**Article details: 2021-0095**

**Title:** Interprovincial variation in antibiotic utilization in Canada, 2019: a retrospective cross-sectional study
**Authors:** Michael Crosby MSc PharmD, Teagan Rolf von den Baumen BSc PharmD, herry Chu MSc, Tara Gomes MHSc PhD, Kevin L. Schwartz MD MSc, Mina Tadrous PharmD MS PhD

**Reviewer 1:** Kevin Afra
**Institution:** Department of Medicine, Fraser Health Authority
General comments (author response in bold)

Thank you for submitting this manuscript.

Antimicrobial stewardship in the outpatient setting is an important topic. The authors provide a description of outpatient antimicrobial prescriptions across the Canadian Provinces, with subgrouping by age and antimicrobial. A statistical approach is employed to identify outliers.
**We thank the reviewer for this comment.**

I have several comments for the authors to consider:

1. National antimicrobial use metrics are published regularly by PHAC in their Canadian Antimicrobial Resistance Surveillance System reports. The same IQVIA database is used by PHAC. How does this manuscript add to what is already known from the PHAC reports?
**We thank the reviewer for this question. This manuscript builds on the most recent Canadian Antimicrobial Resistance Surveillance System (CARSS) report in the following ways:**
**1. our manuscript uses 2019 data, whereas the 2020 CARSS report published 2018 data;**
**2. our manuscript includes provincial comparisons of antimicrobial use that are stratified by age group, whereas the CARSS report publishes age-stratified antimicrobial use at the national level.**
**3. our manuscript uses a statistical approach to assess the significance of interprovincial variation;**
**4. we have generated detailed tables of antimicrobial prescription volume stratified by province, drug class and age group to support future work in this space.**

2. Why were DDDs not reported? This would also account for prescription duration rather than solely number of prescriptions.
**We thank the reviewer for this question. We appreciate the value of the DDD as a metric which can be used to benchmark within and/or between institutions. When used as a measure of overall antibiotic use, however, the aggregate of DDDs is prone to several limitations. First, DDD dosing do not always reflect regional and up-to-date recommended doses for optimization of antibiotic activity. This issue can be compounded by regional differences in antibiotic selection. Further, the DDD can be inaccurate in certain populations, particularly pediatrics and renal impairment. While we believe that the DDD is a valuable metric for comparing**

**specific drugs, we believe that the use of the DDD at the level of overall antibiotic use within a population presents numerous utility-limiting challenges.**

3. I appreciate the statistical approach to identify antimicrobial use outliers amongst the provinces by total and various subgroups. The authors use the generalized extreme Studentized deviate test to identify outliers. This statistical test is not recommended with samples of less than 25 (and particularly not for samples of less than 15). See following references:
-https://www.itl.nist.gov/div898/handbook/eda/section3/eda35h3.htm
-https://www.jstor.org/stable/1268549?seq=1

Could you comment on why you feel this statistical test is valid when making comparisons across 10 provinces?
**We appreciate this comment. As recommended by reviewer #2, we have revised our statistical approach. We have identified outliers using Poisson models, an approach that is more appropriate for this data set. Overall, the Poisson models showed similar results. All results found to be statistically significant using the GESD test were found to be statistically significant using our Poisson models. The Poisson models identified a number of additional statistically significant results, including the overall dispensing rate in British Columbia, the dispensing rates of macrolides in British Columbia, Nova Scotia and Newfoundland and Labrador and a number of age-stratified dispensing rates. The results section of the manuscript was revised accordingly.**

**1. Revised text (Results): Dispensing rates varied between provinces, from 543.3 prescriptions per 1000 population in British Columbia to 920.5 prescriptions per 1000 population in Newfoundland and Labrador. The type III test for overall variation yielded $p < 0.001$. Full model results are available in S Table 4. Saskatchewan (713.7 prescriptions per 1000 population, $p = 0.018$) and Newfoundland and Labrador (920.5 prescriptions per 1000 population, $p < 0.001$) had dispensing rates that significantly exceeded the national rate (Figure 1). British Columbia (543.3 prescriptions per 1000 population, $p = 0.014$) had a dispensing rate significantly below the national rate (Figure 1).**

