A decade of outpatient antimicrobial use in senior residents of Ontario

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Abstract:	Background: Antimicrobials are frequently prescribed to community-dwelling seniors. Our aim was to examine the prevalence, quantity and indications of antimicrobial prescriptions to elderly individuals residing in Ontario, Canada. Methods: We conducted a 10-year population-based analysis of outpatient antimicrobial prescriptions to Ontario's seniors, from 2006 to 2015. Antimicrobial prescriptions, infectious disease diagnoses and prescriber information were determined from linked healthcare databases. Our analyses were primarily focused on antibiotics, which comprise the highest burden of antimicrobial use. Results: We identified 2 879 779 unique senior residents of Ontario over our study period. On average, 40.7% of seniors in any given year received one or more antibiotic prescriptions (range 40.1% to 41.5%). Antibiotic

usage remained stable, averaging 30.1 DDDs per 1000 person days per year (range 28.5 to 31.1 DDDs per 1000 person days per year). Selection of antibiotics evolved, with increasing use of penicillins and decreasing use of trimethoprim-sulfamethoxazole, fluoroquinolones and macrolides. For 67.0% of prescriptions, no infectious disease diagnoses were identified within seven days. Of those with an associated diagnosis, upper respiratory tract infection was most common (16.7%), followed by urinary tract infection (8.6%), lower respiratory tract infection (4.1%), cellulitis (4.0%), and other infection (1.7%). The majority of antibiotics were prescribed by family physicians.

Interpretation: Outpatient antibiotic use among Ontario's seniors has remained stable since 2006. Current methods of measuring usage are not capable of accurately determining indication. Additional data sources to monitor the appropriateness of community antimicrobial use are needed, as well as outpatient stewardship programs specifically targeting family physicians.

A decade of outpatient antimicrobial use in senior residents of Ontario

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Abstract

Background: Antimicrobials are frequently prescribed to community-dwelling seniors. Our aim was to examine the prevalence, quantity and indications of antimicrobial prescriptions to elderly individuals residing in Ontario, Canada.

Methods: We conducted a 10-year population-based analysis of outpatient antimicrobial prescriptions to Ontario's seniors, from 2006 to 2015. Antimicrobial prescriptions, infectious disease diagnoses and prescriber information were determined from linked healthcare databases. Our analyses were primarily focused on antibiotics, which comprise the highest burden of antimicrobial use.

Results: We identified 2 879 779 unique senior residents of Ontario over our study period. On average, 40.7% of seniors in any given year received one or more antibiotic prescriptions (range 40.1% to 41.5%). Antibiotic usage remained stable, averaging 30.1 DDDs per 1000 person days per year (range 28.5 to 31.1 DDDs per 1000 person days per year). Selection of antibiotics evolved, with increasing use of penicillins and decreasing use of trimethoprim-sulfamethoxazole, fluoroquinolones and macrolides. For 67.0% of prescriptions, no infectious disease diagnoses were identified within seven days. Of those with an associated diagnosis, upper respiratory tract infection was most common (16.7%), followed by urinary tract infection (8.6%), lower respiratory tract infection (4.1%), cellulitis (4.0%), and other infection (1.7%). The majority of antibiotics were prescribed by family physicians.

Interpretation: Outpatient antibiotic use among Ontario's seniors has remained stable since 2006. Current methods of measuring usage are not capable of accurately determining indication. Additional data sources to monitor the appropriateness of community antimicrobial use are needed, as well as outpatient stewardship programs specifically targeting family physicians.

Introduction

Antimicrobials are among the most commonly prescribed medications in Canada. The majority are dispensed in an outpatient setting, accounting for 93% of total use in 2014 (1). Many of these prescriptions are unnecessary or inappropriate, with antibiotics given for viral illnesses and increasing use of broad-spectrum agents (2-7). Such misuse of antimicrobials is the primary driver of antimicrobial resistance, which is increasingly recognized as an urgent public health challenge (8). Patients prescribed antibiotics in primary care are more likely to develop antibiotic resistant infections (9), while ecological studies have demonstrated increased rates of resistance in areas with higher outpatient antimicrobial use (10-12). Overuse is also associated with greater healthcare costs and adverse events (13-15).

Judicious use of antimicrobials is particularly important for older adults, who are prescribed these medications more frequently than younger individuals (1, 16-19). Among Ontario's seniors, antimicrobials are the fourth most common drug class prescribed, resulting in public healthcare expenditures of $495 million (20). Given the atypical manifestations of infectious diseases in the elderly, empiric antibiotic therapy is often started in response to non-specific symptoms, signs or laboratory abnormalities (21). Older adults are at higher risk of adverse drug events due to polypharmacy, comorbidities and altered drug metabolism (21, 22). High rates of colonization with antimicrobial-resistant organisms have also been found in this population, in ambulatory, inpatient and long-term care settings (23-25).

