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Title	Unnecessary antibiotic prescribing in a Canadian primary care setting: a descriptive analysis using routinely collected electronic medical record data
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Reviewer 1	Giulio DiDiodato
Institution	Critical Care Medicine, Royal Victoria Regional Health Centre, Barrie, Ont.
General comments (author response in bold)	<p>The study's main objectives were to estimate the overall and condition-specific mean inappropriate antimicrobial prescribing rates per 100 physician-patient encounters observed in a sample of community-based primary care practices in Ontario for 23 common office-based infectious diseases syndromes over the years 2011 to 2016. These rates were estimated by subtracting the condition-specific mean observed antimicrobial prescription rates from the expected antimicrobial prescribing rates that had been developed previously using a Delphi process. The authors used routinely collected data located in linked administrative databases. Specifically, the authors relied on billing codes/notes and ICD codes to identify patient-physician encounters that resulted in antimicrobial prescriptions. The study included 341 unique physicians, 157 187 antimicrobial prescriptions for the 23 pre-specified conditions, and 495 901 encounters. The results were presented as population parameter estimates as no random variables describing variation were included in the study. The results did account for clustering by age group through stratification, but did not account for clustering by physician or year or seasonality. The final results revealed an inappropriate prescribing rate of ~ 15 per 100 encounters for these 23 ID syndromes, with over 80% being due to prescriptions for indications that never require an antimicrobial according to experts. These results are consistent with previous observational studies across many different jurisdictions. Unfortunately, despite many different types of interventions, these prescribing practices seem particularly resistant to change.</p> <p>I commend the authors for undertaking such a difficult study given all the uncertainty around expected prescribing rates, and challenges with accurate and valid clinical diagnoses from the routinely collected data. I think this study provides the rationale for moving forward with interventional studies directed at behavioural change in prescribing practices as had been done previously in other jurisdictions.</p> <p>Thank you</p> <p>My concerns are minor, if not insignificant.</p> <p>1. I was left to wonder why the authors decided to describe the data using population parameters? I assume the degree of uncertainty associated with the expected prescribing rates, including the accuracy of the clinical diagnoses was difficult to quantify and include in any variation estimate? If this was the case or there was some other rationale, I do believe the authors should explain it in some detail as the results may mistakenly give the impression of both high precision and certainty.</p> <p>Thank you for this comment. The reviewer is correct in that quantifying uncertainty in prescribing rates is challenging and the modified Delphi panel chose to present point estimates. We elaborate further on this point in the</p>

	<p>manuscript by Wu et al (reference 19) which discusses the modified Delphi process in more detail. We have edited the following limitation for this point: “Fifth, We chose to use point estimates from our previous Delphi panel results for expected appropriate antibiotic prescribing rates to facilitate knowledge translation into practice however they do not fully capture the degree of error, subjectivity, or uncertainty in this process.¹⁹ These point estimates may not be applicable to all patient populations and regions.” (p. 303)</p> <p>2. I think the analyses would have benefitted from accounting for clustering at the physician level to quantitate the extent of variation among physicians' inappropriate prescribing rates. This might have implications in designing different interventions if the the variation was very small compared to if it was very large. The first might suggest a system-wide intervention whereas the latter may benefit from a much more targeted intervention. It would have also been interesting to account for clustering at the year level to observe for any temporal trends especially given the introduction of the Choosing Wisely Campaign and its emphasis on antimicrobial stewardship in these syndromes. I think the authors should explain the rationale for not including these potential random effects in their analyses.</p> <p>We agree with this point, and our future work will focus on inter-physician variability in inappropriate antibiotic prescribing, and will employ random effect models.</p>
Reviewer 2	Christopher Doig
Institution	Departments of Critical Care Medicine & Community Health, University of Calgary, Calgary, Alta.
General comments (author response in bold)	<p>A few minor comments:</p> <p>1. Unfortunately, your delphi is only in press so understanding the point estimates is difficult. I think there should be a discussion with the editor as to the correct timing of publication (so that the JAMMI paper is available preceding availability of this paper).</p> <p>Expected publication of the JAMMI paper is February 2020</p> <p>2. I find the 27.5% (I think I have the combined % correct) of 'never should be ordered' as the most compelling. I appreciate that your discussion perhaps focuses a bit more on the estimates of overprescribing from the delphi to what you observed in this study: maybe just a slight difference of perspective, but the 27.5% should never be ordered...vs it could be argued that you're not certain that antibiotics weren't indicated...more emphasis on the 27.5% in the discussion? I enjoyed Figure 2. I thought there might be a bit more discussion on where/how to effect inappropriate ordering. I thought this figure gives some clues.</p> <p>Thank you for this comment. We agree this is a compelling result. Therefore we have added a figure (new figure 2) focusing on this aspect and enhanced the discussion on the importance of this result. (Figure 2, Figure 3, pp. 234, 273)</p>
Reviewer 3	Svetlana Puzhko
Institution	Department of Family Medicine, McGill University, Montréal, Que.
General comments (author response in bold)	The authors studied an important topic for Canadian primary care research and practice: unnecessary prescribing of antibiotics. This is a thoroughly conducted and carefully described study with interesting results and a good quality of writing and reporting.

