Interprovincial Variation in Antibiotic Utilization in Canada, 2019

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ABSTRACT

Background Antibiotic overuse is associated with antimicrobial resistance and poses a threat to global healthcare systems. Geographic trends in antibiotic prescribing also demonstrate regional variation in antibiotic overuse and antimicrobial resistance. This study's objective was to examine interprovincial variation in outpatient antibiotic dispensing in Canada in 2019.

Methods We conducted a cross-sectional study of antibiotic prescriptions dispensed in Canadian provinces in 2019, leveraging the IQVIA GPM database. We report annual rates of antibiotic dispensing as prescriptions per 1000 population. We included rates of overall antibiotic dispensing, broad-spectrum antibiotic dispensing and age-specific antibiotic dispensing in each province and nationally.

Results There were 622.7 antibiotic prescriptions per 1000 population dispensed nationally in 2019, with an interprovincial range of 539.0 prescriptions per 1000 population (British Columbia) to 925.0 prescriptions per 1000 population (Newfoundland and Labrador). The overall antibiotic dispensing rates in Newfoundland and Labrador and Saskatchewan (713.7 prescriptions per 1000 population) significantly exceeded the national rate, as did all age-specific rates in Newfoundland and Labrador (1007.1, 803.6 and 1210.5 prescriptions per 1000 population for children, adults and older adults, respectively, compared to national rates of 549.8, 557.2 and 938.9 prescriptions per 1000 population). Fluoroquinolone dispensing rates in Newfoundland and Labrador (86.4 prescriptions per 1000 population) and Québec (82.3 prescriptions per 1000 population) also significantly exceeded the national rate (56.8 prescriptions per 1000 population).

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Interpretation We identified interprovincial variation in antibiotic usage in Canadian provinces in 2019. These findings highlight the need for provincial antibiotic use targets to reduce antibiotic overuse and antimicrobial resistance.

BACKGROUND

Antimicrobial resistance is a recognized threat to human health both in Canada and internationally.(1,2) In the absence of meaningful intervention, it has been estimated that antimicrobial-resistant infections will overtake cancer as a leading cause of death and reduce global economic output by up to $100 trillion USD by 2050.(3) Antibiotic use is considered the most important driver of antimicrobial resistance.(4,5) With up to 50% of antibiotic prescribing being considered inappropriate or unnecessary, the risk posed by antibiotic use is modifiable.(6) Importantly, the success of interventions to combat antimicrobial resistance requires a comprehensive understanding of antibiotic use to identify problematic usage patterns and inform targeted interventions.(1)

Antimicrobial stewardship programs have been present in both community hospitals and large teaching centres in Canada for over a decade.(7,8) Since 2013, Accreditation Canada has considered their presence a required practice for organizations providing acute care services.(9) While these programs have reported benefits at the institutional level, approximately 92% of Canadian antibiotic use occurs in the community setting, where no such requirements exist and effective antimicrobial stewardship interventions are considerably more challenging to implement.(10) High priority opportunities for improved antibiotic prescribing in this setting include conditions for which antibiotics are overprescribed and conditions for which broad-spectrum

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antibiotics are overprescribed.(11) Therefore, surveillance of antibiotic use in the community should pertain to both overall antibiotic use and the use of specific high-risk agents.

Since Canadian healthcare is organized and delivered at the provincial level, community antimicrobial stewardship programs are frequently implemented at that same level.(12–14) Interprovincial variation in antibiotic use thus becomes a valuable indicator of the degree of unnecessary antibiotic prescribing. Understanding the degree of unnecessary antibiotic prescribing is essential to inform national targets for reduction of antibiotic use. The objective of this study was to describe interprovincial variation in antibiotic prescribing in the community setting in Canada in 2019.

METHODS

We conducted a cross-sectional analysis of antibiotic prescriptions in Canadian provinces from January 1, 2019 to December 31, 2019.

Data Sources

Prescription data were obtained from the IQVIA Geographic Prescription Monitor (GPM) database, which uses transactional data from a panel of retail pharmacies and estimates prescriptions at a geographic level using a patented geospatial projection methodology. GPM also leverages other IQVIA data assets (claims and distribution) as input into the projection methodology. The survey design yielded market-level yearly national estimates that have a sampling error of 6% for antibiotics. At the provincial level, the sampling error can reach slightly higher levels although it will not exceed 12%. While their methodology is proprietary, their data are used regularly for research purposes, and have been externally validated for some specific measures of antibiotic

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prescribing and utilization.(15–19) This study included oral antibiotics, which were sorted by drug class into 14 groups: first generation cephalosporins, second and third generation cephalosporins, second generation fluoroquinolones, third generation fluoroquinolones, lincosamides, macrolides, metronidazole, nitrofurantoin, narrow-spectrum penicillins, penicillins with beta-lactamase inhibitors, tetracyclines, trimethoprim and/or sulfonamides, vancomycin and other antibiotics (Table S1). Antitubercular agents were excluded from analysis.

