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JAC-Antimicrobial Resistance

Outpatient antibiotic use in British Columbia, Canada: reviewing major trends since 2000

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Background: With 90% of all antibiotics in Canada being used in the community setting, tracking outpatient prescribing is integral to mitigate the issue of antimicrobial resistance. In 2005, a provincial programme was launched in British Columbia (BC) to disseminate information regarding the judicious use of antibiotics. These efforts include educational campaigns, updated practitioner guidelines and academic detailing. The impact of provincial stewardship on community prescribing requires ongoing evaluation.

Objectives: This study examines outpatient prescribing to quantify rates of antibiotic use, evaluate major trends over time and identify new targets for stewardship.

Methods: A retrospective cohort design using population-level data.

Results: This study included over 3.5 million unique individuals with a total of 51 367 938 oral antibiotic prescriptions dispensed over a 19 year period (2000–18). Overall antibiotic utilization decreased by 23% over the course of the study period. This trend in the reduction of antibiotic prescription was observed across all major antibiotic classes, apart from the class of other antibacterials, which was mostly related to use of nitrofurantoin. The largest magnitudes of decreased prescribing were observed in the paediatric population. Prescribing across two distinct eras of provincial stewardship reaffirmed preliminary findings of programme efficacy, when compared with pre-stewardship levels of antibiotic use.

Conclusions: Outpatient prescribing in BC is decreasing overall, and this study confirms an association between provincial stewardship interventions and improvements in antibiotic use. Pronounced declines in paediatric populations are promising, and further research is underway to examine prescribing quality.

Introduction

Antimicrobials remain among the most prescribed medications in Canada. It is imperative to understand outpatient prescribing as over 90% of antibiotics are prescribed in the community setting.[1] Identifying suboptimal or unnecessary use of these essential medications is vital, as antimicrobial resistance (AMR) continues to jeopardize the future efficacy of these essential medications. In British Columbia (BC), efforts to reduce use of antimicrobials have included: educational campaigns, practitioner guidelines and frequent academic detailing.[2] The latter is a programme by the Ministry of Health that provides evidence-based drug information on the best prescribing practices to primary care physicians. The Community Antimicrobial Stewardship (CAS) programme has been in operation provincially since 2005 educating the public on judicious antibiotic use and encouraging stewardship through the Do Bugs Need Drugs (DBND) campaign.[3] A complementary programme arm works to educate healthcare professionals through accredited courses on antibiotic use, resistance and strategies to prescribe appropriately, and to disseminate timely guidelines and other resources.[4]

Misusing antimicrobials is a primary mechanism driving resistance, and overuse has been associated with increased adverse events and higher financial burdens.[5–7] In 2018, longer hospital stays, lengthier courses of treatment and other expenses attributable to AMR cost the Canadian healthcare system $1.4 billion.[8] Multiple studies have examined prescribing for specific indications and identified respiratory tract infections to be amongst the highest associated diagnoses.[9,10] Upper respiratory tract infections, sore throat, acute cough, sinusitis, common cold and acute bronchitis—all of which are predominantly caused by viruses—are routinely prescribed antimicrobials at high rates, despite incurring no benefit.[11–14] It is vital to understand outpatient prescribing patterns as increased community use has been associated with rising resistance across both outpatient and inpatient healthcare settings.[15,16] Moreover, correlations between inpatient prescribing and associated rates of resistance are weak, which suggests that selection caused by community prescribing may be a primary force underlying rates of resistance.[15,16]

This retrospective cohort study was conducted to evaluate antibiotic use in BC, Canada—at the population level. The objectives of this study were to evaluate prescribing of antimicrobials in outpatient care, identify common agents and indications and examine the relative impact of a formalized provincial stewardship programme on antibiotic use.

Methods and methods

Data sources

In Canada, public health insurance is available to eligible residents. Canadian citizens and permanent residents can apply for provincial health insurance.[17] The Ministry of Health in British Columbia houses several healthcare-related databases, which have comprehensive information on BC residents (population: 5 million). Antibiotic information was extracted from BC PharmaNet, a centralized data system that links all pharmacies with every prescription dispensed through community and hospital outpatient pharmacies.[18,19] All antimicrobials are recorded in this system except those used for treatment of sexually transmitted infections and HIV, as well as medications administered within the hospitals/emergency departments. The Medical Service Plan (MSP) billing system records all claims submitted by physicians for services provided to BC residents, including diagnostic codes.[20] Data were extracted, anonymized and made available to researchers by Population Data BC. All inferences, opinions and conclusions drawn in this study are those of the authors and do not reflect the opinions or policies of the Data Steward(s).

