03) |
| Racialized Q4 | 1.03 (1.02-1.04) | 0.96 (0.95-0.98) | 1.00 (0.99-1.01) |
| Racialized Q5 (highest neighbourhood proportion of racially minoritized groups) | 1.07 (1.05-1.08) | 0.93 (0.92-0.94) | 1.01 (0.99-1.02) |
| Health and Healthcare Use | | | |
| Multimorbidity level | | | |
| 0 conditions | (reference) | (reference) | (reference) |
| 1 condition | 1.71 (1.67-1.76) | 1.60 (1.55-1.64) | 1.66 (1.63-1.70) |
| 2 conditions | 2.17 (2.12-2.23) | 1.99 (1.94-2.05) | 2.10 (2.06-2.14) |
| 3 conditions | 2.58 (2.51-2.65) | 2.34 (2.28-2.41) | 2.48 (2.43-2.53) |
| 4 conditions | 2.96 (2.88-3.05) | 2.65 (2.57-2.73) | 2.83 (2.76-2.90) |
| 5+ conditions | 3.83 (3.70-3.97) | 3.46 (3.35-3.58) | 3.68 (3.57-3.78) |
| Primary care provider | 1.13 (1.12-1.15) | 1.11 (1.10-1.12) | 1.12 (1.12-1.13) |
| Physician visits prior (12 mo) | 1.02 (1.02-1.02) | 1.02 (1.02-1.02) | 1.02 (1.02-1.02) |
| Vaccination Status | | | |
| Pneumococcal vaccinated | 1.07 (1.05-1.08) | 1.07 (1.05-1.10) | 1.07 (1.06-1.09) |
| Influenza vaccinated | 1.18 (1.17-1.19) | 1.13 (1.12-1.13) | 1.16 (1.15-1.16) |
| COVID-19 vaccinated | — | 1.17 (1.16-1.18) | 1.15 (1.14-1.16) |
| Time Period | | | |
| Pandemic period | — | — | 0.64 (0.64-0.64) |

Abbreviations: sHR, subdistribution hazard ratio, 95% CI, 95% confidence interval.

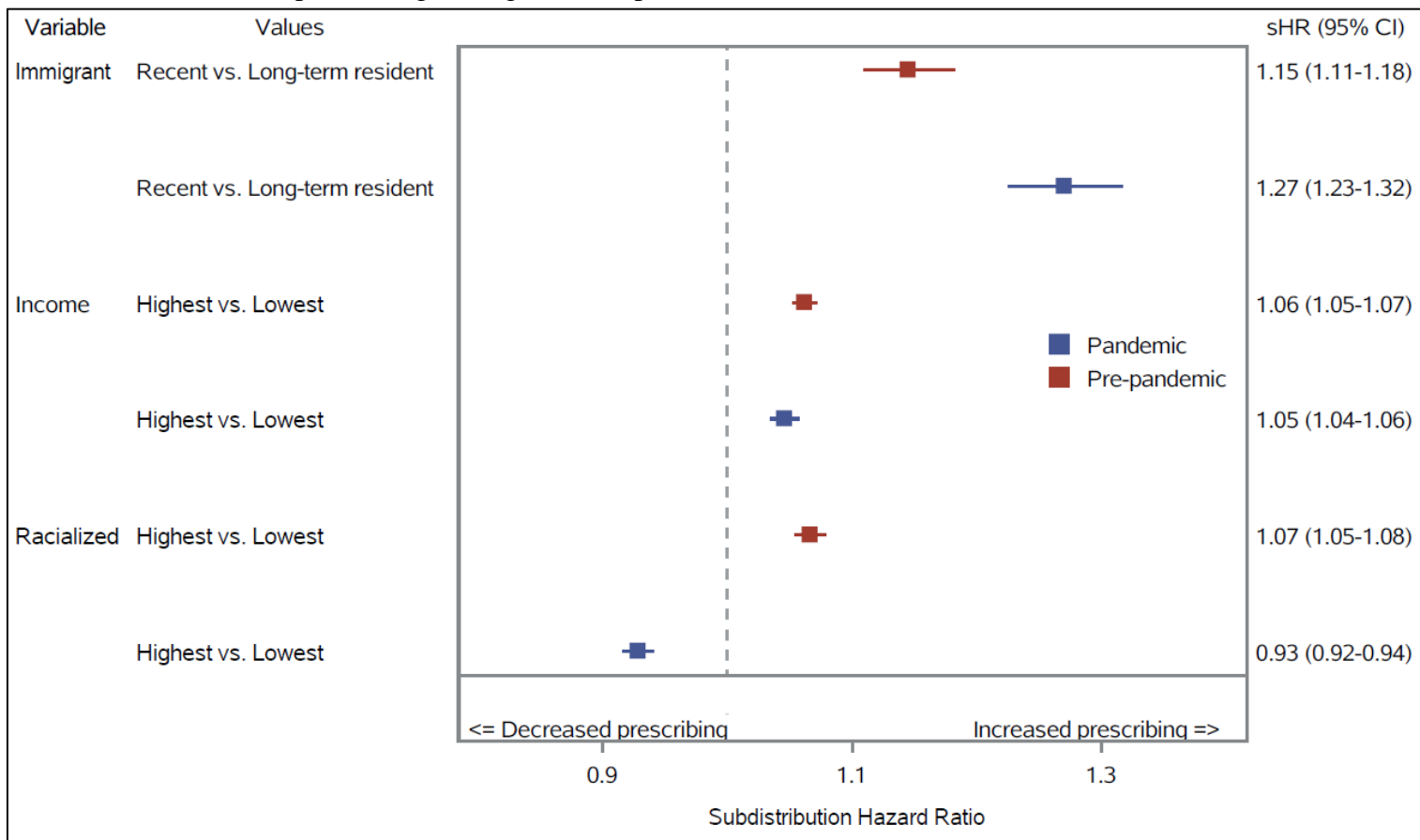
Models adjusted for all variables listed in the table.

Figure 4. Adjusted associations between social determinants of health and antibiotic prescribing among older outpatients in Ontario, Canada



sHR adjusted for demographics (age, sex, rural vs. urban residence), health and healthcare utilization measures (multimorbidity, primary care provider, number of prior physician visits), and vaccination status (influenza, pneumococcal, COVID-19).