Background: The background accurately represents current knowledge in the field. The research question is clear. The reason for choosing the research question is well justified, the knowledge gap is clearly described.

Thank you

1. As a suggestion, I would recommend mentioning other negative consequences of unnecessary antibiotics prescribing for patients (e.g., risk of complications of antibiotics therapy), except the antimicrobial resistance.

Thank you for this suggestion. We have enhanced our discussion around negative antibiotic consequences:

Line 62: “Antibiotics have important adverse effects including up to a 30% risk of side effects, allergic reactions, and C. difficile associated diarrhea.”

Line 248: “It is evident from all of these previous evaluations of outpatient antibiotic prescribing that antibiotics are overused in primary care.

Unnecessary antibiotic use is associated with a 20-30% risk of medication side effects, most commonly nausea, vomiting, diarrhea, rash, headache, and vaginitis. 28,29 In addition, 16% of emergency department visits due to adverse drug events are for antibiotic-associated side effects including allergic reactions and C. difficile associated diarrhea.8 Overuse of antibiotics is an important driver of antimicrobial resistance incurring a four-fold increased risk in individual patients within 1 month of antibiotic exposure,5 in addition to the important public health impacts of increasing antimicrobial resistance in populations with higher antibiotic use.3” (lines 62, 248)

2. Abstract: For the abstract, I recommend adding the specific name for the database used. Just “the Electronic Medical Records Primary Care database” is not specific enough.

“Electronic Medical Record Primary Care” (EMRPC) is the specific name of the main database used. For clarity we added to the abstract: “linked to other administrative datasets at ICES.” (line 40)

1. Methods: Regarding the study design, even though the study was designed appropriately to address the research question (estimating prescribing rates), I disagree that this was a cohort study. As the authors stated, “this study only quantified unnecessary initiation of antibiotics but does not address other features of inappropriate antibiotic prescribing such as ... duration.” (Lines 243-244). Neither patients nor physicians were chosen based on the exposure and followed up to observe the outcome (the definition of a cohort study); no longitudinal time trends were evaluated. Moreover, this was not a hypothesis-testing, or an “analytical” study since no hypothesis was evaluated, no association was tested. It would be, therefore, more appropriate to say that this was a descriptive study using a cohort of Canadian primary care patients and physicians for 2011-2016. The analysis was cross-sectional, not longitudinal.

We agree with this point and have removed all reference to this study being a cohort study and instead describe it as a “descriptive analysis” (lines 1, 39, 90)

Results: The results are reasonable and interesting, they are also in line with the literature data. Tables and figures accurately represent the data.

Thank you

Limitations: The authors mentioned all major limitations in the corresponding section.