Study population

Our study included all residents of BC from 1 January 2000 to 31 December 2018. Antibiotic dispensations were extracted from PharmaNet and then matched to the MSP system using anonymized patient identifiers. Antimicrobials were limited to oral and acute use only (continuous <30 day supply). A prescription and diagnosis were linked using an algorithm that matched the date on which the medication was dispensed to a practitioner service date within 5 days prior. If a practitioner service date was associated with more than one diagnostic code, or multiple service dates fell within a single 5 day period of a prescription dispensing date, then a three-tiered hierarchy was applied to link only the most relevant diagnostic code to the prescription.[21] The tiers have been validated in several studies across the USA and Canada and essentially use the same concept, which is: tier 1 indications are those that always require antibiotic prescription; tier 2: sometimes require antibiotic prescription; and tier 3: antibiotics unnecessary.[21–23] If multiple codes were present within a given linkage period then precedent was given to tier 1 diagnoses followed by tier 2, then 3. If multiple diagnoses were listed from the same tier, the primary physician code was selected for analysis. Prescriptions that did not match to an MSP record were classified as unlinked. Multiple prescriptions per subject were permitted in our analyses. All cells with $n < 5$ were excluded from subsequent analyses to preserve subject anonymity.

Antimicrobial stewardship eras

As the DBND programme launched in 2005, the pre-stewardship era captures 5 years of prescribing prior to any community interventions. Era I reflects the programme goals and initiatives at inception, which included community education on handwashing and the principles of antibiotic use for bacterial infection. During this period, prescribing for upper respiratory tract was the target for optimization with various materials, including updated guidelines and newsletters, disseminated to healthcare professionals.[24] These materials communicated the issues of bacterial resistance and recommended the reservation of broad-spectrum antibiotics.[25] Era II is built on the foundations laid in I, with a shift towards judicious urinary tract prescribing. Prescribing guidelines coupled with interventions across community and long-term care facility settings promoted the prescribing of first-line agents. Suboptimal prescribing in the wake of diagnostic uncertainty or the absence of lab confirmation for urinary tract infections was also discouraged.[26–28]

Outcomes and statistical analyses

Antibiotics were classified based on the Anatomical Therapeutic Chemical (ATC) classification system developed by WHO.[29] Consumption rates were calculated as prescriptions per 1000 population per year, using age and gender specific denominator estimates for the population from Statistics BC.[30] MSP diagnostic codes are ordered by the ninth revision of the International Classification of Diseases developed by WHO, commonly referred to as ICD-9.[31,32] Several indications were grouped within the classifications of upper respiratory tract infections (URTIs), acute otitis media (AOM), lower respiratory tract infections (LRTIs), urinary tract infections (UTIs) and skin/soft tissue infections (SSTIs).

Overall rates of total oral antibiotic use were examined and then stratified by seven major ATC classes and, subsequently, clinically relevant drugs. For each major ATC class, rates of use were further examined by sex, age group (0–2, 3–9, 10–18, 19–49, 50–64, 65–80 and ≥80 years) and indication.

Rate ratios (RR) for the above outcomes were estimated using Poisson regression to assess the impact of the BC provincial stewardship programme. Three time periods of interest were identified: pre-stewardship (2000–04), stewardship era I (2005–13) and stewardship era II (2014–18). Eras were delineated to complement relevant provincial interventions and targets over time.

Overall and age-specific RR were calculated using annual count data with a population offset. Autocorrelation was evaluated using the Durbin–Watson test with values returned ∼2 indicating no issue for serial correlation. A *post hoc* interrupted time series analysis was also undertaken to verify changes in overall antibiotic use over time, for all ages. All analyses were performed using SAS 9.4 and R version 3.3.1.

Results

An average of 1 374 222 unique patients were prescribed an antibiotic in any study year, with over 51 million total antibiotic prescriptions dispensed in the outpatient setting over the 19 year period (Table 1). The BC population grew by roughly 20% over the course of this study, from 4.03 million residents in 2000 to 5.00 million by 2018 ($P < 0.05$ based on linear regression).[30] The mean annual age of our cohort also increased from 39 to 49 years of age by 2018. On average, about 31.1% (range 26.2%–33.7%) of BC residents were dispensed antibiotics in any study year, with a steady downward trend. Those individuals prescribed were commonly older females residing in urban settings. No differences were observed across income quintiles.

Table 1 Cohort characteristics

Cohort characteristics (*N*)	Overall (2000–18)
Total number of patients	26 110 225
Average patients per year	1 374 222
Age	
0–2	769 903
3–9	2 112 836
10–18	2 362 166
19–49	10 774 734
50–64	5 232 075
65–79	3 389 791
≥80	1 468 720
Income quintile[a]	
quintile 1 (lowest)	5 332 067
quintile 2	5 220 283
quintile 3	5 073 879
quintile 4	4 984 898
quintile 5 (highest)	4 780 620
missing[b]	718 478
Rural/urban status[c]	
rural	4 358 270
urban	20 610 581
missing[b]	1 141 374
Total antibiotic prescriptions	51 367 938
Total prescriptions linked[d] to indication	36 526 088

[a]Population Data BC-determined neighborhood income quintile (i.e. household size-adjusted measure of household income) using a postal code-based algorithm standardized by Statistics Canada.
[b]Missing represents absent or not applicable patient demographic information.
[c]Rural status represents local population of 1000 to 29 999; urban status represents local population ≥30 000.
[d]Linked refers to an MSP entry ≤5 days of the dispensation date recorded in PharmaNet.