Figure 5. Adjusted associations between social determinants of health and respiratory antibiotic prescribing among older outpatients in Ontario, Canada



sHR adjusted for demographics (age, sex, rural vs. urban residence), health and healthcare utilization measures (multimorbidity, primary care provider, number of prior physician visits), and vaccination status (influenza, pneumococcal, COVID-19).

4.8 Additional analyses

4.8.1 Adjusted subdistribution hazard ratios of antibiotic prescribing by antibiotic type

When stratifying results from adjusted Fine-Gray subdistribution hazard models of any antibiotic as the outcome of interest by antibiotic type (respiratory vs. non-respiratory), prescribing of antibiotics indicated for respiratory infections (Figure 6, Panel A) was higher among recent immigrants compared to long-term residents in both periods, with a more pronounced increase during the pandemic period (sHR 1.26, 95% CI 1.22-1.31) compared to the pre-pandemic period (sHR 1.13, 95% CI 1.10-1.17). Among residents in neighbourhoods with the highest proportion of racially minoritized groups compared to the lowest, prescribing of antibiotics indicated for respiratory infections was initially higher in the pre-pandemic period (sHR 1.07, 95% CI 1.06-1.08), but lower in the pandemic period (sHR 0.94, 95% CI 0.93-0.95). The subdistribution hazard of respiratory antibiotic prescribing was slightly higher among residents of the highest income neighbourhoods compared to the lowest in the pre-pandemic and pandemic periods (sHR 1.06, 95% CI 1.05-1.07, and sHR 1.05, 95% CI 1.04-1.07, respectively).

Panel B of Figure 6 shows the subdistribution hazard ratios of prescribing of antibiotics indicated for non-respiratory infections by SDOH variables. For recent immigrants, compared to long-term residents, prescribing of non-respiratory antibiotics was higher in both periods, with a slight increase during the pandemic period (sHR 1.14, 95% CI 1.09-1.19) relative to the pre-pandemic period (sHR 1.10, 95% CI 1.05-1.15), although the confidence intervals overlap. The subdistribution hazard of non-respiratory antibiotic prescribing among residents in neighbourhoods with the highest proportion of racially minoritized groups compared to the lowest was lower in both periods, with a slightly more pronounced association during the pandemic period (sHR 0.68, 95% CI 0.67-0.69) compared to the pre-pandemic period (sHR 0.72,

95% CI 0.71-0.73). The subdistribution hazard of prescribing of antibiotics indicated for non-respiratory infections was slightly lower among residents of the highest income neighbourhoods compared to the lowest in the pandemic period (sHR 0.98, 95% CI 0.97-0.99), but was not significantly different in the pre-pandemic period (sHR 0.99, 95% CI 0.98-1.00).

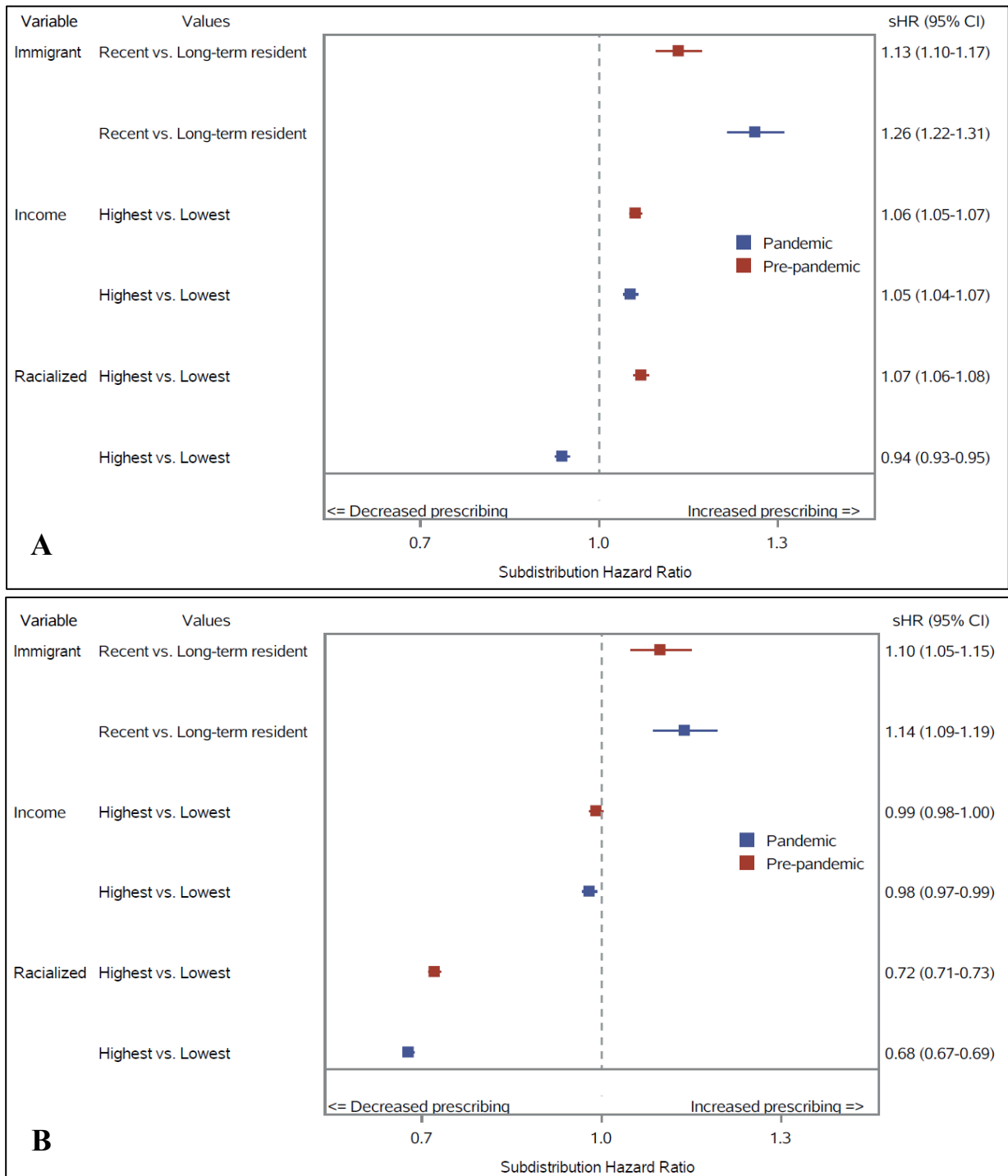
4.8.2 Adjusted subdistribution hazard ratios of antibiotic prescribing by pandemic wave

