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Title	A retrospective cross-sectional study of regional variability in outpatient antibiotic use in Ontario, Canada
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Reviewer 1	Dena Schanzer BMath MSc, PStat
Institution	Public Health Agency of Canada, Infectious Disease and Emergency Preparedness Branch, Ottawa, Ont.
General comments (author response in bold)	Comments to the Author In this manuscript, the authors use the GPMTM database from IQVIA (formerly QuintilesIMS) to describe outpatient antibiotic use in the province of Ontario and describe the geographic variability after controlling for a number of predictors. The authors provide a map outlining the antibody prescription rate for the 14 health regions and there is visual evidence of variation. However, the only quantitative/statistical evidence provided to support the conclusion of significant regional variation is a crude rate ratio of 1.46 (95%CI 1.07-1.98) and adjusted ratio of 1.49 (1.15-1.93) between the highest and lowest of the 14 rates. The confidence intervals for the rate ratio were calculated after selecting the minimum rate as the reference point. It is well documented that this approach significantly overstates the level of statistical significance of all the rate ratios. This statistic does not support the conclusion of significant regional variability once one accounts for the min and max selection process. Unfortunately, the authors have not provided the 95%CI for each regional rate (crude or adjusted), so I cannot assess the magnitude of the error, but suspect that the regional variation in the rate is not statistically significant. 95%CI (or std error) for each estimated rate must be provided, as it cannot be calculated without taking into account the sampling frame. There are a number of options to assess the level of significance of the regional variation. As the authors used a regression model, I'd recommend documenting the model used and reporting the full results including the Type III p-value for the significance of the regional effect. If the authors want to focus on the ratio of max to min rates, I'd suggest looking into a bootstrap/simulation exercise to calculate appropriate confidence intervals. **A: Thank you for this feedback. We have updated our statistical analysis using the suggested bootstrap method for calculating 95% confidence intervals. We have also added an appendix table that includes the full Poisson regression model results including Type III p-values. The points are well taken and we have also softened the language suggesting overall statistically significant variability between health regions. Confidence intervals for all regional rates are provided.** The IQVIA data is available for the most recent 5 years. It is very important in this type of work to also assess consistency from year to year. Is Champlain always the lowest and ERIE the highest? If not, you are likely just seeing random variation at work. I'd also be interested in any trends. Has the effort to reduce antibiotic use been effective? I hope you find these comments helpful, as the study idea of describing antibiotic usage, at a time when efforts to reduce its use are ongoing, is important.

	A: Thank you for this suggestion. Public Health Ontario currently only has 1 year of IQVIA data. We agree with the importance of looking at trends and hope to do this going forward. However, we feel it is currently beyond the scope of this cross-sectional 1-year study with the purpose of evaluating regional variability.
Reviewer 2	David Patrick MD
Institution	School of Population and Public Health, UBC, Vancouver, BC
General comments (author response in bold)	Comments to the Author This is a well written article and contributes new data to the literature about variation in community antibiotic use by region in Ontario. I have a number of questions and suggestions pertaining to each section as follows: Abstract: • The term "number of antibiotics" used is not precise. Either speak to Rx or DDD over population **A: Agree and have made this correction.** • In reporting the rate be sure to characterize as "annual" rate or 621/1000 population PER year **A: Thank you. We clarified throughout the manuscript and tables/figures that this rate refers to 1 year of data.** • The abstract non-specifically states that there were "wide age and sex differences". A more specific statement or example would be more useful.i **A: Thank you. This was modified to: "adult females receiving the highest rate of antibiotic prescriptions."** Background • The overview of community interventions to reduce community use should not be limited to those directed at doctors. See systematic review by Cross PMID:27999058 **A: Thank you this comment. We completely agree and have added this reference to our discussion line 190.** Methods: • Was there no opportunity to get more information on the regions from census data? For example, median income may be a crucial covariate. Proportion of population that is immigrant or indigenous may be useful, especially with the observations about Erie St. Clair. **A: Thank you for this suggestion. Using Census data we have added in population variables of low income prevalence, low education status, immigrant status, and self-identified aboriginal status as covariates in the regression model.** • Physician age would have been useful but career stage is adequate