Overall antibiotic utilization

Oral antibiotics were prescribed at an overall average rate of 609 prescriptions per 1000 population. Outpatient prescribing decreased by 23% over the study period from 652 to 503 prescriptions per 1000 population (Figure 1).

By major ATC class, antibiotic use varied over the study period. Figure 2 shows the details for consumption, by ATC class, between 2000 and 2018. Decreasing use was observed for penicillins (−27%), macrolides (−43%), other β-lactams (−12%), sulphonamides and trimethoprim (−58%) and quinolones (−22%). Tetracycline dispensations remained constant over the study period, while other antibacterials (J01X) increased in use by 97%—nitrofurantoin drove this increase, ending the study period with 35 prescriptions per 1000 population in contrast to only 13 per 1000 population in 2000. Use of metronidazole, the second most prescribed J01X antibacterial, was consistent over the study period.

For penicillins (J01C), a decreasing trend was led by amoxicillin, which accounts for most prescriptions issued (range 169 to 126 prescriptions per 1000 population) and decreased in use by 25%. However, penicillin V (range 40 to 13 prescriptions per 1000 population) and cloxacillin (range 21 to 2 prescriptions per 1000 population) also declined by 2018 with 67.5% and 90.5% reduction, respectively.

Although macrolide use decreased overall, within the class there was a replacement of first-generation drugs by second-generation counterparts like azithromycin (range 13 to 32 prescriptions per 1000 population), which increased 146.2% in lieu of first-generation erythromycin, which decreased by 97.0% with only 2 prescriptions per 1000 population by 2018.

Tetracycline antibiotics remained steady in use overall, however, doxycycline increased by 94.4% (range 14 to 35 prescriptions per 1000 population). This increase was offset by declines in use of both tetracycline (−80.0%) and minocycline (−33.3%), establishing a net stability for the class.

When stratified by age, disparate patterns in use are apparent (Figure 3). Total antibiotic use decreased across all paediatric categories (0–2 years: −60.0%; 3–9 years: −51.0%; 10–18 years: −47.2%), as well as in adults between 19 and 49 years of age (−30.5%). The sharpest declines were seen in our youngest cohorts, with a negative association between increasing age and decreasing magnitude of antibiotic reduction. Individuals aged 50–64 years saw an increase of 8.1% by 2018, while those aged 65–79 years resumed the downward trend with a 10.6% decline by 2018. Those above 80 years were prescribed at rates far above other age groups and remained steady over the study period (range 1021 to 1178 prescriptions per 1000 population).

Antibiotic utilization by indication

In any given study year, URTI was the most commonly linked category of diagnoses (range 75 to 148 prescriptions per 1000 population) (Figure 4). Use within this category was driven by prescriptions for acute bronchitis (range 16 to 33 prescriptions per 1000 population) and acute upper respiratory tract unspecified