Annual population estimates were obtained from Statistics Canada by province and age group.(20) For age group analyses, persons <18 years of age were defined as children, those 18-64 years of age were defined as adults and those >64 years of age were defined as older adults.

Statistical Analysis

We calculated the oral antibiotic prescription dispensing rate per 1000 population in 2019 by province and nationally for all included antibiotics. We reported overall dispensing rates, as well as dispensing rates for specific broad-spectrum antibiotics: macrolides, fluoroquinolones and penicillins with beta-lactamase inhibitors. Additionally, we calculated provincial and national dispensing rates stratified by age group. The Generalized Extreme Studentized Deviate (ESD) test was used to identify provincial dispensing rates that should be considered outliers when compared to the full distribution of provincial dispensing rates. The significance level used for analysis was α=0.05. Microsoft Excel was used for data cleaning and analysis and SAS was used for the statistical analysis.

RESULTS

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Provincial variation in antibiotic dispensing

Across Canada, a total of 23,406,646 antibiotic prescriptions were filled at outpatient pharmacies in 2019, at a rate of 622.7 prescriptions per 1000 population (Figure 1). Dispensing rates varied between provinces, from 539.0 prescriptions per 1000 population in British Columbia to 925.0 prescriptions per 1000 population in Newfoundland and Labrador. Saskatchewan (713.7 prescriptions per 1000 population) and Newfoundland and Labrador (925.0 prescriptions per 1000 population) had dispensing rates that significantly exceeded the national average ($p < 0.05$). Narrow-spectrum penicillins (28.6%), macrolides (14.0%), first-generation cephalosporins (9.1%), tetracyclines (7.6%) and penicillins with beta-lactamase inhibitors (7.6%) were the 5 most commonly prescribed antibiotic classes nationally in 2019 (S Table 2).

Broad-spectrum antibiotics

The national dispensing rates of fluoroquinolones, macrolides and penicillins with beta-lactamase inhibitors in 2019 were 56.8, 88.0 and 47.6 prescriptions per 1000 population, respectively. We observed a maximal interprovincial difference of 119% in the dispensing rate of fluoroquinolones (39.6 prescriptions per 1000 population in Prince Edward Island to 86.4 prescriptions per 1000 population in Newfoundland and Labrador), 119% in the dispensing rate of macrolides (57.6 prescriptions per 1000 population in British Columbia to 126.3 prescriptions per 1000 population in Newfoundland and Labrador) and 73% in the dispensing rate of penicillins with beta-lactamase inhibitors (40.7 prescriptions per 1000 population in British Columbia to 70.7 prescriptions per 1000 population in Newfoundland and Labrador; Figure 2). Fluoroquinolone dispensing rates in Québec and Newfoundland and Labrador were

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found to be significantly higher than the national rate of 56.8 prescriptions per 1000 population ($p < 0.05$), at 82.3 and 86.4 prescriptions per 1000 population, respectively. Trends in second generation fluoroquinolone dispensing did not differ from trends in total fluoroquinolone dispensing (Figure 2, S Figure 1A). When looking specifically at third generation fluoroquinolones, Ontario and Québec had the highest dispensing rates (S Figure 1B).

Age-specific trends in antibiotic dispensing

The national antibiotic dispensing rates for children, adults and older adults were 549.8, 557.2 and 938.9 prescriptions per 1000 population, respectively (Figure 3). The corresponding antibiotic dispensing rates of 1007.1, 803.6 and 1210.5 prescriptions per 1000 population in Newfoundland and Labrador exceeded the national antibiotic dispensing rates for each age group ($p < 0.05$). Narrow-spectrum penicillins, macrolides and first-generation cephalosporins were the most commonly prescribed antibiotics at the national level in all age groups (S Table 3).

INTERPRETATION

In this cross-sectional study, we observed variation in the patterns of antibiotic dispensing across Canadian provinces. We noted interprovincial variation in dispensing for broad-spectrum antibiotic classes, and within specific age groups. Our findings align with previous studies that have shown relatively high antibiotic dispensing rates in Newfoundland and Labrador, and relatively low dispensing rates in British Columbia.(10) The variation observed in this study has relevance to the development of national and provincial targets for reduction of antibiotic use in Canada.

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The observed national annual dispensing rate (623 prescriptions per 1000 population) in Canada is below the recently observed dispensing rate in the United States (791 per 1000 population), but substantially higher than recently observed European prescribing rates (563 in England, 450 in Norway and 285 per 1000 population in Sweden).(21–24) Both international and interprovincial variation in prescribing rates may be in part due to heterogeneity in stewardship initiatives. In British Columbia, where antibiotic use is consistently lower than other Canadian provinces, provincially funded stewardship programs in place since 2005 have led to a substantial reduction in antibiotic use.(25) Similarly, through the formal dedication of resources at the local and national level since 1995, Sweden has dramatically reduced national antibiotic use and antimicrobial resistance to some of the lowest levels in the world.(26) These findings highlight the importance of sustained dedication of resources to antimicrobial stewardship programs for long-term success, as well as substantial antibiotic over prescribing in most parts of the world. The differences in scope and timing of interventions are important to consider when analyzing interprovincial variation in antibiotic prescribing rates.