In response to the threats posed by inappropriate antimicrobial use, several initiatives have been implemented to raise awareness and promote prudent prescribing. These include the Choosing Wisely Canada campaign (26) and Antibiotic Awareness Week (27), which provide education on antimicrobial resistance and recommendations for best practice. However, interventions for antimicrobial stewardship are challenging to implement in outpatient settings (28), and surveillance of ambulatory antimicrobial use and resistance in Canada has been limited despite calls to prioritize such efforts (29).

The objective of our study was to describe patterns of outpatient antimicrobial prescribing in senior residents of Ontario, over a 10-year period from 2006 to 2015.

Methods

General study design

We conducted a 10-year province-wide analysis of antimicrobial prescriptions to Ontario's senior residents, defined as 65 years of age or older, from January 1 2006 to December 31 2015. Approval was obtained from the research ethics board of Sunnybrook Health Sciences Centre.

Data sources

This study used population-based administrative databases housed at the Institute for Clinical Evaluative Sciences. These databases are well validated and have previously been used in studies on antimicrobial prescribing (30-32). The Ontario Drug Benefit (ODB) Program database, which contains records of all publically funded medications prescribed to Ontario residents 65 years or older, was used for information on antimicrobial prescribing. This database exhibits greater than 99% accuracy when compared against pharmacy dispensing data (33). To identify Ontario's seniors and determine infectious disease diagnoses, the following databases were linked to the ODB database at the patient-level, using encoded health card numbers: the Registered Persons database (RPDB), which contains demographic information on the greater than 95% of Ontario residents with publically funded health insurance; the Ontario Health Insurance Plan (OHIP) database, which contains all billing claims made by healthcare providers for services performed in Ontario; the Canadian Institute for Health Information Discharge Abstracts Database (DAD), which contains information on all admissions, discharges and same-day surgeries in Ontario hospitals; and the National Ambulatory Care Reporting System (NACRS), which contains information on all emergency department visits in Ontario hospitals.

Statistical analyses

Antimicrobial prescriptions: The RPDB was used to identify all Ontario residents age 65 or older during our study period. Individuals were assessed for inclusion based on age as of January 1 of each calendar year. Residents who had no health system contact in the seven years preceding assessment, or who died or moved to a different province between calendar years, were excluded. We then used the ODB database to determine the proportion of Ontario senior residents who were prescribed an antimicrobial in each calendar year from 2006 to 2015. Antimicrobials were classified into one of four categories: antibiotics, antivirals, antifungals and antiparasitics (**Supplementary File 1**).

Antibiotic prescriptions: Our subsequent analyses were focused on antibiotics, as this is the most frequently prescribed category of antimicrobials and resistance to antibiotics is of greatest public health concern (8). Using the ODB database, we determined the quantity of each antibiotic class and antibiotic drug prescribed to Ontario's seniors, in every calendar year from 2006 to 2015. Antibiotics were grouped into the following classes: aminoglycosides, cephalosporins, fluoroquinolones, glycopeptides, lincosamides, macrolides, metronidazole, penicillins, tetracyclines, trimethoprim and/or sulphonamides, other urinary anti-infectives (nitrofurantoin, fosfomycin), and other antibiotics. Antibiotic utilization was measured in defined daily doses (DDDs) per 1000 person days. DDDs are a standardized metric of drug use developed by the World Health Organization based on an assumed average daily maintenance dose (34). Person days were calculated as the total number of seniors residing in Ontario in each calendar year, multiplied by the number of days in that year. We also determined the number of seniors in each calendar year who received multiple antibiotic prescriptions.

Indications for antibiotic prescriptions: Each antibiotic prescription was subsequently linked to the physician claim, hospitalization, same-day surgery and emergency room databases to identify any infectious disease diagnoses recorded within seven days before or after the antibiotic being dispensed. Diagnoses were grouped into the following categories: upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), urinary tract infection (UTI), cellulitis, other infection, and no recorded infection. We determined the proportion of each antibiotic class and drug's use associated with each clinical indication.

Antibiotics prescribed for infectious disease diagnoses: We identified all infectious disease diagnoses recorded in the OHIP, DAD and NACRS databases for calendar years 2006 and 2015. These diagnoses were then linked to the ODB database to examine whether a prescription for an antibiotic was filled in the seven days before or after each diagnosis. For the URTI, LRTI, UTI and cellulitis diagnosis categories, we determined the overall numbers of antibiotic prescriptions as well as the 10 most commonly prescribed antibiotics.

Responsible prescribers: To determine the healthcare providers most responsible for outpatient antibiotic use in Ontario's seniors, the proportion of prescriptions, in individual claims and DDDs, attributable to family physicians and specialists was determined. In addition, for residents who received multiple antibiotic prescriptions, we determined how many were provided prescriptions from the same physician compared to multiple physicians. This analysis was conducted for calendar years 2006 and 2015.