	A: We did not have access to physician age • Were any data available on country of training for physicians? **A: We did not have access to this data for this study** • Figures – please see if you can sharpen the colour palate, especially for figure 1 to make the series more distinct from each other **A: Thank you for this comment. Since there are 13 groupings it was challenging to make a separation that was both clear and meaningful. For this reason, we chose to group the antibiotics by "typical indication" so that respiratory antibiotics are in blue, urinary in green, etc. If the editors prefer, we can group them differently. The new appendix table should help clarify these classifications.** Discussion: • There is a plausible confounder in data from Erie St Clair. What is the likelihood of a higher volume of cross border drug purchase in the Detroit-Windsor corridor? Can this be teased out? **A: Thank you for this comment. We have looked into this and do not have the data to evaluate if there was variability in prescriptions for non-Ontario residents, or residents of the United States.** • As per the discussion, there is little doubt that more theory based community stewardship interventions need to be examined, but it may not be logical to confine these to physicians alone. Physician behaviour is paramount, but it is strongly reinforced by patient feed-back, in turn driven by patient knowledge and expectation. Again, refer to Cross et al. **A: We agree with this point and added to the discussion with this reference. Line 219.**
Reviewer 3	Claire Kendall MD
Institution	Elisabeth Bruyere Research Institute, C.T. Lamont Primary Health Care Research Group, Ottawa, Ont.
General comments (author response in bold)	This study is a cross sectional evaluation of antibiotic prescriptions in Ontario. The question is important, and their finding related to regional variability is striking and can lend to potential interventions to mitigate antimicrobial resistance. This is not my area of clinical expertise, but I think most readers will find this important, certainly in Canadian contexts. The study seems well conducted, and the majority of my comments are minor. General comment: I suggest using the term "antibiotic prescribing" rather than "antibiotic use" as these are prescription measures. **A: Thank you for this comment. This data more accurately represents "antibiotic dispensed", and not "antibiotic prescribing". For example, physicians may prescribe an antibiotic that is never filled at the pharmacy and this therefore would not be captured. We prefer the term "antibiotic use" over dispensed or prescribed throughout the manuscript, and this is consistent with the literature. In the methods line 78 we define that that "antibiotic use data were obtained from antibiotics dispensed by outpatient**

	Ontario pharmacies in the GPMTM database from IQVIA". Furthermore in the limitations section, line 234, we highlight that antibiotic dispensing data may not accurately represent "consumption" by the patient. We hope this clarifies the decision process we used to decide on the terminology. Introduction: 1. I have no comments, sets the stage and impetus for the study. Methods: 2. This is the only comment that I feel is critical: Please provide clarification regarding what prescriptions are captured in the 64%. Are these restricted to outpatient prescriptions (I think so?) and/or those under ODB (which might explain 64% of all those in the province)? What prescriptions are missing and how might this introduce bias (for the limitations section). This is hinted at the in the interpretation but should be very clear in the methods for purposes of generalizability and reproducibility. **A: Thank you for this comment. These prescriptions are only outpatients and this data is not based on ODB claims. Please see the detailed explanation to the editors above. Additional text has been added that should clarify how the dataset is made from IQVIA as well as recognizing the limitations in the data (methods line 89 and discussion line 253): "IQVIA creates the GPMTM database by obtaining prescriptions directly from outpatient pharmacies as well as insurance claims and sales data. The Ontario portion of this database is derived from a sample of 65% of prescriptions from pharmacies. Insurance claim and sales databases are merged to supplement the pharmacy data. IQVIA then applies a geospatial projection algorithm so that the antibiotic prescription counts are representative of 100% of the population.(10) Briefly, IQVIA projects antibiotic prescriptions from pharmacies not included in their dataset based on the volume of prescriptions from surrounding pharmacies and the geographical distance between the captured and non-captured stores. Their methodology is proprietary but routinely validated.(11)"** 3. To clarify, did the authors use actual prescription counts or those predicted by the IQVIA algorithm? **A: The data supplied by IQVIA is extrapolated to the 100% of the population. It is not possible to obtain the raw data from the company.** 4. If proportion of generalist physicians really means proportion of family physicians, that should be explicitly stated. There is no licensing body for generalist physicians (and family physicians are just a different kind of specialist). It is possible that as per US definitions generalist includes internal medicine and pediatrics, but reading later I do not think this is the intent of the term in this study. **A: You are correct, and this has been changed to family physician throughout the manuscript.** Results: 5. I have no major comments – analyses are well described and appropriate.