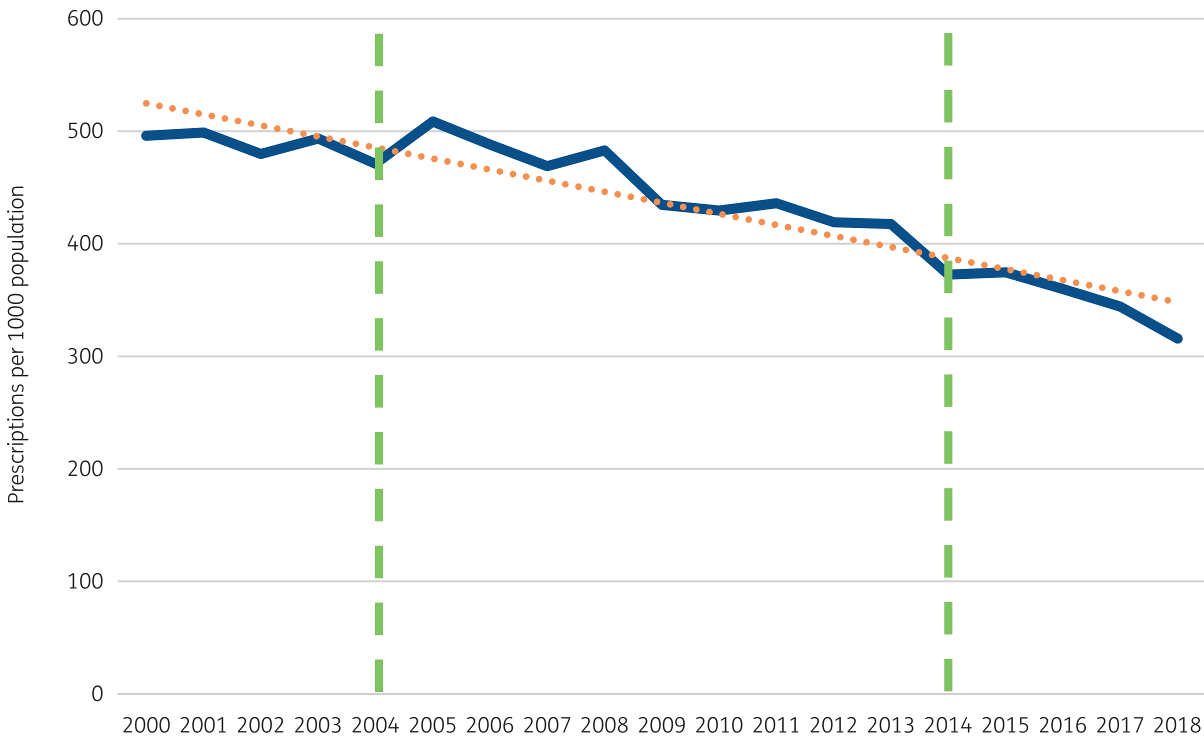


Figure 1. Overall rate of total oral antibiotic prescribing across stewardship eras in British Columbia, 2000–18. The blue line indicates annual rates of total antibiotic prescribing plotted over time and the orange dotted line shows the linear trend of antibiotic prescribing over time. The green dashed lines mark the temporal borders of the three stewardship eras: 2000–04, pre-stewardship era; 2005–13, stewardship era I; 2014–18: stewardship era II.

(range 15 to 32 prescriptions per 1000 population) (Figures S1 and S2, available as Supplementary data at *JAC-AMR* Online). Overall, prescribing for URTIs decreased by 49% with 75 prescriptions per 1000 population in 2018, the highest rate that year for any category of indication.

The second most common indication was UTI (range 48 to 53 prescriptions per 1000 population) (Figure S3). In contrast to URTI, UTI increased by 10% over the study period with cystitis driving this trend (range 31 to 36 prescriptions per 1000 population) (Figure S4). LRTI antibiotic use also increased (50%) over the study period, however, the magnitude of prescribing remained well below all other indications, apart from AOM (Figure S5). By 2018, LRTI diagnoses were dispensed at a rate of 15 prescriptions per 1000 population (Figure S6).

Parallel to URTI, declines in prescribing were also observed for AOM and SSTI diagnoses (Figures S7 and S8). Prescribing for suppurative and unspecified otitis media decreased by 71% over the study period with only 9 prescriptions per 1000 population dispensed in 2018. Moreover, prescribing for this indication was heavily swayed within paediatric age categories. By the end of the study period, SSTI diagnoses decreased by 24%, with most prescriptions issued for other cellulitis and abscess (range 17 to 20 prescriptions per 1000 population) or symptoms involving skin and other integumentary tissue (range 8 to 16 prescriptions per 1000 population) (Figure S9).

Eras of stewardship

Prescribing for common infections in BC decreased overall in both eras of stewardship when compared with pre-stewardship levels of antibiotic use (Tables S1 and S2). Era I saw a 4% decline overall (RR 0.96, 95% CI 0.96–0.97) with a 24% decrease in era II (RR 0.76, 95% CI 0.76–0.76) when compared with pre-stewardship prescribing. The largest magnitudes of change were observed in paediatric populations with children aged 0–2 years prescribed 54% less (RR 0.46, 95% CI 0.46–0.46) by era II. A negative association was identified between increasing age and magnitude of decrease. Children aged 3–9 and those aged 10–18 years saw a 48% (RR 0.52, 95% CI 0.52–0.52) and 42% (RR 0.58, 95% CI 0.58–0.58) decrease in prescribing, respectively, in comparison to pre-stewardship levels. These paediatric age groups all experienced significant declines in era I as well, when compared with the pre-stewardship period (Table 2).