Analyses were performed with SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA) and R statistical software version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Antimicrobial prescriptions

During the study period, 2 879 779 unique residents of Ontario age 65 years or older were identified. The population of seniors increased from 1 646 909 in 2006 to 2 176 736 in 2015. Antibiotics were the most frequently prescribed type of antimicrobial. On average, 40.7% of Ontario's seniors received an antibiotic prescription in any study year, while 2.7%, 1.7% and 0.8% of seniors were prescribed an antiviral, antifungal or antiparasitic, respectively. The proportion of seniors prescribed an antiviral agent increased from 1.9% in 2006 to 4.4% in 2015 ($p<0.001$); antimicrobial use was otherwise stable across the 10 study years (**Figure 1**).

Antibiotic prescriptions

The average quantity of antibiotics prescribed per calendar year was 30.1 DDDs per 1000 person days. Antibiotic usage remained relatively stable over the study period, decreasing slightly from 31.1 DDDs per 1000 person days in 2006 to 28.5 DDDs per 1000 person days in 2015. Seniors were commonly provided multiple antibiotic prescriptions within a single year, with 39.4% of recipients in 2006 and 38.2% in 2015 receiving more than one course.

The five most frequently prescribed antibiotic classes were penicillins, sulphonamides and/or trimethoprim, fluoroquinolones, macrolides and cephalosporins. Trends in their use from 2006 to 2015 are shown in **Figure 2**. Prescriptions for penicillins increased from 6.1 DDDs per 1000 person days in 2006 to 7.8 DDDs per 1000 person days in 2015. Use of sulphonamides and/or trimethoprim, the vast majority (97.8%) of which was comprised by trimethoprim-sulfamethoxazole, declined from 7.4 DDDs per 1000 person days in 2006 to 5.9 DDDs per 1000 person days in 2015. Prescriptions for fluoroquinolones and macrolides decreased as well, while cephalosporin use remained stable. Trends in use of the 10 most prescribed antibiotic drugs over our study period, shown in **Figure 3**, reveal the rise in penicillin prescriptions was driven by greater use of amoxicillin, from 4.7 DDDs per 1000 person days in 2006 to 5.7 DDDs per 1000 person days in 2015, and amoxicillin-clavulanic acid, from 0.68 to 1.8 DDDs per 1000 person days. Among fluoroquinolones, prescriptions for ciprofloxacin and moxifloxacin both declined; among macrolides, clarithromycin use decreased while azithromycin use increased.

Indications for antibiotic prescriptions

From 2006 to 2015, 67.0% of antibiotics prescribed to Ontario's senior residents did not have a corresponding infectious disease diagnosis detectable within seven days of the prescription (**Figure 3, white bar segments**). The most frequently identified diagnosis was URTI, associated with 16.7% of prescriptions, followed by UTI (8.6%), LRTI (4.1%), cellulitis (4.0%), and other infection (1.7%). URTIs were the most common diagnoses associated with penicillins and macrolides, while UTIs were most common for trimethoprim-sulfamethoxazole. Among fluoroquinolones, ciprofloxacin was associated with UTIs, while moxifloxacin was associated with URTIs and LRTIs. For cephalosporins, cellulitis was the most common diagnosis associated with cephalexin, while URTIs were most common for cefuroxime (**Figure 3**).

Antibiotics prescribed for infectious disease diagnoses

URTIs were the most commonly recorded diagnosis associated with an antibiotic prescription among Ontario's senior residents. There were 184 667 URTI episodes associated with outpatient antibiotics in 2006, rising to 211 549 episodes in 2015. Between 2006 and 2015, increased use of amoxicillin (0.80 to 0.98 DDDs per 1000 person days) and amoxicillin-clavulanic acid (0.10 to 0.29 DDDs per 1000 person days), and decreased use of clarithromycin (1.10 to 0.53 DDDs per 1000 person days), trimethoprim-sulfamethoxazole (0.25 to 0.13 DDDs per 1000 person days) and fluoroquinolones were observed (**Figure 4a**).

UTIs were the second most common indication for outpatient antibiotics; 75 645 antibiotic prescriptions for UTI diagnoses were identified in 2006, while 100 648 were identified in 2015. Use of trimethoprim-sulfamethoxazole declined from 0.90 to 0.63 DDDs per 1000 person days between 2006 and 2015, but was the most frequently selected antibiotic in both years. Likewise, prescriptions for fluoroquinolones decreased, largely driven by a fall in norfloxacin use from 0.21 to 0.07 DDDs per 1000 person days, though there was a small increase in ciprofloxacin use. Prescriptions for nitrofurantoin increased as well (**Figure 4b**).