As the largest modifiable driver of antimicrobial resistance, there is an urgent need to reduce antibiotic use in Canada and globally. The United States, for example, was working towards the goal of reducing inappropriate antibiotic prescribing by 50% by 2020.(27) Due in part to the challenges associated with assessing prescription appropriateness at the population level, many European nations have targeted reductions in overall human antibiotic use of 15-50%.(23,28,29) While the challenges of assessing appropriateness apply to Canadian statistics as well, one Ontario-based

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study showed that at least 24% of antibiotic prescriptions written in primary care settings were for conditions for which antibiotics are never or rarely indicated, despite only assessing the appropriateness of 49% of antibiotics prescribed in the study period.(30) We suggest that while there is room for aggressive reduction in Canadian antibiotic use, targets should be evidence-based to ensure that reductions are achieved without causing patient harm.

Targets for Canadian antibiotic use should be developed for both overall antibiotic prescribing and for the prescribing of high-risk and broad-spectrum drug classes. We observed that while the overall dispensing rate in Québec was below the national average, the dispensing rates for all 3 broad-spectrum antibiotic classes of interest were above the national average. In Belgium, a country with historically high antibiotic use, the national target of a 50% reduction in total antibiotic consumption is accompanied by a targeted 4-fold reduction in fluoroquinolone consumption to 5% of total antibiotic consumption.(29) In our study, fluoroquinolones represented 9.1% of total antibiotic consumption nationally, and 13.5% of total antibiotic consumption in Québec. In Prince Edward Island, where the fluoroquinolone dispensing rate was the lowest in Canada, they still exceeded the Belgian target, at 6.2% of total antibiotic consumption. Compared to broad-spectrum agents, narrow-spectrum agents are favourable because they are less likely to provoke antimicrobial resistance.(31) Apart from resistance, fluoroquinolones also carry risk of *C. difficile* associated diarrhea, tendinopathy, peripheral neuropathy and central nervous system disorders.(32,33) Therefore, improving antibiotic use in the community setting should consider the reduction of overall prescribing and prescribing of high-risk and broad-spectrum antibiotics.

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An important consideration with respect to the development of antibiotic use targets is the variation in medical practice and patient demographics across jurisdictions. As medical needs vary across populations, it would therefore be prudent to consider variation in patient demographics when setting targets for antibiotic use. Interestingly, multiple studies have shown that inter-physician variability in antibiotic prescribing cannot be explained by patient factors alone.(34,35) Since a significant portion of variation occurs at the physician level, peer comparison feedback interventions for high-prescribing physicians are an important component of community antimicrobial stewardship programs.(11) In some jurisdictions, pay for performance targets have been developed to encourage primary care physicians to meet objectives.(36,37) As such, organizing community antimicrobial stewardship at the level of jurisdictional healthcare delivery allows the implementation of stewardship strategies that can motivate prescribers to adhere to principles of antimicrobial stewardship. In the Canadian context, this suggests that antimicrobial stewardship programs may be most successful at the provincial level, where they can better appreciate the health needs of the population and regional prescribing practices, with the authority to integrate stewardship strategies into the management and delivery of health care.

Several limitations of our study design warrant discussion. While Statistics Canada classifies children as 0-17 years of age, IQVIA includes 18-year old persons in this age group. Therefore, the age groups did not perfectly overlap between data sources, though the large age groupings were still able to capture trends in dispensing. Secondly, the IQVIA GPM database does not provide patient-level data. Therefore, we were unable to assess the appropriateness of prescriptions, as this data source does

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not capture individual-level information such as patient diagnoses. While the provincial level sampling error of the data source rarely exceeds 5 to 10%, recent estimates suggest that prescription projections in small jurisdictions may be subject to additional variability.(38) Lastly, though we compared the initiation and selection of antibiotics, this study did not assess duration of therapy, which is an easily modifiable indicator of inappropriate antimicrobial use.

CONCLUSION

We observed substantial variation in the rate of antibiotic dispensing across Canadian provinces and age groups, suggesting opportunity to reduce unnecessary antibiotic use across the country. Overall antibiotic dispensing rates were particularly high in Newfoundland and Labrador and Saskatchewan. In Québec, dispensing rates for broad-spectrum antibiotics exceeded the national average. Data from British Columbia should inform minimum benchmarks for antibiotic use targets for the other provinces, as, when compared internationally, it is likely that substantial overprescribing is occurring in all Canadian provinces. These data can also be used as a benchmark for future analyses of antibiotic use in Canadian provinces, and to inform prioritization of targeted stewardship projects.

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DISCLOSURES

No authors have any conflicts of interest to declare.