Changes in adult populations varied by age group, with our most senior age category, ≥80 years, experiencing increases in antibiotic use in both stewardship eras, when compared with pre-stewardship levels (era I: RR 1.17, 95% CI 1.17–1.18; era II: RR 1.12, 95% CI 1.11–1.12). Individuals aged 50–64 and 65–79 years saw minor increases in era I, when compared with pre-stewardship antibiotic use, however, adults between the ages of 19 and 49 years saw no significant changes in prescribing for era I. By contrast, in era II all adult age groups decreased in prescribing apart

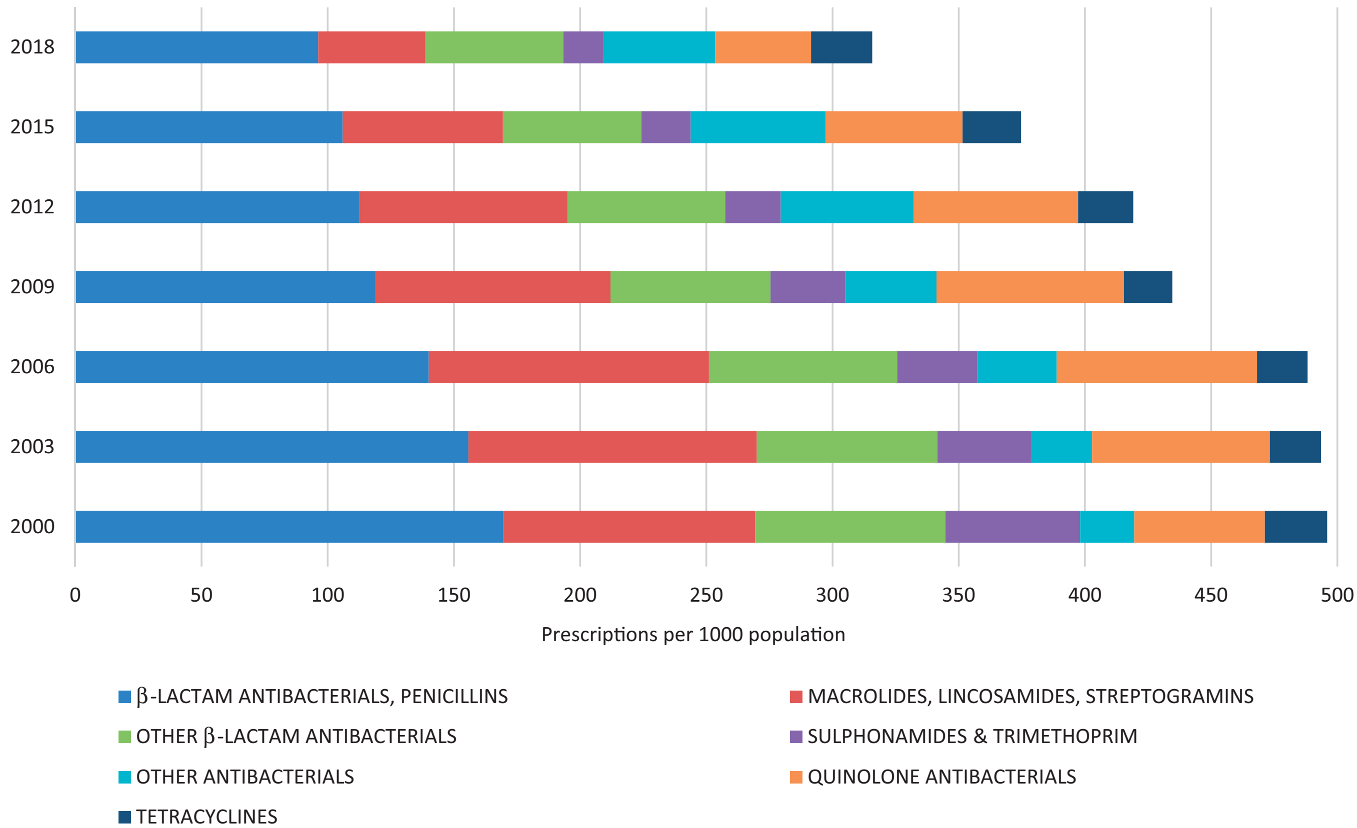


Figure 2. Antibiotic prescriptions in British Columbia by major ATC classification, 2000–18.

from our most senior category as described above. As in paediatrics, a negative association was identified between increasing age and magnitude of changes in prescribing.