LRTIs were the third most common indication for outpatient antibiotic treatment in this population. There were 48 408 LRTI diagnoses with associated outpatient prescriptions in 2006, and 66 273 in 2015. A substantial decrease in macrolide use was observed. Clarithromycin was the most frequently prescribed antibiotic for LRTIs in 2006 (0.29 DDDs per 1000 person days), but use fell to 0.15 DDDs per 1000 person days in 2015, below that of levofloxacin. In contrast, prescriptions for amoxicillin (from 0.05 to 0.14 DDDs per 1000 person days) and amoxicillin-clavulanic acid (from 0.03 to 0.13 DDDs per 1000 person days) increased. There were small declines in prescriptions for the respiratory fluoroquinolones, though levofloxacin was the most commonly prescribed antibiotic for LRTIs in 2015 (**Figure 4c**).

Lastly, for cellulitis, 45 453 outpatient antibiotic treatments were prescribed in 2006, compared to 64 882 in 2015. Cephalexin was the most commonly prescribed antibiotic in both years, increasing from 0.36 DDDs per 1000 person days in 2006 to 0.47 DDDs per 1000 person days in 2015. Cloxacillin, ciprofloxacin and clarithromycin were less commonly prescribed between the two years, while use of trimethoprim-sulfamethoxazole, clindamycin and amoxicillin-clavulanic acid increased (**Figure 4d**).

Responsible prescribers

Family physicians accounted for the majority of outpatient antibiotics prescribed to Ontario's senior residents (**Table 1**). Antibiotic prescriptions by family physicians and specialists both increased from 2006 to 2015, with proportionately more specialist prescriptions in 2015. For patients who received multiple antibiotic prescriptions in 2006, 49.6% received their prescriptions from the same physician, while 50.4% received their prescriptions from multiple physicians. In 2015, multiple prescriptions were provided to 40.1% of recipients by a single physician, with the remaining 59.9% receiving prescriptions from multiple physicians.

Interpretation

This study of 2 879 779 unique elderly residents of Ontario found that in every year from 2006 to 2015, approximately 40% of seniors were prescribed an antibiotic in an outpatient setting. Selection of antibiotics evolved over the study period, with increasing use of amoxicillin and amoxicillin-clavulanic acid, and decreasing use of trimethoprim-sulfamethoxazole, fluoroquinolones and macrolides. More than two thirds of antibiotic prescriptions did not have a corresponding infectious disease diagnosis recorded in Ontario physician claim, hospitalization, same-day surgery or emergency room databases within seven days of the prescription being given. URTI was the most commonly identified indication for antibiotics, as well as the diagnosis with the greatest number of associated prescriptions, and family physicians were responsible for the majority of outpatient antibiotic prescribing to Ontario's seniors.

Our results diverge from the rise in broad-spectrum antibiotic use, including broad-spectrum cephalosporins, fluoroquinolones and macrolides, reported in prior studies (2, 5, 16). This may represent a positive change in antibiotic prescribing practices, with physicians favouring narrow-spectrum agents where appropriate. However, overall outpatient antibiotic use remained stable over our study period, averaging 30.1 DDDs per 1000 person days per year. Although this is higher than rates reported in prior literature (1, 35), benchmarking is difficult for several reasons. Our study was limited to seniors, a population prescribed antibiotics more frequently than other age groups (1, 16-19). Unlike other datasets, the ODB database also includes medications dispensed in other ambulatory settings, such as long-term care facilities, in addition to community pharmacies. Nevertheless, this finding suggests that total antibiotic prescribing has not been curtailed by existing stewardship interventions. Indeed, although recommendations from Choosing Wisely Canada and the Get Smart: Know When Antibiotics Work program in the United States are directed to ambulatory care, formalized antimicrobial stewardship programs have predominantly targeted inpatient settings. Since more than 90% of antimicrobials are prescribed in outpatient care, further stewardship efforts in Ontario, directed at family physicians in particular, are urgently needed.

The antibiotics prescribed for URTIs changed over our study period. Prescriptions for fluoroquinolones and macrolides declined while penicillin use increased, contrasting with previous analyses demonstrating rising selection of the former classes (2-4, 6, 7). This is in keeping with society guidelines recommending amoxicillin or amoxicillin-clavulanic acid as first-line therapy for bacterial URTIs (36, 37). However, URTIs remained the most common diagnoses associated with antibiotic prescriptions, even though most cases are viral in origin and do not require antibiotics. This highlights the potential impact a community-based antimicrobial stewardship program could have in reducing overall antibiotic use. Other jurisdictions have similarly found high rates of antibiotic use for URTIs (1, 5, 16), despite guidelines discouraging routine antibiotic therapy (36, 38, 39).