Results from adjusted subdistribution hazard models including a pandemic categorical wave variable show a significant and gradual decrease in the hazard of overall antibiotic prescribing associated with later waves of the COVID-19 pandemic (Figure 7). Compared to the first wave, the subdistribution hazard of overall antibiotic prescribing was highest during the second wave of the pandemic (sHR 1.02, 95% CI 1.01-1.03), and lowest during the sixth wave (sHR 0.69, 95% CI 0.62-0.76).

4.8.3 Adjusted subdistribution hazard ratios of antibiotic prescribing among individuals in the Toronto Public Health unit

We identified 493,715 individuals in the pre-pandemic period and 517,592 in the pandemic period when limiting our study sample to older community-dwelling adults residing in the Toronto PHU. Of the individuals in the pre-pandemic cohort residing in the Toronto PHU, 1.6% were recent immigrants (compared to 1.2% when considering all older outpatients in Ontario; Table 1), whereas 1.3% were recent immigrants in the pandemic cohort (compared to 1.0% when considering all older outpatients in Ontario; Table 1). The association between prescribing and immigration status was stronger when restricting the sample to the Toronto PHU (Figure 8). In adjusted models, overall antibiotic prescribing was higher among recent immigrants compared to long-term residents in both periods, with a more evident increase during the pandemic (sHR 1.41, 95% CI 1.33-1.50) than pre-pandemic period (sHR 1.26, 95% CI 1.19-1.32).

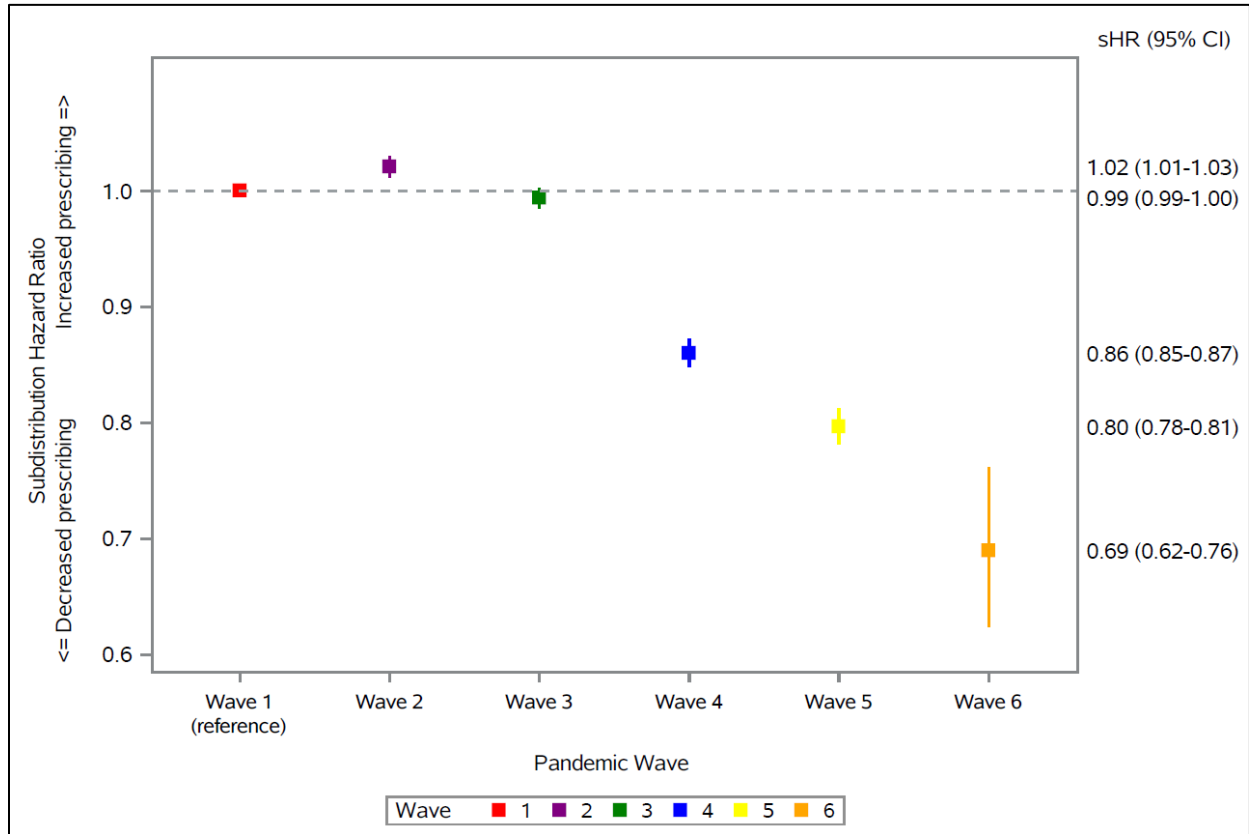
Figure 6. Adjusted associations between social determinants of health and antibiotic prescribing stratified by antibiotic type among older outpatients in Ontario, Canada



sHR adjusted for demographics (age, sex, rural vs. urban residence), health and healthcare utilization measures (multimorbidity, primary care provider, number of prior physician visits), and vaccination status (influenza, pneumococcal, COVID-19).