**2. Revised text (Results): 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 (Figure 2). The type III test for overall variation in fluoroquinolone and macrolide dispensing rates both yielded $p < 0.001$. For penicillins with beta-lactamase inhibitors, the test yielded $p = 0.274$. Full model results are available in S Table 4. Dispensing rates for fluoroquinolones and macrolides in Newfoundland and Labrador significantly exceeded the national rates (86.4 prescriptions per 1000 population for fluoroquinolones, $p = 0.014$; 125.7 prescriptions per 1000 population for macrolides, $p = 0.010$) (Figure 2). The fluoroquinolone dispensing rate in Québec (82.3 prescriptions per 1000 population, $p = 0.031$) significantly exceeded the national dispensing rate (Figure 2). Trends in second generation fluoroquinolone dispensing did not differ from trends in total fluoroquinolone dispensing (Figure 2, S Figure 1A). Third generation fluoroquinolone dispensing was highest in Ontario and Québec (S Figure 1B). Macrolide dispensing rates in British Columbia (58.1 prescriptions per 1000 population, $p = 0.014$) and Nova Scotia (60.2**

**prescriptions per 1000 population, p = 0.023) were significantly below the national rate (Figure 2).**

**3. Revised text (Results): 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 type III test for overall variation in dispensing rates within all three age groups yielded p < 0.001. Full model results are available in S Table 4. The corresponding antibiotic dispensing rates of 1007.1, 803.6 and 1210.5 prescriptions per 1000 population in Newfoundland and Labrador all significantly exceeded the national antibiotic dispensing rates for each age group (p < 0.001 for each; Figure 3). The age group-specific rates of 425.8, 492.3 and 803.2 prescriptions per 1000 population in British Columbia were all significantly below the corresponding national rates (p < 0.001, p = 0.046, p = 0.001; Figure 3). Dispensing rates for children (679.5 prescriptions per 1000 population, p < 0.001) and adults (661.4 prescriptions per 1000 population, p = 0.003) in Saskatchewan significantly exceeded the national rate (Figure 3). The dispensing rate for children in Prince Edward Island (646.3 prescriptions per 1000 population, p = 0.005) significantly exceeded the national rate (Figure 3). The dispensing rate for older adults in Ontario (1030.3 prescriptions per 1000 population, p = 0.040) significantly exceeded the national rate, while the rate in New Brunswick (839.0 prescriptions per 1000 population, p = 0.018) was significantly below the national rate (Figure 3).**

4. Are health authority/hospital operated long term care prescription data included in this dataset? Such prescriptions would usually be dispensed by hospital pharmacies, not community pharmacies. This potential measurement error could make interpretation of antimicrobial use amongst older adults difficult, particularly across different jurisdictions and health system structures.
**We thank the reviewer for this question. Interprovincial differences in models of care and health system structure could result in situations where antimicrobials for certain patient groups are dispensed through community pharmacies in one jurisdiction and through hospital pharmacies in another. We have revised our manuscript to include this limitation.**
**Revised text (Interpretation): Hospital-operated long-term care facility prescriptions are likely not captured in our dataset, as they are likely dispensed through hospital pharmacies, contributing a potential confounding factor to our results as provinces may leverage differing mechanisms for dispensing drugs.**

**Reviewer 2:** Simon Otto
**Institution:** School of Public Health, University of Alberta
General comments (author response in bold)

This is an interesting and well-written paper on antimicrobial dispensing patterns (by prescriptions) across Canadian provinces in 2019. The fact that the data are from retail pharmacies is good because it represents actual prescriptions dispensed to patients, rather than prescriptions provided to patients by doctors, which do not necessarily represent actual dispensation/use.
**We thank the reviewer for this comment.**

I do, however, have some concerns with the statistical methods. I strongly recommend that the authors run the analysis using Poisson models for all comparisons (see my comments below). I took the overall dispensing rate data and set up a Poisson model that worked nicely.
**We appreciate this suggestion, and the reviewer's effort in setting up a Poisson model to test our data. We have taken this suggestion and switched to Poisson models for our statistical analysis. Overall, the Poisson models showed similar results. All results found to be statistically significant using the GESD test were found to be statistically significant using our Poisson models. The Poisson models identified a number of additional statistically significant results:**

- **-the overall dispensing rate in British Columbia**
- **-the dispensing rates of macrolides in British Columbia, Nova Scotia and Newfoundland and Labrador**
- **-the dispensing rates for children in British Columbia, Saskatchewan and Prince Edward Island**
- **-the dispensing rates for adults in British Columbia and Saskatchewan**
- **-the dispensing rates for older adults in British Columbia, Manitoba, Ontario and New Brunswick**

**We have revised our results section accordingly, as highlighted in our response to reviewer #1 (see previous response).**

Page 3 - Line 19: Define GPM in the abstract - it is defined in the Methods but should also be defined here.
**We have revised the Abstract to define GPM.**

***Revised text (Abstract): We conducted a cross-sectional study of antibiotic prescriptions dispensed in Canadian provinces in 2019, leveraging the IQVIA Geographic Prescription Monitor (GPM) database.***