Similarly, for LRTIs we found increased prescriptions for penicillins, while macrolide use fell. Although macrolides have been recommended as first-line therapy for outpatient community-acquired pneumonia (40), resistance rates in *Streptococcus pneumoniae* have approached 25% in Canada. Thus, macrolides should not be used as monotherapy in this context (41, 42). The need for 'atypical' coverage in treating community-acquired pneumonia has also been questioned, which may explain some of the reductions in macrolide use (43). Within the macrolide class, growing preference for azithromycin over clarithromycin was observed. This finding may be explained by ease of administration, with single daily versus twice daily dosing, as well as studies demonstrating equivalency between three-day courses of azithromycin and longer courses of clarithromycin (44, 45). Another reason may be greater awareness of drug interactions involving cytochrome P450, with CYP3A4 inhibited by clarithromycin but not azithromycin (46).

For UTIs, we found a decline in the use of trimethoprim-sulfamethoxazole. This may reflect increasing recognition of its adverse effects (47), particularly among elderly patients co-prescribed common cardiovascular and renal medications (32, 48, 49). In addition, the Infectious Diseases Society of America recommends against trimethoprim-sulfamethoxazole for UTIs if local uropathogen resistance rates are above 20% (50). Community resistance rates in Ontario are on the rise, but remain below 20% (51-53), while inpatient resistance has exceeded this threshold (54). Prescriptions for ciprofloxacin around UTI diagnoses decreased as well. This may be due to rising awareness of the risks associated with fluoroquinolones, including tendinopathies, aortic aneurysm and dissection, and peripheral neuropathy (55-58). In contrast, use of nitrofurantoin increased, in accordance with recent guidelines recommending it as first-line therapy for UTIs due to high susceptibility rates and low risk to host flora (50).

Cephalexin was consistently the most prescribed antibiotic for cellulitis. We saw increases in the use of trimethoprim-sulfamethoxazole and clindamycin, which may reflect a change in practice to cover methicillin-resistant *Staphylococcus aureus*. However, clindamycin exposure is associated with the highest risk of *Clostridium difficile* infection among antibiotics (59, 60)

Despite these changes in antibiotic selection, 67.0% of antibiotics prescribed to Ontario's seniors were not associated with a recorded infectious disease diagnosis. This suggests that our databases were unable to capture the majority of antibiotic indications, even in the context of a universal single-payer healthcare system, a research institute with access to linkable physician claim, hospitalization, same-day surgery and emergency room databases, and the use of a broad seven-day window around prescriptions to identify diagnoses. Therefore, effective surveillance of community antibiotic use will require more comprehensive methods of capturing antibiotic indication, such as linkage to electronic medical records or province-wide mandatory reporting of diagnosis with each prescription.

This study was subject to limitations. Our database was restricted to elderly individuals age 65 years or older and are not generalizable to the entire population. Additional data sources are needed to capture outpatient antimicrobial use in children and younger adults. Our use of administrative databases may have led to misclassification of antibiotic prescriptions and diagnoses. However, these databases have been used extensively in prior studies, and the ODB and DAD databases have undergone rigorous validation (33, 61). In addition, we linked antibiotic prescriptions and infectious disease diagnoses through their presence within seven days of one another. Although these antibiotic-diagnosis associations are likely accurate given their temporal proximity, causation could not be ascertained. For inpatient diagnoses, which were captured in the DAD, date of admission was taken as the date of diagnosis. Diagnoses around outpatient antibiotic prescriptions, and vice versa, may consequently have been missed, particularly in cases of prolonged hospital stays and infections fully treated in hospital. Furthermore, the OHIP database only allows for a single diagnosis to be recorded in each billing claim; infectious disease diagnoses could have been unrecorded in physician visits involving multiple diagnoses and comorbidities. Lastly, DDDs may be an inaccurate measure of drug utilization in patients with renal impairment, a common comorbidity in elderly populations.

Conclusion

In our analysis of outpatient antimicrobial use among senior residents of Ontario, a trend towards greater selection of narrow-spectrum antibiotics was observed. However, total antibiotic use was stable from 2006 to 2015, and antibiotics were frequently prescribed for URTIs. This emphasizes that misuse and overuse of antibiotics remains a problem. Interventions to improve antibiotic prescribing in ambulatory care are therefore warranted, and should specifically target family physicians. In addition, more than two-thirds of antibiotic prescriptions were not associated with an infectious disease diagnosis, demonstrating that existing methods of surveillance in Ontario are not capable of determining antibiotic indication. Given the lack of information on outpatient antibiotic use in Canada, this study suggests that efforts to monitor the quantity, composition and appropriateness of community use need to be strengthened. Our results can be used to guide such efforts and benchmark outpatient antimicrobial stewardship interventions.

Disclaimer

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Contributors

Nick Daneman and Erin Graves conceptualized and designed the study, and developed the statistical analysis plan. Nick Daneman and Charlie Tan analyzed and interpreted the data and drafted the manuscript. Hong Lu, Anna Chen and Shudong Li contributed to data acquisition and analysis. Kevin Schwartz contributed to data interpretation and manuscript revision. All authors reviewed the manuscript and approve the final version for publication.