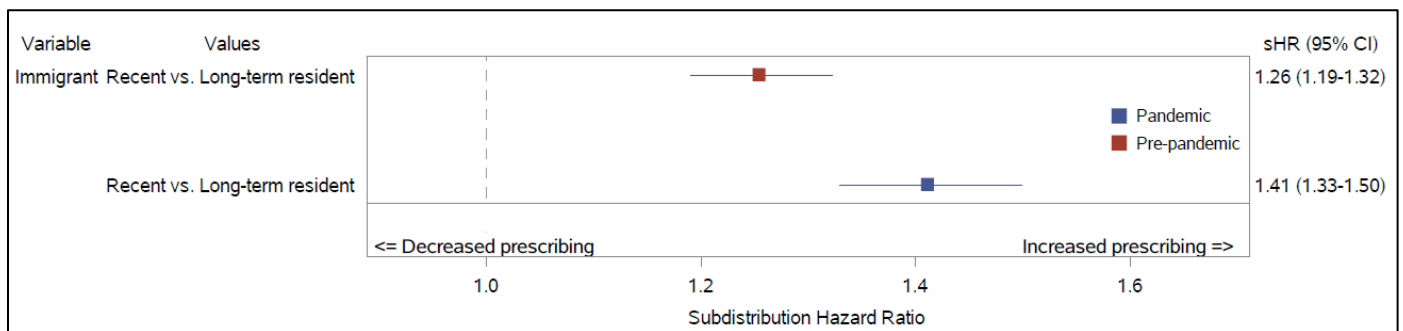
Adjusted associations between social determinants of health and antibiotic prescribing stratified by antibiotics indicated for respiratory infections (Panel A) and antibiotics indicated for non-respiratory infections (Panel B).

Figure 7. Adjusted association between waves of the COVID-19 pandemic and antibiotic prescribing among older outpatients, Ontario, Canada



sHR adjusted for demographics (age, sex, rural vs. urban residence), health and healthcare utilization measures (multimorbidity, primary care provider, number of prior physician visits), and vaccination status (influenza, pneumococcal, COVID-19).

Figure 8. Adjusted associations between immigration status and antibiotic prescribing among older outpatients in the Toronto public health unit, Ontario, Canada



sHR adjusted for demographics (age, sex, rural vs. urban residence), health and healthcare utilization measures (multimorbidity, primary care provider, number of prior physician visits), and vaccination status (influenza, pneumococcal, COVID-19).

Chapter 5: DISCUSSION

5.1 Principal findings

In this population-based retrospective cohort study of community-dwelling older adults in Ontario, we found that incident antibiotic prescribing (overall and for respiratory infections) varied according to study period and was higher during the two years before the COVID-19 pandemic (pre-pandemic period) compared to the first two years of the pandemic (pandemic period). Moreover, we observed variations in incident antibiotic prescribing in both study periods according to various neighbourhood- and individual-level SDOH variables. Overall antibiotic prescribing was higher among recent immigrants, slightly higher among residents in higher-income neighbourhoods, and lower among residents in neighbourhoods with an increasing proportion of racially minoritized persons in the pre-pandemic and pandemic periods. Similarly, in both periods, prescribing of antibiotics indicated for respiratory infections was higher among recent immigrants and residents in higher-income neighbourhoods. Among residents in neighbourhoods with a higher proportion of racially minoritized persons, respiratory antibiotic prescribing was initially higher in the pre-pandemic period, but lower in the pandemic period. There was evidence for meaningful effect modification by the COVID-19 pandemic for several of these associations, with residents in neighbourhoods with a higher proportion of racially minoritized persons experiencing a more pronounced decrease in overall and respiratory antibiotic prescribing during the pandemic period, and recent immigrants experiencing a more pronounced increase.

5.2 Comparison with other findings

5.2.1 Incident antibiotic prescribing

After accounting for the competing risk of death, approximately half of this older cohort of adults filled an outpatient antibiotic prescription over the two-year pre-pandemic period. These findings are consistent with a previous investigation including 62 million health insurance plan enrollees in the United States and over 100 million claims for outpatient antibiotic prescriptions from 2011 to 2014, which revealed that approximately half of the study population filled a prescription over two years.¹⁴⁷ While studies have yet to evaluate the cumulative probability of receiving an antibiotic prescription over time during the COVID-19 pandemic, there have been reported reductions in outpatient antibiotic prescribing across several different regions following the start of the pandemic, consistent with the results of this study.^{62,101,102,107} In Ontario, from March to December 2020, total outpatient antibiotic prescriptions decreased by over 30%, with the largest reductions observed for antibiotics indicated for respiratory infections compared to other indications.¹⁰¹ This significant reduction may stem from the reduced transmission of other seasonal respiratory infections and associated reductions in healthcare visits for respiratory infections due to the public health measures implemented to mitigate the spread of SARS-CoV-2, including physical distancing, masking, and hand hygiene.^{101,103–106} Changes in healthcare delivery during the COVID-19 pandemic and challenges in accessing healthcare services and primary care providers could also have contributed.^{100,148}

5.2.2 Antibiotic prescribing by social determinants of health

To date, research on the influence of social and economic factors on antibiotic prescribing has largely focused on younger populations, with relatively few studies conducted in Canada. To our knowledge, this study represents one of the largest evaluations of outpatient antibiotic

prescribing across a range of social determinants of health and is one of the first to evaluate the impacts of the COVID-19 pandemic on prescribing across several potentially marginalized older populations in Canada.

5.2.3 Antibiotic prescribing by income

Studies assessing the influence of patient income on antibiotic prescribing have produced mixed results depending on the healthcare setting, country, and population. Consistent with the results of this study, Schwartz et al. (2019) previously used neighbourhood-level income quintile as a measure of socioeconomic status and found that residents in neighbourhoods with the highest income were prescribed slightly more antibiotics compared to residents of neighbourhoods in the lowest income quintile (adjusted OR 1.09, 95% CI 1.07-1.10) over five years in Ontario.³⁴ In contrast, another Canadian study found that individuals with a household income below \$60,000 reported more frequent use of antibiotics in the last 12 months compared to those with a higher income; however, this study is limited by its relatively small sample size (n=1,515) and self-reported data on antibiotic use.⁸⁴ Using an older cohort of 239,981 Australian adults (45+ years of age) and antibiotic dispensing data from the Pharmaceutical Benefits Scheme (PBS), Chen et al. (2019) similarly reported that individuals with higher annual household income (\geq \$70,000) were slightly less likely to use antibiotics compared to those with an income of less than \$20,000.⁵³ However, the authors hypothesized that the lack of data on private prescriptions in the PBS database could have accounted for the observed variations.