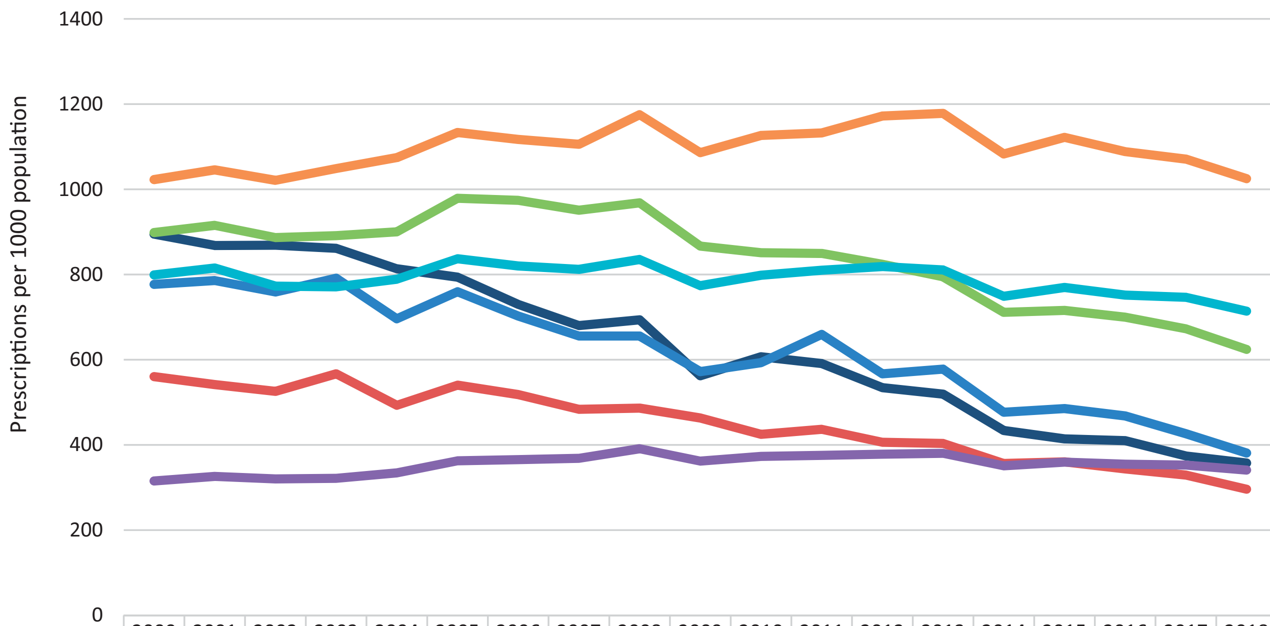
Discussion

Over a 19 year study period, more than 51 million prescriptions for antibiotics were dispensed, and by 2018 prescribing had decreased by 23.1% across the province. This downward trend was most pronounced for those aged between 0 and 49 years. In contrast, increases in prescribing rates were identified in those aged 65 years and above, while our eldest cohort of ≥80 years remained steady throughout the study period. As our cohort included an average of 1 374 222 unique patients in any given study year, the corresponding average of 2.7 million prescriptions per annum suggests that some individuals received multiple prescriptions, either through repeat clinician visits or multiple prescriptions per visit.

Notwithstanding an overall decrease in use, URTIs persist as the most prescribed indication in 2018, despite their self-limiting nature, viral aetiology and absence of guideline recommendations. Moreover, β-lactams and macrolides were the most prescribed classes across the study period. These findings suggest that the use of antibiotics in BC continues to decline overall, but as the misuse of antibiotics for respiratory tract infections has long been a hallmark target for stewardship intervention, their ongoing prescription demands increased scrutiny of prescriptions issued for their quality, as well as contributing patient and prescriber factors.

The prevalence of respiratory tract diagnoses as leading recipients of inappropriate or unnecessary antibiotic prescriptions has been corroborated across multiple geographic regions.[21,22,33] Fleming-Dutra *et al.* (2016)[21] identified sinusitis as the most prescribed indication in US ambulatory care. Regions of lower prescribing were not found to experience increased adverse consequences due to potential under treatment, moreover, residual levels of overprescribing were found. In Ontario (ON), another Canadian province, respiratory tract infections were again identified as the most prescribed category of indication.[34] Another ON study found approximately 25% of antibiotic prescribing either unnecessary or suboptimal across all indications.[22,35] With respect to URTI, bronchitis led inappropriate prescribing, with 52% of bronchitis-associated antibiotics issued unnecessarily.[22] Further investigation is underway to examine the quality of prescribing in terms of appropriate, suboptimal and inappropriate/unnecessary use in order to compare BC quality with other health authorities.[21,22,35,36]

The plateau in antibiotic use observed in our eldest cohort is not unique to BC, with other regions having reported similar elevated rates.[34,36] As this sub-population is especially vulnerable to adverse events and are more likely to experience concurrent comorbidities, delineating rates of overuse or misuse of antibiotics for older adults in BC is integral to calibrate stewardship interventions. Despite the positive implications of a decreasing trend overall, and the success achieved within BC paediatric populations, the failure to curb prescribing to those aged ≥65 years requires urgent intervention as the misuse of antibiotics within this population confers