Page 3 - Lines 35-40: The NL estimate is missing from the abstract, but should be included to mirror the text for the estimates from each province like are present in Page 7 Lines 15-20. It appears that only the SK estimate is included in the abstract.
**We thank the reviewer for this comment. We have revised our manuscript accordingly.**

***Revised text (Abstract): Overall antibiotic dispensing rates in Newfoundland and Labrador (920.5 prescriptions per 1000 population) and Saskatchewan (713.7 prescriptions per 1000 population) significantly exceeded the national rate, while the rate in British Columbia (543.3 per 1000 prescriptions per 1000 population) was significantly below the national rate.***

**Page 4 - Lines 14-20: We all know about this report, and it is an important document, albeit with some concerns about how the estimates were derived. I suggest that the more recent, Canadian-focused document from the CCA with Canadian economic estimates might be better placed to set up the study than the O'Neill report. CCA report: https://cca-reports.ca/wp-content/uploads/2018/10/When-Antibiotics-Fail-1.pdf**

**We thank the reviewer for this suggestion and have replaced the O'Neill report estimates with Canadian-focused estimates from the CCA report in our introduction.**

***Revised text (Introduction): A recent report estimates that antimicrobial resistance was directly responsible for 5,400 deaths and $1.4 billion in healthcare costs in Canada in 2018.(3)***

Page 4 – Lines 23-27: Suggest providing context for this statement - 50% of prescribing in the US (based on reference 6).
**We thank the reviewer for this comment. We have added geographical context to this statement.**

***Revised text (Introduction): An American study estimates that up to 50% of antibiotic prescribing is inappropriate or unnecessary, suggesting that the risk posed by antibiotic use is modifiable.(6)***

Page 5 – Lines 28-31: please clarify that this is in all ten Canadian provinces and that the there are no data from the three territories.
**This statement was revised for clarity.**

***Revised text (Methods): We conducted a cross-sectional analysis of antibiotic prescriptions in Canadian provinces from January 1, 2019 to December 31, 2019. This analysis captured prescriptions from all ten Canadian provinces and no Canadian territories.***

Page 6 – Lines 42-48: I am intrigued and a bit concerned by the use of the GESD test to detect outliers as the authors' chosen statistical test. Do the data meet the test assumption of normality? Also, in the results (see my next comment), the authors state that the significant outliers are higher than the Canadian overall dispensing rate, but the methods as stated, say that the outlier detection is considered among the provincial dispensing rates. This does not make sense. More importantly, I would like to know why the authors did not consider a Poisson model to look at differences in prescribing rates between provinces. I set up the data myself (total dispensations per 1,000 by province) and a Poisson model runs nicely and would allow for statistical comparisons between high and low provinces, or comparison to the Canadian overall rate, as they state in their results. I strongly recommend the authors rerun the analysis as Poisson models for all comparisons and report relevant comparisons. It is more robust than the GESD test. For example, when I run this model including an estimate for Canada as the referent, SK and PEI are significantly higher than the Canadian overall rate, BC is significantly lower (for overall dispensation), and the rest of the provinces do not differ statistically. If the Canadian estimate is excluded, all 9 other provinces have statistically significantly higher AMU dispensation that BC. Hence my concern with limiting the comparison to the GESD detection of outliers.
**We appreciate the reviewer's statistical rigor. As mentioned above, our revised manuscript includes Poisson models for statistical analysis, comparing provincial rates of dispensing to the Canadian rate. Overall, the Poisson models showed similar results. All results found to be statistically significant using the GESD test were found to be statistically significant when using our Poisson models to compare provincial dispensing rates to the corresponding national rates. The Poisson models identified a number of additional results which were statistically**

**significantly different from the corresponding national rate of dispensing, including the overall dispensing rate in British Columbia, the dispensing rates of macrolides in British Columbia, Nova Scotia and Newfoundland and Labrador and a number of age-stratified dispensing rates. We revised the results section of our manuscript to reflect these changes, as detailed above.**