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Table 1 Proportion of outpatient antibiotic prescriptions to Ontario's senior residents provided by family physicians and specialists, in 2006 and 2015

Provider	Antibiotic prescriptions, in individual claims (%)		Antibiotic prescriptions, in defined daily doses (%)	
	2006	2015	2006	2015
Family physician	195 745 (76.7)	227 569 (69.8)	2 230 258 (75.4)	2 409 323 (68.1)
Specialist	59 499 (23.3)	98 412 (30.2)	726 659 (24.6)	1 127 512 (31.9)

Figure 1 Proportion of Ontario's senior residents who received one or more outpatient antimicrobial prescriptions, divided by antimicrobial class, from 2006 to 2015

Figure 2 Total outpatient prescriptions, in DDDs per 1000 person days, of the five antibiotic classes most commonly prescribed to Ontario's senior residents, from 2006 to 2015

Figure 3 Total outpatient prescriptions, in DDDs per 1000 person days, of the 10 antibiotics most commonly prescribed to Ontario's senior residents, divided by infectious disease indication, from 2006 to 2015. TMP/SMX = trimethoprim-sulfamethoxazole.

Figure 4 Outpatient prescriptions, in DDDs per 1000 person days, of the 10 antibiotics most commonly prescribed for **a.** upper respiratory tract infections, **b.** urinary tract infections, **c.** lower respiratory tract infections, and **d.** cellulitis to Ontario's senior residents, in 2006 and 2015. TMP/SMX = trimethoprim-sulfamethoxazole, Amox/Clav = amoxicillin-clavulanic acid.

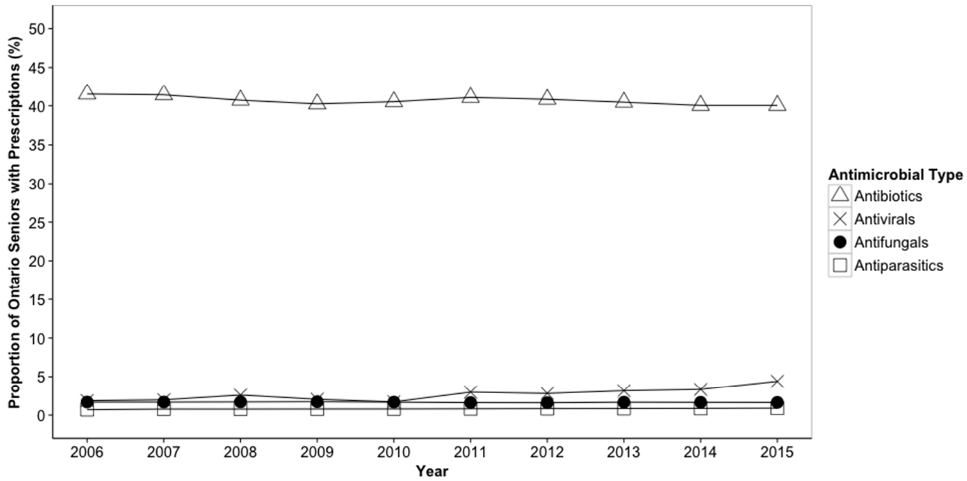

Figure 1: Proportion of Ontario's senior residents who received one or more outpatient antimicrobial prescriptions, divided by antimicrobial class, from 2006 to 2015

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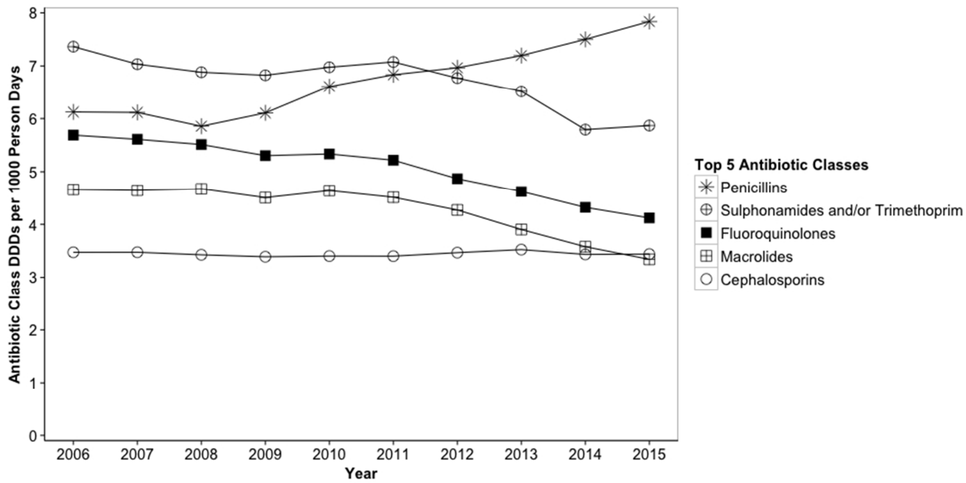