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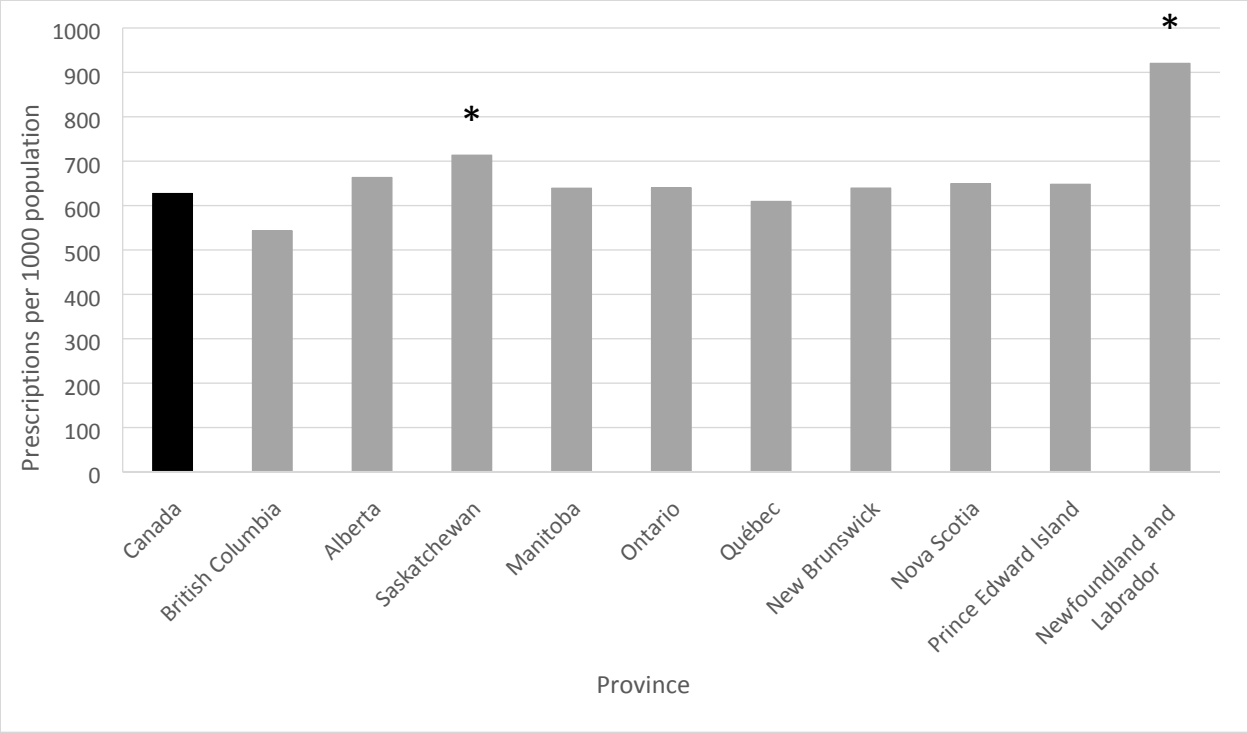

Figure 1. Rate of outpatient prescription of oral antibiotics per 1000 population in Canada in 2019, stratified by province. * indicates provincial rate is a significant outlier ($p<0.05$).