Although small but statistically significant neighbourhood income-based variations in antibiotic prescribing were identified in this study, these differences may not be relevant from a population antibiotic-use perspective. Among low-income individuals, drug cost is a well-established barrier to obtaining prescription medications.^{3,149} Disparities in primary care visits and specialist

referrals have also previously been reported among low versus high income neighbourhoods in Canada.⁶⁴ However, this research may have limited applicability to older adults due to their unique circumstances. For example, most of the cost of prescription medications for older adults is covered under the ODB program in Ontario. It could, therefore, be possible that income may not be as significant a determinant of antibiotic prescribing and use among older Ontarians as it might be for younger individuals.

5.2.4 Antibiotic prescribing by immigration status

The influence of immigration status on antibiotic prescribing remains poorly described in Canada as research on the topic has been largely limited to European studies in various populations. While results from these studies are mixed, in line with our findings, a slight majority suggest that foreign-born populations are more likely to receive an antibiotic prescription compared to host populations.^{44,74-76} Although more research is needed, these findings could be attributable to differences in knowledge and behaviours regarding antibiotic use among recent immigrant populations. Previous literature has revealed that general practitioners may feel more pressured to prescribe an antibiotic to patients with an immigrant background,^{150,151} and that physicians trained outside of North America are more likely to prescribe antibiotics for respiratory infections.^{30,31} These behaviours and expectations may arise from certain cultural habits, such as previously being used to high consumption of easily accessible antibiotics or certain beliefs around antibiotics helping to treat viral infections and prevent illness from worsening.^{152,153} Language barriers may also contribute by creating potential communication challenges and misunderstandings, which could complicate the diagnostic process and increase diagnostic uncertainty among primary care providers.¹⁵¹

The pronounced increase in antibiotic prescribing observed in this study among recent immigrants during the COVID-19 pandemic compared to the pre-pandemic period may be partially explained by differences in infection outcomes among marginalized groups in the community. In Ontario, despite making up around one-quarter of the population, immigrants, refugees, and other newcomers accounted for over 43.5% of all COVID-19 cases during the first 6 months of the pandemic.⁹⁸ Higher COVID-19 percent positivity among recent immigrants and refugees has been linked to employment (healthcare workers), living in overcrowded housing, and lack of host language ability (English or French).⁹⁸ This disproportionate rate of infection may have increased the number of healthcare visits for respiratory infections and associated risk of antibiotic therapy among these populations during the pandemic. This is due to the fact that antibiotics were frequently prescribed inappropriately to patients with COVID-19 due to suspected bacterial co-infections.¹⁵⁴

5.2.5 Antibiotic prescribing by race and/or ethnicity

The influence of race and/or ethnicity on antibiotic prescribing equally remains under-researched in Canada; however, many international studies have evaluated this association.^{4,29,43,49,60,82,87-92} In general, regardless of variability in the patient population across studies, racially minoritized individuals were less likely to receive antibiotics, findings consistent with the results of the current study. For example, among a population of adults 65 years of age and older in the United States, non-Hispanic Black and Asian persons were less likely to receive an outpatient antibiotic prescription compared to non-Hispanic White persons over a period of seven years.⁹² Another recent nationwide study in England also found that compared to White British patients, racially minoritized persons were less likely to receive antibiotic prescriptions during the pandemic period versus the pre-pandemic period.¹⁵⁵ While the drivers of these prescribing differences

remain largely unknown, it has been suggested that these inequities may result from disparities in healthcare utilization among racially minoritized persons, which would influence the number of opportunities for antibiotics to be prescribed.^{4,52,66} The complex nature of the patient-physician relationship, racial discordance between patients and physicians, and/or physician implicit bias could also be contributing.^{156–159}

Although differences in healthcare visits may account for some of the variation observed in antibiotic prescribing among racially minoritized persons, results from studies evaluating predictors of outpatient antibiotic prescribing specifically for respiratory tract infections offer alternative explanations. When assessing the influence of race on prescribing of antibiotics indicated for respiratory infections, we observed that residents of neighborhoods with the highest proportion of racially minoritized persons were more likely to be prescribed an antibiotic pre-COVID-19. Barlam et al. (2014) similarly found that Hispanic persons were more likely to be prescribed an antibiotic compared to Black persons during a respiratory tract infection visit,¹⁶⁰ and Shaver et al. (2019) observed that Black persons were more likely than White persons to receive an antibiotic for an acute respiratory tract infection diagnosis.¹⁶¹ Moreover, in our additional analysis stratifying results from our models by antibiotic type, we observed reduced prescribing for antibiotics indicated for respiratory infections among racially minoritized persons during the pandemic period, while prescribing of antibiotics for non-respiratory infections remained largely unchanged among this population from the pre-pandemic to the pandemic period. Although further research is needed, these results may begin to suggest that: 1) decreased prescribing among residents of neighbourhoods with more racially minoritized persons during the pandemic period was driven by reduced prescribing of antibiotics indicated for respiratory infections; and 2) factors other than differential healthcare utilization modified antibiotic

prescribing among this population during the pandemic period. One such factor may include a pronounced decrease in the transmission of seasonal respiratory infections within communities with a higher proportion of racially minoritized persons. These types of infections tend to disproportionately affect individuals facing social disadvantages and may have led to the increased prescribing observed among these individuals in the pre-pandemic period.^{68,162–164}

5.3 The healthy immigrant effect

Of note, we observed that recent immigrants had a lower crude cumulative incidence of antibiotic prescribing (overall and for respiratory infections) compared to long-term residents in unadjusted models, but that this association switched direction in adjusted models, with antibiotic prescribing becoming higher among recent immigrants. The reversal of this association was noted after adjustment for multimorbidity. This finding may be due to a phenomenon referred to as the healthy immigrant effect, which suggests that recent immigrants tend to be healthier than the native-born population upon arrival in the country. The effect is believed to stem from the selective nature of immigration, which typically favours the healthiest and wealthiest individuals.¹⁶⁵ However, this health advantage is known to diminish the longer individuals reside in the host country.¹⁶⁵ The population of recent immigrants included in this study may have been healthier and had fewer comorbidities than long-term Canadian residents. Therefore, the apparent unadjusted association between immigration status and antibiotic prescribing may have resulted from the fact that long-term residents had more chronic conditions. The latter is a risk factor for antibiotic prescribing and may have directly contributed to increased prescribing. Individuals with more chronic conditions may also use healthcare services more often, which could increase the number of opportunities for antibiotics to be prescribed to those individuals.