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
0 - 2 YEARS	895	868	869	862	813	794	730	680	694	562	607	591	534	519	434	414	410	374	358
3 - 9 YEARS	777	786	759	791	696	760	703	656	656	572	593	659	567	578	476	485	468	426	381
10 - 18 YEARS	560	542	526	567	493	540	518	484	486	463	425	436	406	403	356	360	344	329	296
19 - 49 YEARS	898	916	887	891	900	979	974	951	968	867	851	849	824	794	711	716	700	672	624
50 - 64 YEARS	315	326	320	322	334	363	365	369	391	362	373	375	378	380	351	359	355	353	341
65 - 79 YEARS	799	815	773	771	789	837	820	812	835	774	798	810	819	811	749	770	752	747	714
≥80 YEARS	1023	1046	1021	1049	1074	1134	1117	1106	1175	1086	1126	1132	1172	1178	1083	1122	1089	1071	1025

Figure 3. Overall antibiotic use in British Columbia, stratified by age, 2000–18.

far greater patient risk. The risk posed relates to the ongoing contribution of antimicrobial misuse to bacterial resistance but also related to potential antibiotic related adverse events, including *Clostridioides difficile*.[37]

In 2016, it was reported that 30% of all antibiotic use in US ambulatory care is inappropriate.[21] Similar studies on prescribing quality in BC are underway, however, a paper from Hersh *et al.* (2021)[36] corroborates the age-specific trends reported here. Hersh *et al.*[36] describe immobility in quality of antibiotic use for adult populations with a concerning 2% decrease reported over a 5 year period. However, paediatrics has experienced a 41% relative reduction with optimizations attributed to stewardship interventions, including educational campaigns and updated clinical guidelines. Improvements in quality for US outpatient prescribing have been tied to antibiotics used to treat acute respiratory infections. Relatedly, prescribing for these infections in BC was found to have declined by 39% (RR 0.61) by 2018, with even more pronounced reductions for children (Table S2).

As reported by Glass-Kaastra *et al.* (2014),[38] prescribing in BC reflects some of the most conservative rates of antibiotic use in Canada. Following an internal review, the CAS programme has been found to have consistently met programme goals and objectives in disseminating critical information across the province.[4] At time of publication, McKay *et al.*[4] stipulated that further efforts were necessary to achieve clear population-level effects.

This study has limitations inherent to all retrospective studies using administrative health data. As the nature of our data prevents nested analyses, multiple prescriptions were permitted per individual, and our standard error may be biased. Further, our rates do not account for unfilled prescriptions issued, and levels of compliance to dispensed medications are unknown. Records of indications are reliant on accurate coding by billing physicians. However, it is notable that Canadian primary-care physician claims data have a high positive-predictive value for diagnosis of common infections including acute non-bacterial URTIs (0.84, 95% CI 0.81–0.88).[39] Further, as lab data did not confirm the presence of infection and comorbidity data were unavailable, our use of ICD-9 codes may be subject to misclassification bias.

Conclusions

Since 2000, the landscape of antimicrobial use has changed in BC, with a community antimicrobial stewardship programme working to disseminate provincial stewardship materials and promote a cultural shift towards the judicious use of antibiotics. Although this study cannot attribute causation, a substantial decline in antibiotic