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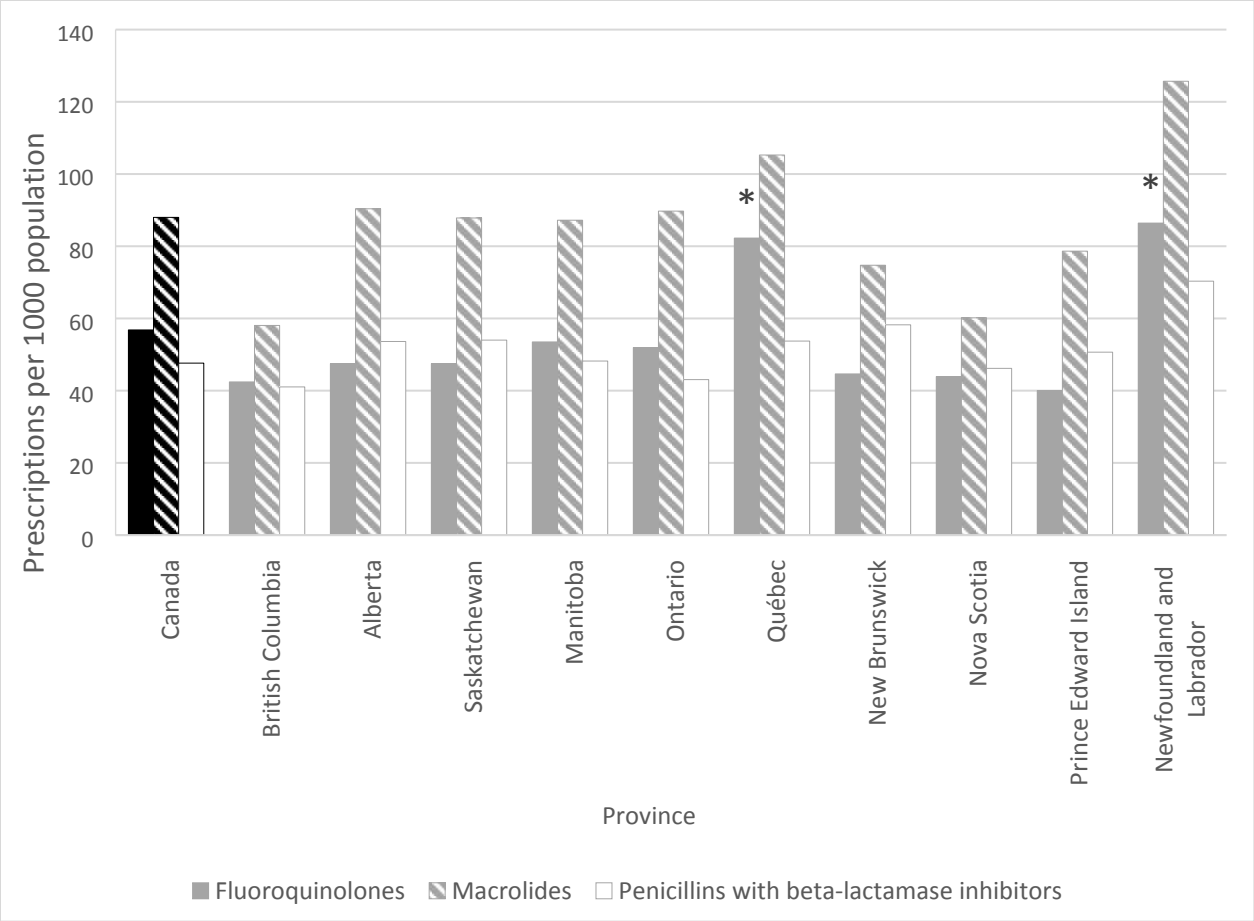

Figure 2. Rate of outpatient prescription of broad-spectrum oral antibiotics per 1000 population in Canada in 2019, stratified by class and province. * indicates provincial rate is a significant outlier ($p<0.05$).

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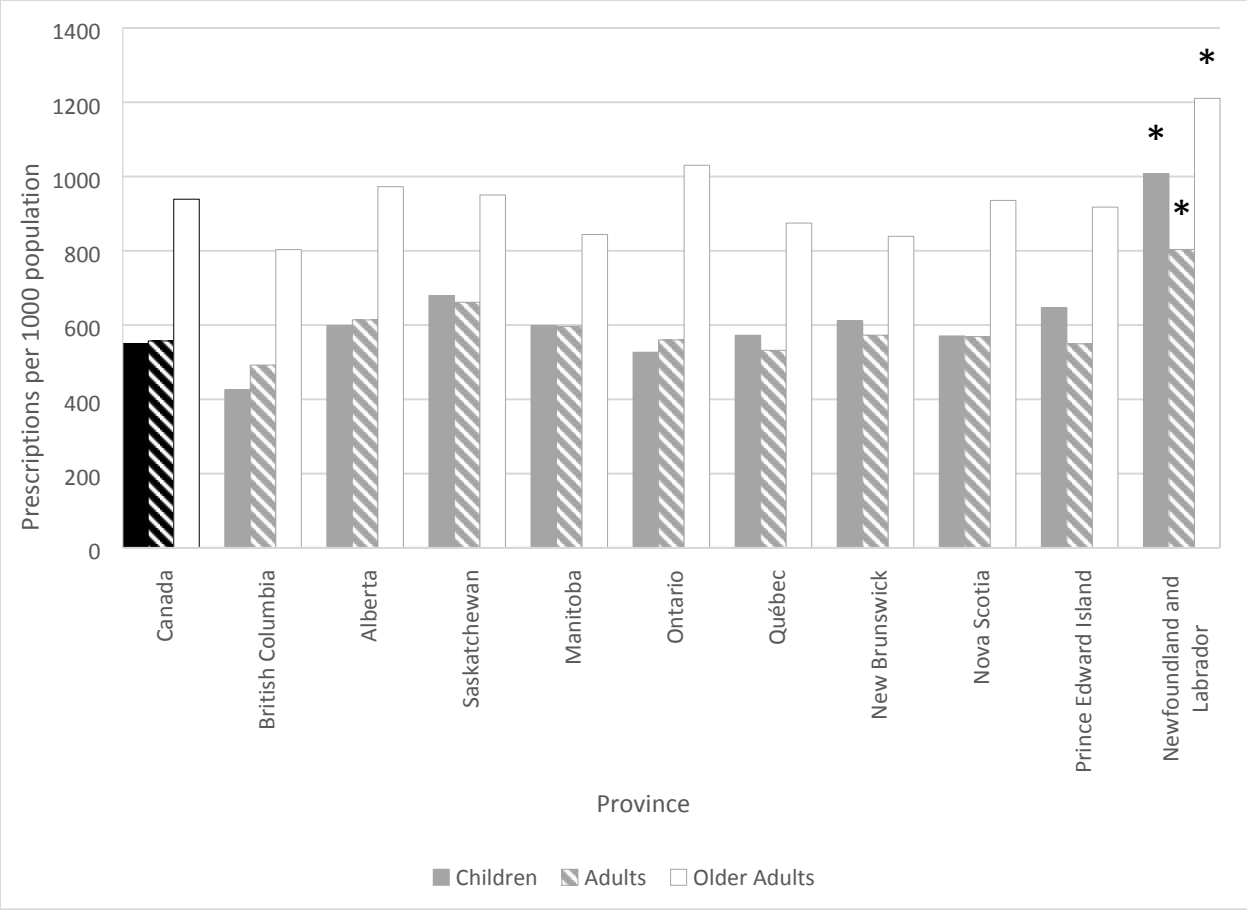