Figure 2: Total outpatient prescriptions, in DDDs per 1000 person days, of the five antibiotic classes most commonly prescribed to Ontario's senior residents, from 2006 to 2015

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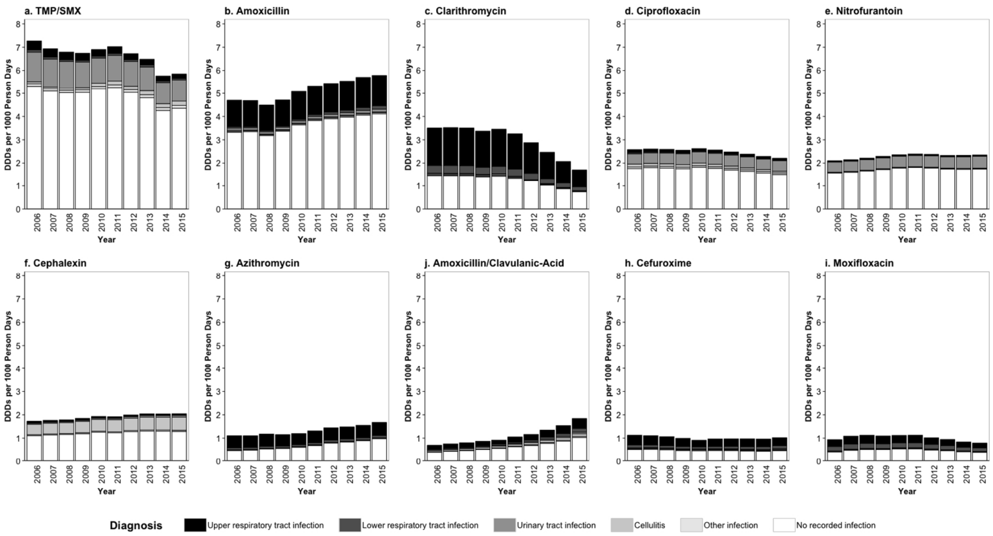

Figure 3: Total outpatient prescriptions, in DDDs per 1000 person days, of the 10 antibiotics most commonly prescribed to Ontario's senior residents, divided by infectious disease indication, from 2006 to 2015. TMP/SMX = trimethoprim-sulfamethoxazole.

635x352mm (72 x 72 DPI)