5.4 Strengths

The main strength of this study was the large and representative sample of older outpatients, including almost every community-dwelling older adult in Ontario, for which we were able to obtain extensive and complete information by linking individual records across multiple datasets at ICES. The findings are anticipated to be generalizable to older populations in other regions with similar healthcare systems.

To our knowledge, this is the first study to assess the influence of multiple SDOH variables on the cumulative incidence of receiving an antibiotic prescription over time. Given the older and more vulnerable population under study, considering mortality as a competing risk and using Fine-Gray subdistribution hazard models compared to traditional Cox proportion hazard models prevented overestimation of the cumulative incidence of antibiotic prescribing over time.

Further, we increased the precision of our estimates by assigning random index dates to eligible individuals to prevent seasonality from inflating measures of antibiotic use. Aside from patient demographics, our models also adjusted for various measures of health and healthcare use, including vaccination status, which most previous studies have not adjusted for.

Another strength of this study comes from the fact that we were able to categorize immigration status into either recent immigrant (within 5 years) or long-term resident. Previous studies evaluating the influence of immigration status on antibiotic prescribing have not considered the amount of time spent in a host country since migration and have generally categorized immigrants as either first-generation (born in another country) or second-generation (at least one parent born in another country). Using landing dates to define immigration status within the last 5 years could have allowed us to examine associations that may not have been captured in other studies.

5.5 Limitations

This study has several limitations requiring comment, many of which arise from the datasets used and the nature of the health administrative data available at ICES. First, we could only obtain information on recent immigrants who possessed a valid OHIP card, and second, we were unable to obtain information on individuals who may have immigrated to Ontario during the pandemic period. Before the COVID-19 pandemic (March 2020), recent immigrants to Ontario were subject to a 3-month waiting period for OHIP coverage. Moreover, although our study identified individuals within the timeframe of the pandemic period (March 2020-March 2022), the immigration information provided by the IRCC CIC database at ICES is current to September 2020. Therefore, this study was not able to capture individuals who immigrated to Ontario after September 2020 and may not have captured certain new immigrants to Ontario that were still subject to the 3-month waiting period for OHIP coverage. If these individuals were more likely to be prescribed an antibiotic, then failing to capture them could have underestimated the association between recent immigration and antibiotic prescribing.

Third, while individual-level data on immigration are available at ICES, we were limited to using neighbourhood-level measures of both visible minority status and income. This could have led to residual confounding by social determinants and an underestimation of the strength of the association between SDOH variables and antibiotic prescribing. The reported agreement between individual- and neighbourhood-level SDOH measures has varied in previous research. Notably, in a patient cohort from Alberta, the agreement between self-reported income and neighbourhood-level measures of income was found to be poor ($\kappa = 0.07$);¹⁶⁶ however, the agreement was higher in patient cohorts from larger metropolitan cities including Montreal (Spearman's $\rho = 0.31-0.39$)¹⁶⁷ and Vancouver (Spearman's $\rho = 0.23-0.35$).^{168,169} Despite this

research, neighbourhood-level measures may still be useful in estimating important associations as they can capture information on both individual-level factors and shared environmental circumstances that cannot be captured by individual-level measures alone.

In addition, while data in the ODB was used to identify antibiotic prescriptions, this data ultimately provides information on dispensed drug claims and may not fully reflect either prescriptions received or actual antibiotic use. However, drug claims are often used to estimate antibiotic use in the outpatient setting as information on direct use is not routinely collected in this setting.²⁵ We are also unable to comment on whether the prescribed differences in antibiotic use detected in this study were harmful or beneficial as we were unable to assess the appropriateness of antibiotic prescriptions. The goal of this research, however, was to first describe those changes, as a basis for subsequent evaluation of the impacts of those differences on populations at risk. This is under the notion that differences in patterns of care across populations indicate the potential for underlying disparities,^{5,67} which are especially cause for concern in populations at risk for marginalization. Another limitation is that we identified and grouped antibiotics by type (respiratory versus non-respiratory) based on knowledge of which antibiotics are typically prescribed for certain indications. This grouping method, however, may not be entirely accurate as antibiotics not listed or considered could have been prescribed to treat either respiratory or non-respiratory infections. Alternatively, individuals could have been prescribed an antibiotic categorized as respiratory for a non-respiratory indication, and vice versa.

Finally, the ODB database only routinely captures outpatient drug claims for adults over the age of 65 years in Ontario. The findings of this study, therefore, are limited to community-dwelling older adults in Ontario and may not be generalizable to other settings, age groups or regions

within or outside of Canada. Despite this limitation, the findings of this study remain consistent with the body of previous research on antibiotic prescribing and social determinants of health in different patient populations.

5.6 Implications and areas for future research

The findings of this study provide evidence that outpatient antibiotic prescribing varies according to different SDOH variables. While we were unable to determine the appropriateness of antibiotic prescriptions, these preliminary results indicate that populations with the potential for marginalization may be at disproportionate risk of antibiotic use in Canada. Identifying and acknowledging these differences can inform future research and help shape healthcare strategies that optimize antibiotic use and treatment of bacterial infections, addressing concerns of both excessive and inadequate antibiotic usage. Future studies in this area should consider adjusting for provider characteristics to determine whether prescribing patterns among marginalized individuals in the community differ according to the demographics or characteristics of the prescribers themselves. This may help design and develop stewardship interventions that aim to improve physician training with respect to antibiotic prescribing practices among certain marginalized groups in the community.