Figure 3. Rate of outpatient prescription of antibiotics per 1000 population in Canada in 2019, stratified by patient age group and province. * indicates provincial rate is a significant outlier ($p<0.05$).

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S Table 1. Oral outpatient antibiotic drugs and classes included in the study

Class	Drug
Cephalosporins (first generation)	Cefadroxil Cephalexin
Cephalosporins (second and third generation)	Cefaclor cefixime Cefuroxime Cefprozil
Fluoroquinolones (second generation)	Ciprofloxacin Norfloxacin Ofloxacin
Fluoroquinolones (third generation)	Gatifloxacin Levofloxacin Moxifloxacin
Lincosamides	Clindamycin
Macrolides	Azithromycin Clarithromycin Erythromycin Spiramycin
Metronidazole	Metronidazole
Nitrofurantion	Nitrofurantoin
Penicillins	Amoxicillin Ampicillin Cloxacillin Dicloxacillin Oxacillin Penicillin G potassium Penicillin V potassium
Penicillins with beta-lactamase inhibitors	Amoxicillin-clavulanate
Tetracyclines	Doxycycline Minocycline Tetracycline
Trimethoprim and/or sulfonamides	Sulfadiazine Sulfamethoxazole Sulfamethoxazole-trimethoprim Trimethoprim
Vancomycin	Vancomycin
Other antibiotics	Dapsone Fidaxomicin Fosfomycin

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Fusidic acid
Linezolid
Methenamine

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S Table 2. Rate of outpatient prescription of oral antibiotics per 1000 population in Canada in 2019, stratified by province, and class.

Province	Penicillins (narrow spectrum)	Macrolides	First generation cephalosporins	Tetracyclines	Penicllins with beta-lactamase inhibitors	Nitrofurantoin	Second generation fluoroquinolones	Trimethoprim and/or sulfonamides	Second or third generation cephalosporins	Metronidazole	Lincosamides	Third generation fluoroquinolones	Vancomycin	Other
National	178.3	87.3	56.9	47.4	47.3	41.5	40.7	32.2	22.7	22.6	17.4	15.7	1.1	11.5
British Columbia	147.8	57.6	56.6	56.7	40.7	41.9	32.9	25.3	22.8	20.9	16.4	9.2	1.1	9.2
Alberta	206.9	89.6	65.2	58.3	53.2	36.3	34.9	24.6	24.7	25.4	18.9	12.2	0.8	7.1
Saskatchewan	206.6	87.5	87.0	74.9	53.8	57.1	35.8	38.0	10.4	23.5	19.1	11.5	0.5	5.5
Manitoba	189.8	86.7	73.6	46.9	47.9	38.2	38.0	45.2	11.6	20.6	18.9	15.2	0.5	2.5
Ontario	199.0	89.0	60.6	33.6	42.7	47.7	33.9	32.5	23.1	25.8	16.5	17.6	0.6	12.2
Québec	136.9	104.6	37.2	48.7	53.4	29.9	61.9	36.2	20.8	17.3	18.1	19.9	2.4	18.4
New Brunswick	159.9	74.4	57.7	73.8	57.9	42.7	33.0	33.2	46.2	19.9	20.4	11.4	0.8	5.1
Nova Scotia	187.7	59.8	70.3	80.1	45.9	50.7	30.7	32.8	30.6	21.8	16.4	13.0	0.7	5.1
Prince Edward Island	178.4	77.7	61.9	93.4	50.1	47.3	28.4	27.5	24.8	18.6	14.5	11.1	0.6	6.3
Newfoundland and Labrador	288.9	126.3	80.8	62.5	70.7	60.2	72.2	50.3	40.6	32.2	23.0	14.7	0.9	1.8