Page 7 – Lines 15-19 + Page 8 – Lines 3-5: based on the GESD test, the authors state that provinces identified as statistically significant outliers that "had dispensing rates that significantly exceeded the national average" or that were "significantly higher than the national rate of…". First, in Page 7 (Lines 19-20) – it is not a national average, it is an overall national rate. I may not completely understand how the GESD test works, but as the authors describe it in the methods, it detects significant outliers in the dataset, which in this case is each provincial dispensing rate. I am confused why authors then state that these outliers are significantly higher than the national overall rate. To me, it means that the test indicates that these results are significant outliers in that they are higher than the other group of provincial results. This inherently makes me uncomfortable with the GESD method and goes back to my question of this as the chosen statistical method that needs to be addressed. I think a Poisson model is a much better approach. Once run, the authors will need to include tables of the Poisson output (e.g., Incidence Rate Ratios, p-values and 95% confidence intervals for each province compared to the referent province for the dispensing value in question – overall, by drug, stratified by age, etc). The authors should also test the overall significance for the provincial indicators for each Poisson model. It was significant for the overall dispensation Poisson model that I ran. Lastly, they should assess Poisson model fit for the data using accepted methods. I have attached a document with screen shots of the model I set up for overall dispensing rates for reference (data derived from adding up dispensing by drug from S Table 2).
**Our revised statistical analysis is based on a Poisson model. We have included tables of the Poisson output in S Table 4. Our models used the national rate as the referent, and thus, our results discuss provincial rates which exceeded or fell below the national rate.**

Results section: I am not sure that reporting the maximal interprovincial differences (%) adds much to the manuscript. I like that the authors have included some bar graphs to show the provincial trend in numbers, and I like that they have included the raw data in tables (it allowed me to look at the Poisson model). They will need room to discuss the Poisson models, so I suggest they remove the text about maximal interprovincial differences and include interprovincial comparisons from their Poisson models. It will make the paper much stronger. I don't know how this will impact their interpretations, but this is an important point to make their analysis more robust.
**We thank the reviewer for this suggestion and have revised our manuscript accordingly.**

***Revised text (Results)*: *Significant interprovincial variability was observed for all drug classes. Dispensing rates for all three drug classes in Newfoundland and Labrador significantly exceeded the national rates (86.4 prescriptions per 1000 population for fluoroquinolones, p = 0.014; 125.7 prescriptions per 1000 population for macrolides, p = 0.010; 70.3 prescriptions per 1000 population for penicillins with beta-lactamase inhibitors, p = 0.038). The fluoroquinolone dispensing rate in Québec (82.3 prescriptions per 1000 population, p = 0.031) significantly exceeded the national dispensing rate. Trends in second generation***

***fluoroquinolone dispensing did not differ from trends in total fluoroquinolone dispensing (Figure 2, S Figure 1A). Third generation fluoroquinolone dispensing was highest in Ontario and Québec (S Figure 1B). Macrolide dispensing rates in British Columbia (58.1 prescriptions per 1000 population, p = 0.014) and Nova Scotia (60.2 prescriptions per 1000 population, p = 0.023) were significantly below the national rate.***

***Revised text (Results): The age group-specific rates of 425.8, 492.3 and 803.2 prescriptions per 1000 population in British Columbia were all significantly below the corresponding national rates (p < 0.001, p = 0.046, p = 0.001). Dispensing rates for children (679.5 prescriptions per 1000 population, p < 0.001) and adults (661.4 prescriptions per 1000 population, p = 0.003) in Saskatchewan significantly exceeded the national rate. The dispensing rate for children in Prince Edward Island (646.3 prescriptions per 1000 population, p = 0.005) significantly exceeded the national rate. The dispensing rate for older adults in Ontario (1030.3 prescriptions per 1000 population, p = 0.040) significantly exceeded the national rate, while the rate in New Brunswick (839.0 prescriptions per 1000 population, p = 0.018) was significantly below the national rate.***

Page 10 – Lines 21-27: to my previous point, the authors make comments about the overall dispensing rate in Quebec being lower than the national average, but higher for all three broad spectrum antibiotics. The Poisson model that I ran showed that the Quebec overall rate did not differ significantly from the Canadian rate.
**We have revised our manuscript accordingly. The statement highlighted by the reviewer, which referred to an overall dispensing rate in Québec that was nominally lower than the national average has been removed. All references to differences between provincial and national rates now reflect differences observed from Poisson models. Overall, the Poisson models showed similar results. All results found to be statistically significant using the GESD test were also found to be statistically significant in our Poisson models. We revised the results section of our manuscript accordingly.**

***Revised text (Interpretation): We observed that while the overall dispensing rate in Québec was similar to the national rate, the provincial rate of fluoroquinolone dispensing was significantly higher.***

Page 10 – Lines 44-45: suggest changing “they are less likely to provoke antimicrobial resistance” to “they are less likely to select for resistance in non-target bacterial species or multi-drug resistance”.
**We have made this change.**

***Revised text (Interpretation): Compared to broad-spectrum agents, narrow-spectrum agents are favourable because they are less likely to select for resistance in non-target bacterial species or multi-drug resistance.(31)***

Page 11 – Lines 3-10 + Page 12 Lines 28-36: The authors talk a lot about setting antimicrobial use targets for human medicine. I am glad to see the qualifications they provide throughout the discussion about making sure these are specific to and consider population demographics, knowing that a broad mandate to reduce overall AMU by a certain percentage may not adequate address AMR and may result in negative patient

consequences in some regions over others. It does, then, concern me that the authors make the statement in the conclusions that BC should be used as the minimum benchmark. I think we can all agree that inappropriate AMU needs to be reduced, but do we have evidence that BC is the appropriate benchmark? The authors have not presented data to support this other than the statistical comparison for 2019 dispensing data.