Although the results of this research support the notion that SDOH variables are associated with outpatient antibiotic prescribing, to our knowledge this is one of the first studies to assess whether these associations were modified by the COVID-19 pandemic. Additional research is needed to corroborate the observed variations in antibiotic prescribing during the pandemic period among populations with the potential for social and/or economic marginalization. Moreover, while previous research has evaluated the influence of SDOH variables on antibiotic prescribing among various patient populations, the drivers of these prescribing differences

remain under-researched. Although these differences are likely attributable to a multitude of interconnected factors, there is a need to understand their underlying causes to better design and tailor prescribing-based strategies that improve antibiotic use without amplifying any existing inequities in health outcomes and care access among potentially marginalized populations.

To support future high-quality Canadian research on this subject, there is also a need to collect better race-based data and standardize the definitions of SDOH variables. As it stands in Canada, race and ethnicity data are rarely routinely collected and researchers are largely limited to relying on proxy measures such as neighbourhood proportion of visible minority persons from the long-form census rather than person-level data.¹⁷⁰ Grouping racially minoritized individuals into a single visible minority category threatens to homogenize the experiences of different groups. Race disaggregated data are needed in Canada to better understand health disparities and promote health equity.

Finally, placing these results in the larger context of AMR, future research is needed to assess whether prescribed differences in antibiotic use among populations with the potential for marginalization could potentially lead to disproportionate rates of antibiotic-resistant infections and disparities in resistance-related infection outcomes among these populations.

5.7 Conclusion

This study sought to examine associations between individual- and neighbourhood-level SDOH variables and incident antibiotic prescriptions among older outpatients during the two years before and first two years of the COVID-19 pandemic, and to assess whether these associations were further modified by the COVID-19 pandemic. The results indicated that antibiotic prescribing (overall and for respiratory infections) was slightly higher among residents in highest-income neighbourhoods and higher among recent immigrants both pre-pandemic and

during the pandemic, with a more pronounced increase in prescribing to recent immigrants observed during the COVID-19 pandemic. In contrast, overall antibiotic prescribing was lower among residents in neighbourhoods with a higher proportion of racially minoritized persons both pre-pandemic and during the pandemic, and this association was more pronounced during the pandemic; similarly, a pronounced decrease in prescribing of respiratory antibiotics to residents in more racially minoritized neighbourhoods was observed during the pandemic than pre-pandemic period. These findings contribute to the body of research highlighting the idea that social and economic factors may be important for identifying populations who could be disproportionately prescribed antibiotics in the outpatient setting. Although further research to understand the drivers of these prescribing differences, acknowledging that variations exist in antibiotic prescribing among different populations in the community is important for informing future interventions that attempt to improve antibiotic prescribing.

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APPENDIX

Appendix A. ICES data sources for covariates used in the study.

| Source | Covariates |
|--|--|
| Registered Persons Database (RPDB) | Age, sex, death (censored), loss of OHIP eligibility (censored), neighbourhood income quintile, multimorbidity |
| Ontario Drug Benefits (ODB) Database | Outcome (antibiotic prescriptions), influenza and pneumococcal vaccination, multimorbidity |
| Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) | Hospitalizations (censored), multimorbidity |
| Continuing Care Reporting System (CCRS) | Long-term care admissions (censored) |
| Ontario Census Area Profiles (CENSUS) | Neighbourhood proportion of racially minoritized groups quintile |
| IRCC Permanent Residents Database (CIC) | Immigration status |
| Ontario COVID-19 Vaccine Data (COVAXON) | COVID-19 vaccination |
| Client Agency Program Enrolment Data (CAPE) | Designated primary care provider |
| Estimated Schedule of Benefits (ESTSOB) | Designated primary care provider |
| Ontario Health Insurance Plan (OHIP) | Physician visits, influenza and pneumococcal vaccination, designated primary care provider, multimorbidity |
| Postal Code Conversion File (PCCF) | Area of residence (rural vs. urban) |
| National Ambulatory Care Reporting System (NACRS) | Multimorbidity |
| Drugs List (DIN) | Multimorbidity |
| Ontario Mental Health Reporting System (OMHRS) | Multimorbidity |
| ICES Physician Database (IPDB) | Multimorbidity |
| Same Day Surgery (SDS) | Multimorbidity |
| Drugs List (DIN) | Multimorbidity |

Appendix B. Description of additional ICES data sources used in the study.

Ontario COVID-19 Vaccine Data (COVAXON)

COVAXON is a cumulative provincial dataset which records individual-level data on COVID-19 vaccination events for Ontario residents.¹⁷¹ These data are compiled by the Ontario Ministry of Health and provided to ICES by Public Health Ontario.¹⁷¹ Each record in the database represents a single individual and includes information on the date(s) the doses were administered, and vaccine product information, including vaccine manufacturer name for each dose.

Client Agency Program Enrolment Data (CAPE)

The CAPE dataset is used to identify whether an individual is rostered to a specific physician who is in a primary care enrolment model.¹⁷² For patients who are not rostered in CAPE, information in the Estimated Schedule of Benefits (ESTSOB) must be used to identify the primary care provider for the individual.

Postal Code Conversion File (PCCF)

The PCCF is a digital file which allows for Canadian postal codes to be linked to standard Statistics Canada geographic areas for which CENSUS data are produced, including income and location of residence (rural vs. urban).¹⁷³

Ontario Health Insurance Plan Claims Database (OHIP)

The OHIP dataset contains information on claims made by healthcare providers for insured inpatient and outpatient services in Ontario.¹⁷⁴

Drugs List (DIN)

The DRUGLIST file at ICES contains a comprehensive list of drug identification number (DINs) used in Canada. This information is based on ODB data and data from IQVIA Solutions Canada.¹⁷⁵

National Ambulatory Care Reporting System (NACRS)

The NACRS is compiled by the Canadian Institute of Health Information (CIHI) and contains patient-level data on visits to ambulatory care centers in Ontario.¹⁷⁶

Ontario Mental Health Reporting System (OMHRS)

The OMHRS collects patient-level and administrative information on individuals admitted to designated adult inpatient psychiatric beds in Ontario.¹⁷⁷

ICES Physician Database (IPDB)

The IPDB contains information about all physicians in Ontario, including physician speciality and various measures of physician activity.¹⁷⁸

Same Day Surgery (SDS)

The SDS contains patient-level data for day surgery institutions in Ontario.¹⁷⁶

Appendix C. Systemic oral antibiotics considered in the study.