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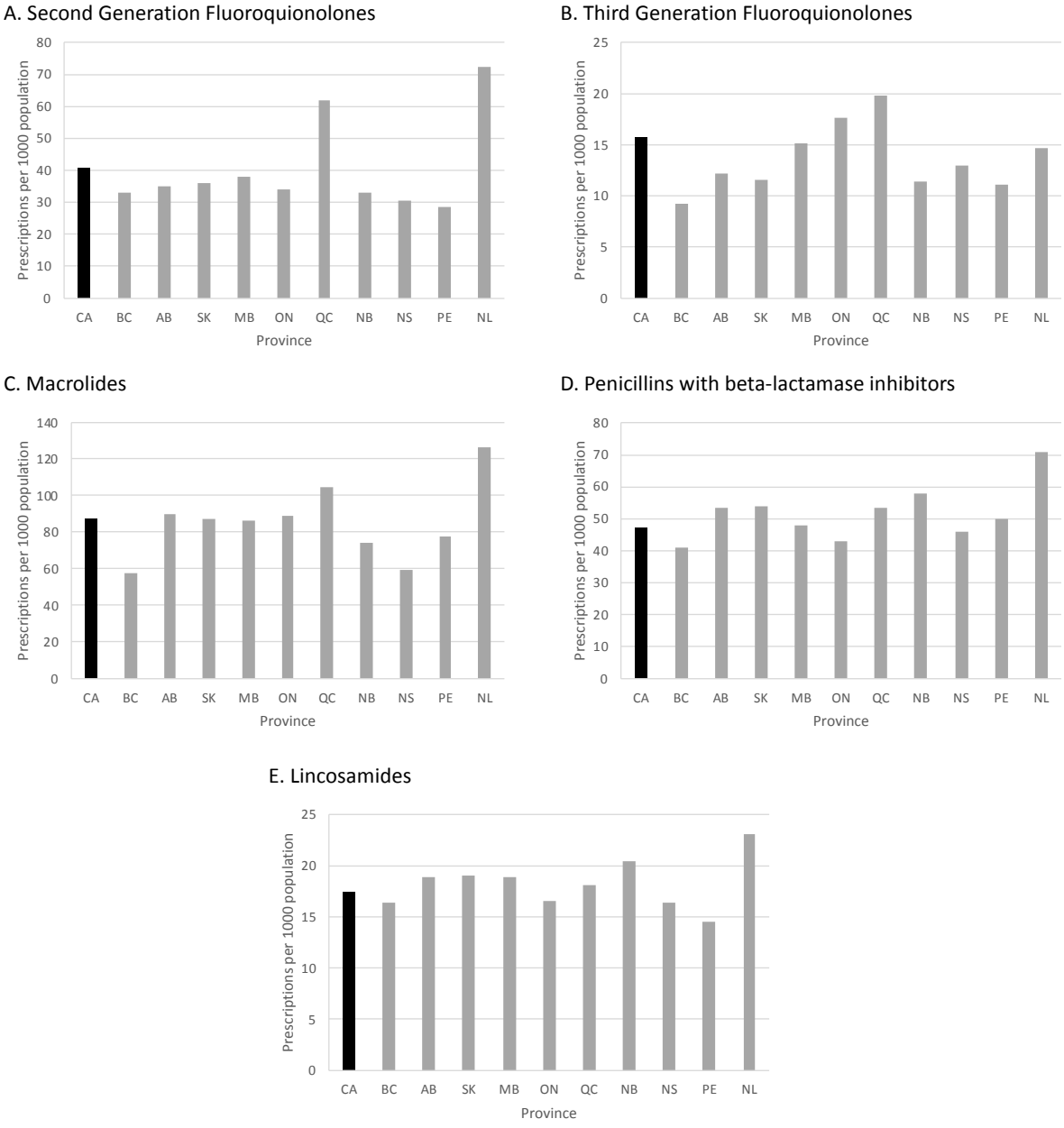
S Table 3. Rate of outpatient prescription of oral antibiotics per 1000 population in Canada in 2019, stratified by patient age, province, and class.