	6. The authors refer to high risk antibiotic use and use related to certain conditions – should probably be specified in methods (or saved for interpretation). **A: Thank you. The indication for use has now been pre-specified in the methods and summarized in appendix table e1.** 7. Last para: I might state "After adjustment, x of the regions had prescribing that was significantly greater than the reference region", then state the Erie St. Clair finding. **A: Thank you. Based on reviewer 1, and editors', suggestions the statistical analysis and results have been modified.** Interpretation: 8. First para – probably to be clear, this finding is not explained by the patient and physician characteristics measured in our study (or most commonly related to antibiotic prescribing perhaps). I am just thinking there is no measure of patient comorbidity, for example. **A: Thank you. This suggestion was incorporated.** 9. The interpretation becomes a bit long, but I will leave that to editorial preference.
Reviewer 4	Mohamed Gazarin DPharm
Institution	Winchester District Memorial Hospital, Research, Winchester, Ont.
General comments (author response in bold)	Comments to the Author Background section 2nd paragraph: Very good background however can you adjust the flow of thoughts in the second paragraph. Are you concerned that there is no comparable requirement or that hospital- based ASP interventions cannot be applied to community? **A: We are concerned about both. We reorganized the sentences so hopefully this point is clearer.** Methods: Data Source: Can you elaborate more about IQVIA source of data? Is data driven from OHIP patients only or private plans and cash patients as well? This should help clarify under reporting bias In hospital's ASP, usage reports get sent regularly from pharmacy department and an annual antibiogram from lab. If the province to start ASP per regions, can the regions easily get Abx usage data from IQVIA? Also is part of the paper's objective to recommend using IQVIA to do that or you are just using it as a one-time usage to describe geographical variability of antibiotic use? **A: See response to editors regarding the database. This antibiotic database is built from data directly from pharmacies, claims data, and sales data. It is then extrapolated to 100% of the population using a proprietary geospatial extrapolation algorithm by IQVIA. The methods section has been modified to better explain the data: line 89: "IQVIA creates the GPMTM database by obtaining prescriptions directly from outpatient pharmacies as well as insurance claims and sales data. The Ontario portion of this database is derived from a sample of 65% of prescriptions from pharmacies. Insurance**

	claim and sales databases are merged to supplement the pharmacy data. IQVIA then applies a geospatial projection algorithm so that the antibiotic prescription counts are representative of 100% of the population.(10) Briefly, IQVIA projects antibiotic prescriptions from pharmacies not included in their dataset based on the volume of prescriptions from surrounding pharmacies and the geographical distance between the captured and non-captured stores. Their methodology is proprietary but routinely validated.(11)" Access to the IQVIA data is limited by cost, but certainly one potential strategy is to continue to acquire this data over time for the purposes of outpatient ASP. Interpretation: Page 6 line 37, I suggest to either remove or give more details on the sentence "It is noteworthy that variability in antibiotic use persists within a province at the smaller health region level". **A: Sentence removed**. Page 7 line 29: "There was variability in use of high risk antibacterial agents, such as fluoroquinolones" What is your high-risk definition? (high risk for developing resistance or for side effects?) Which agents do you consider to be high risk? Please write figure 3 next to this sentence **A: Thank you for this point. The use of the term "high risk" was not necessary here so removed. We have instead emphasized that there was variability in FQ use and that this class of drugs has a Health Canada warning due to toxicity.** **A: Thank you. The modelling section in the methods was expanded upon.**
Reviewer 5	Lauri Hicks DO
Institution	Centers for Disease Control and Prevention, Atlanta, GA.
General comments (author response in bold)	Comments to the Author The authors used Ontario IQVIA pharmacy data to assess regional variability in outpatient antibiotic prescribing by health region using Poisson regression models adjusted for physician characteristics and stratified by patient age and sex. Measuring antibiotic use is an important step in identifying where there are opportunities to improve antibiotic use. Comments Background • The authors give a good description of the issue of antibiotic use and resistance in Canada and worldwide and state the objective of their study in the last paragraph. Methods • The authors need to specifically state that the dataset they are using captures only outpatient antibiotic prescriptions (if this is the case). On page 4 line 48, the authors state that the "data were obtained from antibiotics dispensed by Ontario pharmacies in the GPM database." Were these all pharmacies or just outpatient/community pharmacies? Also, in the next sentence (page 4 line 49) the authors state that the "dataset consists of aggregated antibiotic prescription counts at the level of the Forward Sortation Area." Again, suggest specifying they were outpatient antibiotic prescription counts (if true) or explain how they identified only outpatient antibiotic use from this data. **A: This is correct. To clarify "outpatient" was added to the abstract and methods**