**We agree with the reviewer's assessment that antimicrobial use targets should consider population demographics and potential negative consequences. We have revised the statement to remove the assertion that BC should be used as a minimum benchmark.**

***Revised text (Conclusion): These data should inform minimum benchmarks or goals for provincial antibiotic use targets, as, when compared internationally, it is likely that substantial overprescribing is occurring in all Canadian provinces.***

Page 12 – Lines 10-15: I feel the authors missed another important limitation. I don't believe that the IQVIA data can identify if a single patient receives more than one antibiotic dispensation in a given year. Therefore, the dispensing rate per 1,000 population cannot account for patients filling multiple prescriptions in a year. This likely won't have a large impact on the findings, and standardizing total dispensations by population as they have done is appropriate, but in my opinion, this should be mentioned.

**We thank the reviewer for this comment. The limitations section of the manuscript was revised accordingly.**

***Revised text (Interpretation): We were also unable to identify situations where a single patient received multiple antibiotics at once or within a given year.***

Page 12 – Lines 19-40: Conclusions may need to be revised pending the results of the Poisson models. See my note above about my concerns with recommending BC as the minimum benchmark.

**We have revised our conclusions to match the results of the Poisson models. We have also removed the recommendation of BC as a minimum benchmark.**

***Revised text (Interpretation): We observed particularly high overall antibiotic dispensing rates in Newfoundland and Labrador and Saskatchewan. These data should inform minimum benchmarks or goals for provincial antibiotic use targets, as, when compared internationally, it is likely that substantial overprescribing is occurring in all Canadian provinces.***

Page 20 Figure 1: remove asterisks showing outliers and instead include Table of Poisson model outputs for interprovincial comparisons and/or provincial comparisons to Canadian overall dispensing rate. This figure should ideally include error bars (or include standard errors for supporting data in S Table 2).

Page 21 Figure 2: remove asterisks showing outliers and instead include Table of Poisson model outputs for interprovincial comparisons and/or provincial comparisons to Canadian dispensing rates for broad spectrum antibiotics. This figure should ideally include error bars. I also strongly recommend the authors include a supplementary data table with the dispensing rates for each drug by province like they did for the age stratification.

Page 21 Figure 3: remove asterisks showing outliers and instead include Table of Poisson model outputs for interprovincial comparisons and/or provincial comparisons to

Canadian dispensing rates by age group. This figure should ideally include error bars (or include standard errors for supporting data in S Table 3).
**We have removed all asterisks related to the GESD test outputs. We have kept these figures as a visual representation of interprovincial variation, with asterisks denoting statistical significance observed from our Poisson models. Poisson model outputs for provincial comparisons to Canadian dispensing rates can be found in S Table 4.**

Page 25 S Table 2: Thank you for providing these raw data so they can be used by others for future work. Please add a "Total" column to support Figure 1.
**We have added this column for both S Table 2 & S Table 3. We are happy to provide these data to support future work.**

**Reviewer 3:** Khaled AlSager, John Conly
**Institution:** Medicine, University of Calgary Cumming School of Medicine
General comments (author response in bold)

Background:
- Missing key references including the CCA Report in 2019 which provides a much better Canadian context – see below

**We thank the reviewer for this suggestion. This point was also raised by Reviewer #1, and the introduction section of the manuscript was revised accordingly.**

***Revised text (Introduction): A recent report estimates that antimicrobial resistance was directly responsible for 5,400 deaths and $1.4 billion in healthcare costs in Canada in 2018.(3)***

- Missing key references to previous similar Canadian data, Glass-Kaastra et al in 2014 who reported on the 10 year (2000-2010) variation in outpatient oral antimicrobials among Canadians provinces and used a much more sophisticated analytic approach with the same database