Age Group	Province	Penicillins (narrow spectrum)	Macrolides	First generation cephalosporins	Tetracyclines	Penicllins with beta-lactamase inhibitors	Nitrofurantoin	Second generation fluoroquinolones	Trimethoprim and/or sulfonamides	Second or third generation cephalosporins	Metronidazole	Lincosamides	Third generation fluoroquinolones	Vancomycin	Other
Children	National	304.5	86.3	38.3	23.0	34.8	7.2	3.0	10.9	29.5	3.8	6.6	0.7	0.1	1.2
	British Columbia	246.3	56.2	38.0	21.5	21.3	7.3	2.1	6.9	15.5	3.3	6.0	0.4	0.1	0.9
	Alberta	331.6	102.1	41.4	26.8	39.1	7.3	2.8	9.1	25.3	3.8	7.2	0.8	0.1	0.7
	Saskatchewan	371.5	112.9	72.7	26.6	37.2	11.5	2.3	16.3	15.1	3.8	8.6	0.6	0.1	0.4
	Manitoba	349.8	91.4	60.8	19.1	24.0	6.0	2.2	13.7	18.3	3.5	9.4	0.4	0.1	0.2
	Ontario	305.4	76.2	38.1	20.6	23.0	7.5	2.5	9.4	32.3	4.0	6.2	0.7	0.1	1.1
	Québec	277.7	104.1	25.7	25.7	63.8	5.2	5.1	13.4	38.5	3.6	6.5	0.9	0.1	2.4
	New Brunswick	325.3	99.1	41.8	22.3	29.6	10.0	2.8	15.9	49.1	3.6	9.1	1.8	0.1	0.6
	Nova Scotia	351.9	61.9	40.1	24.0	22.1	10.0	2.1	13.9	33.1	4.2	6.2	0.5	0.2	0.5
	Prince Edward Island	381.9	110.3	38.2	22.3	37.0	9.1	1.7	11.7	24.4	3.4	5.2	0.5	0.3	0.4
	Newfoundland and Labrador	634.8	155.8	60.9	28.6	44.4	12.7	3.7	33.8	19.9	4.7	7.4	0.3	0.1	0.2
Adults	National	142.9	80.3	51.3	48.2	43.6	39.5	37.2	28.2	16.0	27.9	19.4	12.1	0.6	10.0
	British Columbia	123.4	52.9	53.8	55.9	39.8	40.6	27.9	23.5	16.7	24.8	17.8	6.7	0.7	7.7
	Alberta	163.7	82.3	62.8	63.3	53.5	39.0	33.6	24.2	19.5	32.4	21.1	10.8	0.7	7.1
	Saskatchewan	160.1	75.3	83.2	81.9	53.9	59.8	31.6	40.5	7.0	31.1	22.3	9.3	0.5	4.9
	Manitoba	143.2	81.3	70.6	51.4	52.0	38.3	36.1	49.4	8.7	27.5	21.5	14.0	0.4	2.3
	Ontario	162.1	84.2	51.9	34.4	39.9	44.4	28.2	28.1	15.8	30.9	17.2	12.7	0.4	10.0
	Québec	105.7	93.0	33.5	48.9	43.1	26.2	62.8	27.8	13.1	21.9	22.1	16.0	1.0	16.8
	New Brunswick	126.7	67.5	52.1	73.3	54.8	42.9	28.8	29.1	34.3	24.9	24.5	8.9	0.6	4.4
	Nova Scotia	150.2	60.6	59.7	72.4	41.4	46.8	25.7	28.5	24.0	27.1	18.6	9.3	0.5	4.3
	Prince Edward Island	127.4	69.2	57.6	87.2	44.2	45.6	25.2	24.6	16.4	22.8	16.6	8.7	0.4	3.9
	Newfoundland and Labrador	220.0	108.5	74.1	60.5	66.9	55.2	62.8	44.2	32.6	38.4	27.6	10.5	0.7	1.6
Older Adults	National	167.9	113.8	97.2	71.0	74.0	86.3	94.7	70.2	39.8	24.5	22.1	45.3	3.9	28.2
	British Columbia	141.5	75.1	83.0	91.3	61.6	77.9	78.5	48.3	50.6	23.3	21.0	25.8	3.3	22.1
	Alberta	208.2	104.5	116.3	87.0	75.3	71.8	94.9	52.5	48.6	27.5	27.5	37.8	2.9	17.9
	Saskatchewan	143.9	97.5	122.7	118.8	77.7	113.6	101.6	60.2	16.5	23.2	21.7	36.3	1.2	15.3
	Manitoba	143.2	101.3	103.9	69.4	66.6	84.0	97.2	74.2	13.5	18.0	22.5	41.3	1.7	7.1
	Ontario	218.3	120.7	117.8	45.2	74.9	104.0	89.4	74.3	40.0	31.1	25.6	54.6	2.0	32.6
	Québec	101.0	142.4	60.2	70.3	76.3	65.7	113.8	85.5	28.5	15.7	16.8	50.8	9.0	39.0
	New Brunswick	119.3	73.6	86.7	117.3	90.4	68.9	70.2	59.3	78.0	18.8	17.8	26.2	1.9	10.7
	Nova Scotia	165.2	55.8	126.8	149.4	78.8	96.1	69.1	61.0	48.2	20.3	17.9	34.2	1.7	11.3
	Prince Edward Island	140.9	73.0	98.4	180.8	80.9	89.5	64.2	51.5	51.0	20.5	17.0	29.0	1.3	19.5
	Newfoundland and Labrador	217.9	154.6	115.5	94.4	101.9	111.7	152.4	81.0	79.9	35.5	22.2	37.9	2.0	3.7



S Figure 1. Rate of outpatient prescription of broad-spectrum oral antibiotics per 1000 population in Canada in 2019, stratified by class and province. CA = Canada; BC = British Columbia; AB = Alberta; SK = Saskatchewan; MB = Manitoba; ON = Ontario; QC = Québec; NB = New Brunswick; NS = Nova Scotia; PE = Prince Edward Island; NL = Newfoundland and Labrador.