	• The authors mention on page 5 line 27 in the methods what denominator they used to calculate rates (population counts) but do not mention the source for that denominator—this would be helpful to know for methodology. Was this from the same dataset or did they need to use a different data source (e.g., census data)? **A: the population data was obtained from Census. This was added to the methods line 108.** • On page 5 lines 35-37, the authors state what variables were included in their model but need to describe their modeling strategy. **A: More details on the modified modelling strategy have been added to the methods. As an appendix table we have also included the full model results.** o Why were patient demographics (age and sex) stratified on but not included in the model? **A: Thank you for this comment. We have incorporated some additional patient covariates from census data including proportion low income, proportion aboriginal, proportion no post-secondary education, and proportion of immigrants. In addition, we incorporated age and sex into the model as a covariate to remove the stratifications.** o The authors should also describe how variables were selected to be included in the model and how the final model was chosen. There was no explanation on how confounders were identified, no mention of univariate analysis to identify significant predictors, and no explanation of model selection. **A: Model covariates were selected a priori by the potential clinical importance of these variables. The methods section on the model and covariate selection has been modified to reflect this. The full crude and adjusted models have been added as an appendix table.** Results • Page 6 line 20 should refer to Table 3 not Table 2. **A: corrected. Thank you.** • Table 2, Figure 1, Figure 2, and Figure 3 should specify that these are crude antibiotic use rates **A: Tables and figures modified as suggested.** • On page 6 lines 5-7, the authors refer to Figure 1 to describe fluoroquinolone variability by patient age and sex. However, the point the authors are trying to make is very difficult to see in Figure 1 because there are several categories and fluoroquinolones are divided into two groups. Could fluoroquinolones be collapsed into one category or at least placed adjacent to each other on the figure so the reader can easily see total fluoroquinolone use?

	A: Thank you for this comment. It was challenging balancing how to display the figures in a meaningful, yet clear way. We decided to colour coordinate by most common indication. We highlighted the fluoroquinolone numbers in the text specifically because they are harder to easily identify by looking at the figure. If we collapse fluoroquinolones then it would not be easy to see the relative use by indication (lines 128-131). After considering the various comments from reviewers we would like to keep the current organization of the figures. However if the editors prefer we are open to reconsidering the presentation. Interpretation • In the first paragraph (page 6 line 26) the authors state that they adjusted for patient and physician factors; however based on the methods, only physician factors were adjusted for in the model and patient age and sex were stratified on. This should be clearly stated when describing the model. **A: Analysis modified to include population and physician covariates in the model.** • In the first sentence of paragraph 6 (page 7 line 50) the authors state that they adjusted for regional physician factors and population differences. "Population differences" is very broad—would suggest specifically stating the variables (population age and sex) since there were other potential population differences not measured and stratified on. Again, should also clarify that these demographics were stratified on and not included in the Poisson model. **A: Analysis modified to include physician and population covariates in the model. This has been clarified in the text.** • Several places the authors state that the variability in antibiotic use was not explained by population differences (e.g., page 6 line 27 & page 6 line 45). However, the model accounted more for physician factors rather than population differences and the authors only stratified these models on patient age and sex. There could still be unmeasured population differences including race, comorbidities/underlying health status, etc. Are there ways to incorporate any of these measures into the model or were these looked at and found not to be significant factors? Based on methods and how the model was formulated, it seems like they adjusted more for physician differences than population differences. **A: The model has been updated to include some population covariates. We have recognized in the limitations that not all variables could be accounted for.** Overall • Overall, the research question is very interesting and describes an important public health topic. The authors should describe their methodology in more detail and explain why they decided to adjust for particular variables.