**We thank the reviewer for this suggestion. We have added references to the Glass-Kaastra et al. publications.**

***Revised text (Introduction): While previous publications have used statistical approaches to assess the significance of interprovincial variation in antimicrobial use, the most recent editions of these reports use 2010 data.(17,18) Given the ever-changing landscape of antimicrobial use and resistance, the objective of this study was to further examine interprovincial variation in antibiotic prescribing in the community setting in Canada in 2019, comparing overall antibiotic dispensing, broad-spectrum antibiotic dispensing and age-specific antibiotic dispensing across provinces.***

***Revised text (Interpretation): While fluoroquinolone dispensing rates in Canada have declined since 2000, they still exceed international targets.(18)***

- Missed referencing or even acknowledging the CIPARS data which analyzed the same metric of scripts per 1000 population and comparing and contrasting how the 2019 data compares

**We thank the reviewer for this suggestion. In recent years, the CARSS report has integrated data from CIPARS and other Public Health Agency of Canada (PHAC) surveillance programs. We believe the most relevant data for comparison to our work is PHAC's CARSS report. We have added additional references to this report in our introduction. We have also added a reference to an older version of PHAC's Human Antimicrobial Drug Use Report for historical context.**

***Revised text (Introduction): While reports from the early 2000s suggest declines in antibiotic use in Canada, more recent data suggests that annual antibiotic consumption in Canada has been rising since 2014.(7,8)***

***Revised text (Introduction): The Public Health Agency of Canada regularly publishes data on outpatient antimicrobial use in Canada.(11,16) While previous publications have used statistical approaches to assess the significance of interprovincial variation in antimicrobial use, the most recent editions of these reports use 2010 data.(17,18) Given the ever-changing landscape of antimicrobial use and resistance, the objective of this study was to further examine interprovincial variation in antibiotic prescribing in the community setting in Canada in 2019, comparing overall antibiotic dispensing, broad-spectrum antibiotic dispensing and age-specific antibiotic dispensing across provinces.***

***Revised text (Interpretation): In this cross-sectional study, we reported an annual dispensing rate for oral antibiotics filled at Canadian community pharmacies that was 5.8% lower than the rate observed in 2009, one decade earlier.(26)***

- Suggesting stewardship has only been active for just over a decade is misleading and inaccurate as had references to its status across Canada and multiple followup published reports, including in the CMAJ following the seminal Consensus Conference held almost 2 and a half decades ago ( 1997) on AMR in which the stewardship piece was emphasized and initiated

**We thank the reviewer for highlighting this. We apologize if our introduction was interpreted that way. We have added a sentence to our introduction for additional clarity.**

***Revised text (introduction): In Canada, systematic efforts to control antimicrobial resistance began in 1997.(7) Antimicrobial stewardship programs have now been present in both community hospitals and large teaching centres in Canada for over a decade.(8,9)***

- No reference to the variation in provincial formularies and how that might affect interprovincial variation. Glass-Kaastra et al looked at inter-provincial formularies' differences in 2014

**We thank the reviewer for this suggestion. We read with interest this publication which investigated the possible role of formulary differences in interprovincial variation in antimicrobial prescribing. The authors found that, while provincial formularies differed, these differences did not explain interprovincial variation in prescribing. These negative findings strengthen our discussion on antimicrobial stewardship strategies in the community setting. We have revised our manuscript accordingly.**

1. ***Revised text (Interpretation): While formulary restriction offers another tool to guide prescribing from an antimicrobial stewardship perspective, it has not been found to correlate with outpatient antibiotic dispensing in the Canadian context.(43)***
2. ***Added citation to: Glass-Kaastra et al., "Does Variation among Provincial Drug Formulary Antimicrobial Listings in Canada Influence Prescribing Rates?", 2014.***

- Multiple other published papers in the Canadian context have looked at specific antibiotic classes in Canada and comparing across provinces including beta-lactams, macrolides, lincosamides, tmp-smx, and quinolones

**We thank the reviewer for this suggestion. We have read with interest these publications. They are in line with the more recent data from PHAC's CARSS report, which we have cited. We have added a specific citation to the suggested reference on quinolones, which adds historical context to our discussion on antibiotic use targets for fluoroquinolones.**

***Revised text (Interpretation): While fluoroquinolone dispensing rates in Canada have declined since 2000, they still exceed international targets.(37)***

- No citations mentioned of the progress made to date on reducing outpatient prescribing which has been previously published in the CMAJ as far back as 2002

**We thank the reviewer for this suggestion. We have added citations to strengthen our background on the recent history of antimicrobial use in Canada.**

***Revised text (Introduction): While reports from the early 2000s suggest declines in antibiotic use in Canada, more recent data suggests that annual antibiotic consumption in Canada has been rising since 2014.(7,8)***

Method:

- No information provided about the IQIVA GPM database in terms of coverage and areas of possible gaps such as non-insured claims or vulnerable populations (for example: First Nations) or other recipients of non-insured health benefit recipients
- Gaps in the IQIVA GPM database have been described previously and only references to its external validation are mentioned but not its shortcomings

**The IQVIA GPM database is able to capture non-insured claims as well as non-insured health benefit recipients. However, the IQVIA GPM database does have multiple limitations. A number of these limitations are discussed in our interpretation section.**

***Text (Interpretation): 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 not capture individual-level information such as patient diagnoses. We were also unable to identify situations where a single patient received multiple antibiotics at once or within a given year. We were also unable to identify situations where a single patient received multiple***

***antibiotics at once or within a given year. Hospital-operated long-term care facility prescriptions are likely not captured in our dataset, as they would typically be dispensed through hospital pharmacies, contributing a potential confounding factor to our results. 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.(39)***

- Consider adding a segment to explain the broad-spectrum antibiotics grouping – many would not include macrolides as broad spectrum- and reference for the decision behind this categorization

**The decision to select macrolides, fluoroquinolones and penicillins with beta-lactamase inhibitors was based on the combination of spectra & resistance potential. While macrolides are traditionally seen as a broad-spectrum class[1,2], they have also been identified by the WHO as agents that should be prioritized as key targets of stewardship programs because of their high resistance potential.[3]**

[1] **https://www.sciencedirect.com/topics/neuroscience/macrolide-antibiotics**
[2] **https://www.pharmgkb.org/pathway/PA166160731**
[3]
**https://www.who.int/medicines/news/2019/WHO_releases2019AWaRe_classification_antibiotic s/en/**

- A fairly rudimentary metric was used of scripts per 1000 population but PHAC in its annual reporting of the same data and other publications have used more sophisticated analytic techniques that really should have been used

**While we acknowledge the limitations of "prescriptions dispensed per 1000 population" as a metric of antimicrobial use within the interpretation section of our manuscript, we also recognize the limitations of the DDD metric for our data set, which we discussed above in response to reviewer #1. We would also like to highlight again that we believe our manuscript builds on the CARSS report in numerous ways, outlined in our response to the next point.**

- No mention that the PHAC in its CARSS report covers the exact same reporting and we would expect the 2019 data soon to be released within their reporting system with multiple metrics including DDDs/1000 inhabitant days which may be more meaningful

**We thank the reviewer for this comment. We believe our manuscript builds on the CARSS report in the following ways, including but not limited to the recency of our data:**

1. **our manuscript uses 2019 data, whereas the 2020 CARSS report published 2018 data;**
2. **our manuscript includes provincial comparisons of antimicrobial use that are stratified by age group, whereas the CARSS report publishes age-stratified antimicrobial use at the national level.**
3. **our manuscript uses a statistical approach to assess the significance of interprovincial variation;**
4. **we have generated detailed tables of antimicrobial prescription volume stratified by province, drug class and age group to support future work in this space.**

**We have added another reference to the CARSS report for additional clarity.**

***Revised text (Introduction): The Public Health Agency of Canada regularly publishes data on outpatient antimicrobial use in Canada.(8,17) While previous publications have used statistical approaches to assess the significance of interprovincial variation in antimicrobial use, the most recent editions of these reports use 2010 data.(18,19) Given the ever-changing landscape of antimicrobial use and resistance, the objective of this study was to further examine interprovincial variation in antibiotic prescribing in the community setting in Canada in 2019, comparing overall antibiotic dispensing, broad-spectrum antibiotic dispensing and age-specific antibiotic dispensing across provinces.***

- While a one-year cross-sectional study gives a snapshot looking at more than one year to assess trends would have been more valuable

**We appreciate the value of multi-year analyses to assess trends in antimicrobial use. Our goal with this work was to use a statistical approach to assess the significance of interprovincial variation in as up-to-date a time period as possible.**

Interpretation:

- A fairly rudimentary interpretation
- No comparisons of the results to previous Canadian data - see above Glass-Kaastra et al and PHAC that repeatedly have had similar findings that demonstrated that Newfoundland and Labrador had significantly higher prescribing rates than all other provinces. In contrast, Quebec exhibited significantly lower prescribing than all other provinces. Some explanation might have been suggested as well.