Thank you

4. I have one comment regarding the limitations. The inclusion criteria (lines 90-91) were “Physicians had to have at least one year of data in EMRPC and were included for a calendar year if they had seen 200 or more patients in that year and prescribed at least 7 antibiotic prescriptions in that year.” Therefore, the physicians who prescribed less than 7 antibiotics prescriptions per year were not included. Even though one cannot state with certainty, these physicians could have been more careful about antibiotic prescribing and more prone to prescribing them only when necessary. Therefore, this inclusion criterion may have contributed to overestimation of unnecessary prescribing rates. In fact, the unnecessary prescribing rates calculated in the study seem to be only generalizable for Canadian primary care physicians prescribing at least 7 antibiotics per year in at least one of the years for the period 2011-2016. If the authors disagree and have a rational explanation for this inclusion criterion, it would be better to include it in the methods. It would also be interesting to know what proportion of physicians was excluded due to prescribing less than 7 antibiotics prescriptions per year.

Depending on the number of encounters for certain diagnoses (since one of the explanations could be that these physicians did not have enough encounters for the diagnoses for which antibiotic prescribing is recommended), this population of prescribers may be responsible for another problem related to “inappropriate prescribing”: not prescribing antibiotics when it is necessary (or recommended). I understand that this problem is beyond the scope of the present study but this is one of the reasons not to discuss the “inappropriate prescribing” but rather the “unnecessary prescribing” in the discussion

We appreciate this comment, but respectfully disagree. This exclusion criteria was selected to remove low volume and essentially non-antibiotic prescribing physicians. These physicians are not relevant to antimicrobial stewardship efforts. The exclusions of <7 antibiotics per year removed only 16 physicians. We have added a new flow diagram to clarify the exclusions. We looked at the data and all of these physicians prescribed 0 antibiotics. We do not feel it is necessary to further specify that this study on antibiotic prescribing is not applicable to non-antibiotic prescribing physicians. To justify this to the reader we added this line in the methods: “This exclusion criteria was used as rare physicians who prescribe very few antibiotics (<1/month) likely have quite different practices and/or very small volumes, and are therefore likely not applicable to antimicrobial stewardship efforts.” We agree with the reviewer that under-prescribing, while may be an issue in some settings, is beyond the scope of this study. (Figure 1, line 166)

Discussion: The interpretation of results is supported by the data. Study findings are placed in the context of the literature; the relevance for primary care research and practice is well explained.

Thank you.

5. As a suggestion, I would recommend expanding the interpretation of results in the context of possible complications of antibiotics treatment to make the discussion more patients-oriented. In the context of importance for physicians, it would be interesting to name putative reasons for an inappropriate prescribing and negative consequences for not prescribing antibiotics when it is necessary to

prescribe, thus highlighting the complexity of the problem.

Thank you for this suggestion. We have added the following paragraph: “It is evident from all of these previous evaluations of outpatient antibiotic prescribing that antibiotics are overused in primary care. Unnecessary antibiotic use is associated with a 20-30% risk of medication side effects; most commonly nausea, vomiting, diarrhea, rash, headache, and vaginitis.^{28,29} In addition, 16% of emergency department visits for adverse drug reactions were for antibiotic-associated side effects including allergic reactions and C. difficile associated diarrhea.⁸ Overuse of antibiotics is an important driver of antimicrobial resistance incurring a four-fold increased risk in individual patients within one month of antibiotic exposure.⁵ There are additional important public health impacts of increasing antimicrobial resistance in populations with higher antibiotic use.³ However, decisions regarding antibiotic prescribing and drivers of unnecessary prescribing are complex. Physicians are required to balance emotionally salient factors such as diagnostic uncertainty, time constraints, and perceived patient expectations for antibiotics, against antibiotic-related harms and the public health impact of antimicrobial resistance.^{2,30}” (lines 255-266)

6. The sentence “Previous studies have assumed that missing or non-infectious diagnoses (e.g. diabetes or anxiety) are inappropriate” (Lines 226-227) is a bit unclear and would benefit from rephrasing. Also, the authors use the terminology “unnecessary prescribing” throughout the manuscript but then switch to the “appropriateness” of prescribing in the discussion section. Since “unnecessary” and “inappropriate” are not exactly the same, it would be better to make sure the discussion is related to the unnecessary prescribing.

This sentence has been removed and the point re-phrased. Thank you for drawing our attention to use of both terms. We have changed to “unnecessary” throughout the manuscript for consistency. (line 279)