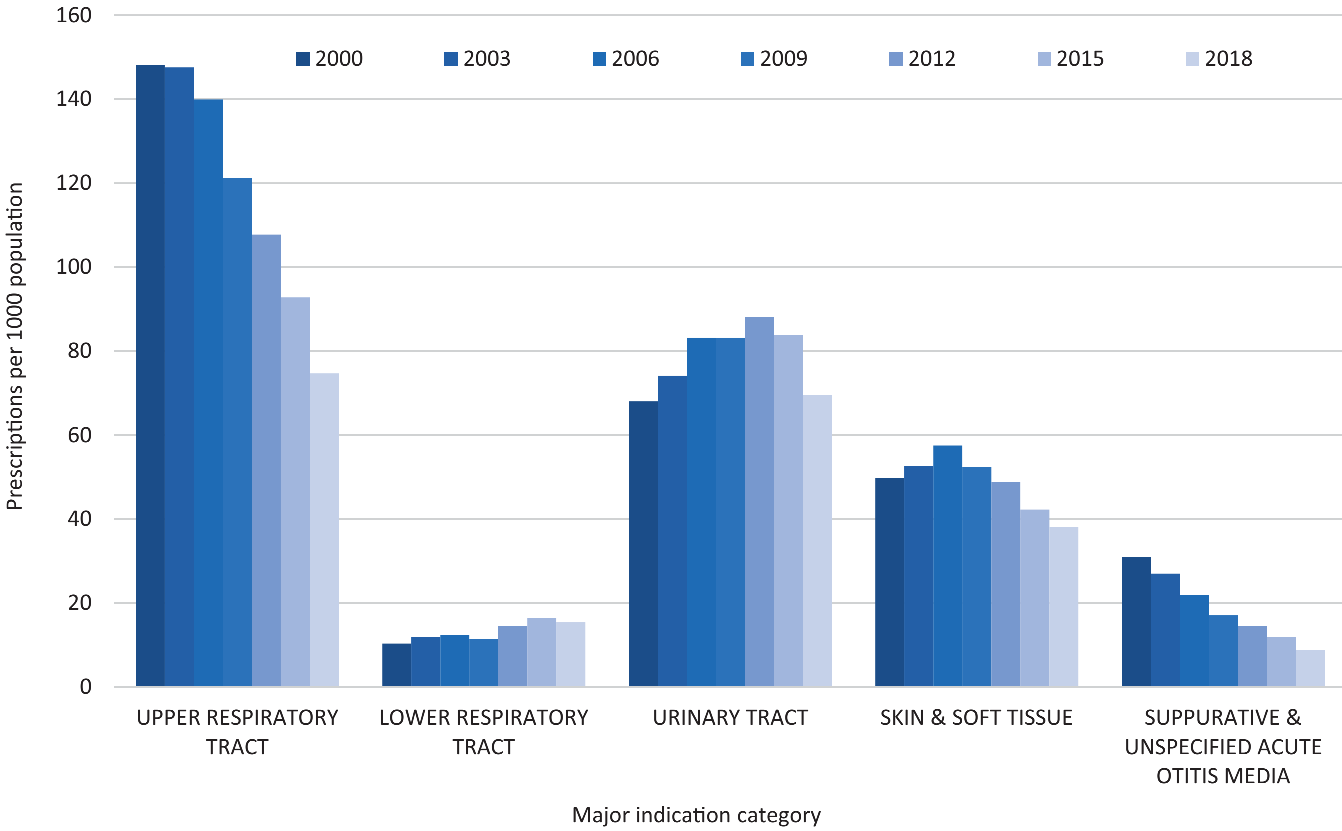


Figure 4. Antibiotic prescribing in British Columbia by categories of infection, 2000–18.

Table 2. Antibiotic use across eras of provincial stewardship in British Columbia, 2000–18

	Pre-stewardship, 2000–04		Stewardship era I, 2005–13		Stewardship era II, 2014–18		Rate ratios (95% CI)	
	N[a]	rate[b]	*N*	rate	*N*	rate	pre-stewardship versus stewardship era I	pre-stewardship versus stewardship era II
All ages	6 275 895	306	11 713 713	295	5 647 643	233	0.96 (0.96–0.97)	0.76 (0.76–0.76)
0–2 years	358 995	580	469 739	402	158 799	234	0.73 (0.73–0.74)	0.46 (0.46–0.46)
3–9 years	790 822	481	1 077 262	388	412 661	251	0.81 (0.81–0.81)	0.52 (0.52–0.52)
10–18 years	621 726	257	940 752	222	333 951	148	0.87 (0.86–0.87)	0.58 (0.58–0.58)
19–49 years	2 524 699	265	4 625 845	266	2 062 919	203	1.00 (1.00–1.00)	0.77 (0.76–0.77)
50–64 years	963 047	271	2 240 083	274	1 185 191	223	1.01 (1.01–1.01)	0.82 (0.82–0.83)
65–79 years	699 512	343	1 505 111	352	955 176	302	1.02 (1.02–1.03)	0.88 (0.88–0.88)
≥80 years	317 094	451	854 921	529	538 946	505	1.17 (1.17–1.18)	1.12 (1.11–1.12)

[a]Number of antibiotic prescriptions.
[b]Rate of prescribing per 1000 population.

use was observed in our 19 year study period, with temporal correlations between targeted stewardship eras and related optimizations in antibiotic use. Despite this progress, prescribing in our eldest cohorts is increasing, and optimizing prescribing to our most vulnerable population remains a provincial target. Moreover, URTIs are routinely prescribed in the wake of substantial evidence that antimicrobials do not confer a benefit against these self-limiting indications. Further research efforts to characterize the quality of prescriptions issued in BC, to complement the quantity in use examined here, are underway.

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Transparency declarations

Population Data BC subsidized funding for the data that were required for A.S.'s doctoral thesis project. The remainder of the data acquisition costs and a portion of A.S.'s salary were covered by the Canadian Institutes of Health Research project grant.

Author contributions

A.S. conceptualized the study under the guidance of F.M.; conducted the literature review, data cleaning, analysis and interpretation; and wrote the initial draft. A.S. drafted antibiotic case capture code and reviewed the manuscript. J.R. and S.S. provided guidance on confounding adjustment and sensitivity analyses. All authors provided critical feedback on data interpretation and the final draft of the manuscript.

Disclaimer

All inferences, opinions and conclusions drawn in this research are those of the authors and do not reflect the opinions or policies of the Data Steward(s) from Population Data BC.

Supplementary data

Tables S1 and S2 and Figures S1 to S9 are available as Supplementary data at *JAC-AMR* Online.

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