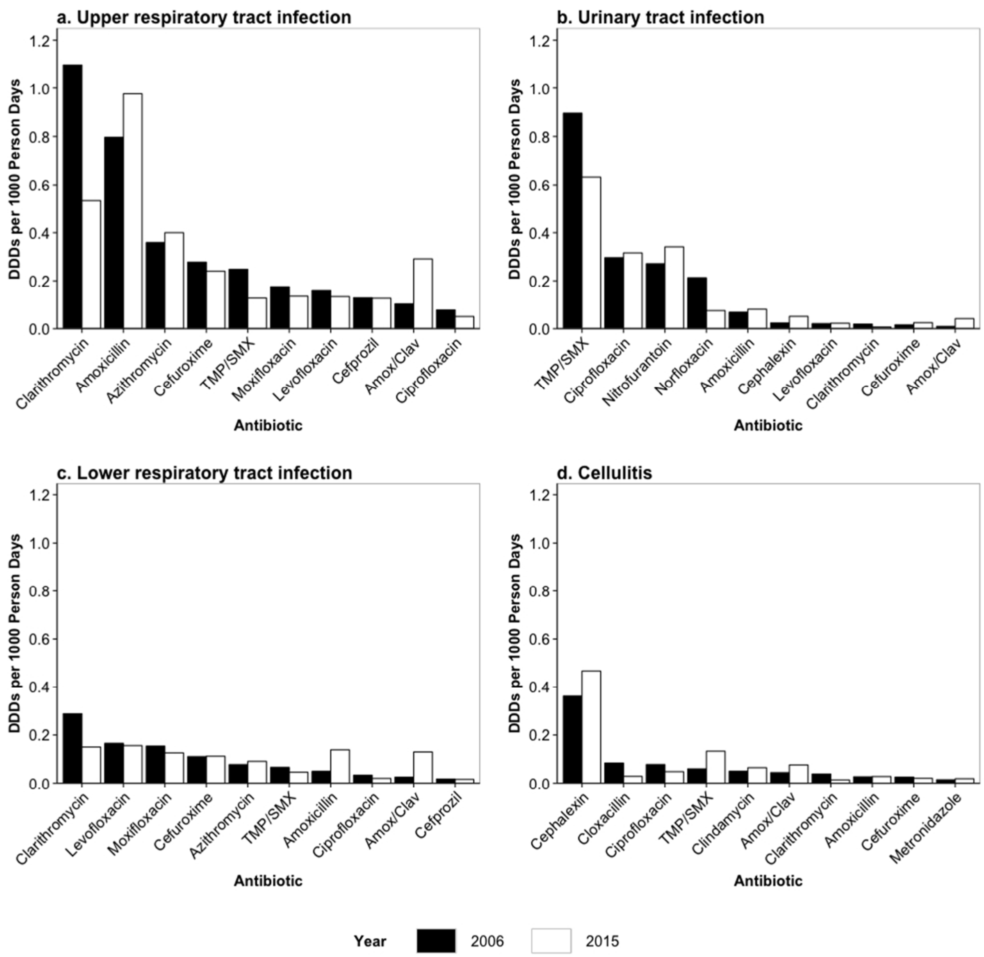

Figure 4: Outpatient prescriptions, in DDDs per 1000 person days, of the 10 antibiotics most commonly prescribed for a. upper respiratory tract infections, b. urinary tract infections, c. lower respiratory tract infections, and d. cellulitis to Ontario's senior residents, in 2006 and 2015. TMP/SMX = trimethoprim-sulfamethoxazole, Amox/Clav = amoxicillin-clavulanic acid.

352x352mm (72 x 72 DPI)

Supplementary File 1 Drugs included in each antimicrobial class

Antibiotics
- Amikacin
- Amoxicillin
- Amoxicillin & clavulanic acid
- Ampicillin
- Azithromycin
- Cefaclor
- Cefadroxil
- Cefazolin
- Cefixime
- Cefotaxime
- Cefoxitin
- Cefprozil
- Ceftazidime
- Ceftriaxone
- Cefuroxime
- Cephalexin
- Ciprofloxacin
- Clarithromycin
- Clindamycin
- Cloxacillin
- Colistin
- Dapsone
- Daptomycin
- Demeclocycline
- Doxycycline
- Ertapenem
- Erythromycin
- Ethambutol
- Ethionamide
- Fidaxomicin
- Fosfomycin
- Fusidic acid
- Gatifloxacin
- Gentamicin
- Isoniazid
- Levofloxacin
- Linezolid
- Meropenem
- Metronidazole
- Minocycline
- Moxifloxacin
- Nitrofurantoin
- Norfloxacin
- Ofloxacin
- Paromomycin
- Penicillin V
- Penicillin V benzathine
- Piperacillin & tazobactam
- Pivampicillin
- Pyrazinamide
- Rifabutin
- Rifampin
- Streptomycin
- Trimethoprim & sulfamethoxazole
- Telithromycin
- Tetracycline
- Tigecycline
- Tobramycin
- Trimethoprim
- Vancomycin

Antivirals
- Abacavir
- Abacavir & lamivudine
- Abacavir & dolutegravir & lamivudine
- Abacavir & lamivudine & zidovudine
- Acyclovir
- Adefovir
- Amantadine
- Amprenavir
- Atazanavir
- Boceprevir
- Cobicistat & elvitegravir & emtricitabine & tenofovir
- Darunavir
- Dasabuvir & ombitasvir & paritaprevir & ritonavir
- Delavirdine
- Didanosine
- Dolutegravir
- Efavirenz
- Efavirenz & emtricitabine & tenofovir
- Emtricitabine & rilpivirine & tenofovir
- Emtricitabine & tenofovir
- Enfuvirtide
- Entecavir
- Etravirine
- Famciclovir
- Fosamprenavir
- Ganciclovir
- Indinavir
- Lamivudine
- Lamivudine & zidovudine
- Ledipasvir & sofosbuvir
- Lopinavir & ritonavir
- Maraviroc
- Nelfinavir
- Nevirapine
- Oseltamivir
- Peg-Interferon alfa 2B
- Peg-Interferon alfa-2B & ribavirin
- Raltegravir
- Ribavirin
- Rilpivirine
- Ritonavir
- Saquinavir
- Simeprevir
- Sofosbuvir
- Stavudine
- Telaprevir
- Tenofovir
- Tipranavir
- Valacyclovir
- Valganciclovir
- Zidovudine

Antifungals
- Amphotericin B
- Atovaquone
- Caspofungin
- Fluconazole
- Griseofulvin
- Itraconazole
- Ketoconazole
- Micafungin
- Nystatin
- Pentamidine isethionate
- Posaconazole
- Terbinafine
- Voriconazole

Antiparasitics
- Chloroquine
- Hydroxychloroquine
- Mebendazole

- Praziquantel
- Pyrimethamine
- Pyrvinium
- Quinine

STROBE Statement—checklist of items that should be included in reports of observational studies

Note: Since our study was a descriptive study of outpatient antimicrobial use, there was no specific EQUATOR reporting guideline available. We have completed the STROBE checklist for observational studies. Many of the items were not applicable since our study did not follow a cohort, case-control or cross-sectional design.

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	NA

Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	NA
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10–13
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14–17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1,19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.