**We thank the reviewer for this comment. We have added additional references to previous Canadian data for historical context. We have also highlighted our suggested explanation for interprovincial differences, adding international context.**

***Revised text (Interpretation): In this cross-sectional study, we reported an annual dispensing rate for oral antibiotics filled at Canadian community pharmacies that was 5.8% lower than the rate observed in 2009, one decade earlier.***

***Text (Interpretation): 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.(26)***

***Revised text (Interpretation): While fluoroquinolone dispensing rates in Canada have declined since 2000, they still exceed international targets.(19)***

***Text (Interpretation): 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.(31) 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.(32) 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.***

- Consider looking at Canadian interprovincial formularies data and if they would explain the differences in specific antibiotics classes prescription. Also, this might affect the interpretation of antibiotics classes result as different provinces might have different formulary restrictions. For example, the Glass-Kaastra et al group found that formularies varied considerably among the Canadian provinces. Quebec had the most flexible formulary, while Saskatchewan's had the lowest number of general benefits and most restrictions

**We read this publication with interest. While there is interprovincial variation in the listing status of fluoroquinolones in particular, we did not observe congruence between provincial listing status and utilization. For example, despite listing all commonly used fluoroquinolones as general benefits, dispensing rates in Ontario did not exceed the national average. While there may be relationship between third generation fluoroquinolone dispensing and listing status, these agents contributed less than 30% of overall fluoroquinolone dispensing, and were not a focus of our results or discussion. In most provinces, despite formulary restriction, fluoroquinolone dispensing exceeded international targets. This may be in part due to the fact that about 50% of all Canadian antibiotic prescriptions are dispensed to patients without provincial drug coverage, and thus are unaffected by restrictions in provincial formularies. Nonetheless, we believe the results of the Glass-Kaastra et al. paper strengthens our discussion on strategies to reduce prescribing in the community setting. We have revised our manuscript to add a reference to this paper.**

1. ***Revised text (Interpretation): While formulary restriction offers another tool to guide prescribing from an antimicrobial stewardship perspective, it has not been found to correlate with outpatient antibiotic dispensing in the Canadian context.(43)***
2. ***Added citation to: Glass-Kaastra et al., "Does Variation among Provincial Drug Formulary Antimicrobial Listings in Canada Influence Prescribing Rates?", 2014.***

- No discussion why DDDs/!000 inhabitant days was not pursued

**We thank the reviewer for this comment. We received a similar comment from reviewer #1 as well. Our response: We appreciate the value of the DDD as a metric which can be used benchmark within and/or between institutions. When used as a measure of overall antibiotic use, however, the aggregate of DDDs is prone to several limitations. First, DDD dosing may not reflect regional and up to date recommended doses for optimization of antibiotic activity. This issue can be compounded by regional differences in antibiotic selection. Further, the DDD can be inaccurate in certain populations, particularly pediatrics and renal impairment. While we believe that the DDD is a valuable metric for comparing specific drugs, we believe that the use of the DDD at the level of overall antibiotic use within a population presents numerous utility-limiting challenges.**

- No discussion about previous targets that were set within Canada

**We thank the reviewer for this comment. We are not aware of previous national targets that have been set in Canada. However, a recent report from the Chief**

**Public Health Officer of Canada has identified improved research & surveillance as a necessity for the development of such targets. A study of primary care practices in Ontario was recently carried out to try to address this need. The authors identified that 15% of visits for an infectious indication were associated with an unnecessary antibiotic and that conservatively approximately 25% of all antibiotic prescriptions were likely unnecessary. We have revised our manuscript to discuss these points.**

1. ***Revised text (Interpretation): The Chief Public Health Officer of Canada recently identified the need for detailed research on antibiotic use and appropriateness to explain interprovincial variation and develop appropriate Canadian antibiotic use targets.(34) A study of primary care practices in Ontario identified that 15% of visits for an infectious indication were associated with an unnecessary antibiotic and that conservatively approximately 25% of all antibiotic prescriptions were likely unnecessary; suggesting opportunity for safely reducing antibiotic prescribing in Canadian primary care.(35)***
2. ***Added citation to: "Handle with care: preserving antibiotics now and into the future — Chief Public Health Officer of Canada's 2019 spotlight report", 2019.***

• A rather thin limitations section given the many missing references and comparisons that should have been made

**We thank the reviewer for this comment. We have strengthened the limitations section of our manuscript in accordance with reviewer comments.**

***Revised text (Interpretation): We were also unable to identify situations where a single patient received multiple antibiotics at once or within a given year. Hospital-operated long-term care facility prescriptions are likely not captured in our dataset, as they would typically be dispensed through hospital pharmacies, contributing a potential confounding factor to our results.***

Conclusion:

• Consider re-enforcing the recommendation by mentioning previous trends noted in Canada.

**We thank the reviewer for this suggestion and have revised our manuscript accordingly.**

***Revised text (Conclusion): Antibiotic dispensing rates across Canada have declined 5.8% since 2009, but remain well above the rates observed in many European nations.***