| Name | Class | Type |
|-----------------------------------|---|-----------------|
| Ampicillin | Penicillins | Respiratory |
| Amoxicillin | | |
| Phenoxymethylpenicillin | | |
| Cloxacillin | | |
| Amoxicillin and enzyme inhibitor | | |
| Cefadroxil | 1 st Generation Cephalosporins | Non-respiratory |
| Cephalexin | 2 nd Generation Cephalosporins | Respiratory |
| Cefaclor | | |
| Cefuroxime | | |
| Cefixime | 3 rd Generation Cephalosporins | Respiratory |
| Cefprozil | | |
| Moxifloxacin | Fluoroquinolones | Respiratory |
| Levofloxacin | | Non-respiratory |
| Ciprofloxacin | | |
| Norfloxacin | | |
| Ofloxacin | | |
| Azithromycin | | Macrolides |
| Clarithromycin | | |
| Erythromycin | | |
| Doxycycline | Doxycycline/Tetracycline | Respiratory |
| Minocycline | | Non-respiratory |
| Tetracycline | | |
| Clindamycin | Lincosamides | Non-respiratory |
| Linezolid | Oxazolidinone | Non-respiratory |
| Sulfamethoxazole and trimethoprim | Trimethoprim/sulfamethoxazole | Non-respiratory |
| Trimethoprim | | |
| Nitrofurantoin | Nitrofurans | Non-respiratory |
| Fosfomicin | Fosfomicin | Non-respiratory |
| Metronidazole | Imidazole | Non-respiratory |

Appendix D. OHIP fee codes and ODB DIN codes used to identify influenza and pneumococcal vaccination status.

| Covariate | OHIP Fee Codes | ODB DINs |
|----------------------|--|--|
| Influenza vaccine | G590, G591, G592, Q130, Q590, Q690, Q691 | 02015986, 02223929, 02269562, 02346850, 02362384, 02365936, 02420643, 02420686, 02420783, 02426544, 02428881, 02432730, 02473283, 09857501 |
| Pneumococcal vaccine | G846 | 02436442, 02335204, 02527049, 02320541 |

Appendix E. List of validated algorithms used at ICES to identify the 17 chronic conditions used to identify multimorbidity level.

| Condition [reference for validated algorithm] | ICD 9 / OHIP | ICD 10 | Drug Subclass |
|--|---|--|--|
| Acute Myocardial Infarction (AMI) [1] | 410 | I21 | |
| Osteo- and other Arthritis: | | | |
| (A) Osteoarthritis | 715 | M15-M19 | |
| (B) Other Arthritis (includes Synovitis, Fibrositis, Connective tissue disorders, Ankylosing spondylitis, Gout Traumatic arthritis, pyogenic arthritis, Joint derangement, Dupuytren's contracture, Other MSK disorders) | 727, 729, 710, 720, 274, 716, 711, 718, 728, 739 | M00-M03, M07, M10, M11-M14, M20-M25, M30-M36, M65-M79 | |
| Arthritis - Rheumatoid arthritis [2] | 714 | M05-M06 | |
| Asthma [3] | 493 | J45 | |
| (all) Cancers | 140-239 | C00-C26, C30-C44, C45-C97 | |
| Cardiac Arrhythmia | 427 (OHIP) / 427.3 (DAD) | I48.0, I48.1 | |
| Congestive Heart Failure [4] | 428 | I500, I501, I509 | |
| Chronic Obstructive Pulmonary Disease [5] | 491, 492, 496 | J41, J42, J43, J44 | |
| Coronary syndrome (excluding AMI) | 411-414 | I20, I22-I25 | |
| Dementia [6] | 290, 331 (OHIP) / 046.1, 290.0, 290.1, 290.2, 290.3, 290.4, 294, 331.0, 331.1, 331.5, F331.82 (DAD) | F00, F01, F02, F03, G30 | Cholinesterase Inhibitors |
| Diabetes [7] | 250 | E10, E11, E13, E14 | Oral anti-glycemics, Insulin, Anti-diabetic agents: Misc |
| Hypertension [8] | 401, 402, 403, 404, 405 | I10, I11, I12, I13, I15 | |
| (Other) Mental Illnesses | 291, 292, 295, 297, 298, 299, 301, 302, 303, 304, 305, 306, 307, 313, 314, 315, 319 | F04, F050, F058, F059, F060, F061, F062, F063, F064, F07, F08, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, F20, F21, F22, F23, F24, F25, F26, F27, F28, F29, F340, F35, F36, F37, F430, F439, F453, F454, F458, F46, F47, F49, F50, F51, F52, F531, F538, F539, F54, F55, F56, F57, F58, F59, F60, F61, F62, F63, F64, F65, F66, F67, F681, F688, F69, F70, F71, F72, F73, F74, F75, F76, F77, F78, F79, | |

| | | | |
|--|-------------------------------|--|--|
| | | F80, F81, F82, F83, F84, F85, F86, F87, F88, F89, F90, F91, F92, F931, F932, F933, F938, F939, F94, F95, F96, F97, F98 | |
| Mood, anxiety, depression and other nonpsychotic disorders | 296, 300, 309, 311 | F30, F31, F32, F33, F34 (excl. F34.0), F38, F39, F40, F41, F42, F43.1, F43.2, F43.8, F44, F45.0, F45.1, F45.2, F48, F53.0, F68.0, F93.0, F99 | |
| Osteoporosis | 733 | M81, M82 | |
| Renal failure | 403, 404, 584, 585, 586, v451 | N17, N18, N19, T82.4, Z49.2, Z99.2 | |
| Stroke (excluding transient ischemic attack) | 430, 431, 432, 434, 436 | I60-I64 | |

NOTES:

Abbreviations: ICD = International Classification of Disease; ODB = Ontario Drug Benefit program database; OHIP = Ontario Health Insurance Plan, physician billings database.

AMI, Asthma, COPD, CHF, Dementia, Diabetes, Hypertension, and Rheumatoid Arthritis are based on validated case algorithms.¹⁷⁹⁻¹⁸⁶ All other conditions required at least one diagnosis recorded in acute care or two diagnoses recorded in physician billings within a five-year period.