

Article details: 2017-0100	
Title	A decade of outpatient antimicrobial use in senior residents of Ontario: a descriptive study
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Reviewer 1	David Patrick
Institution	British Columbia Centre for Disease Control
General comments (author response in bold)	<p>This is a well-written paper describing a linked data study of antimicrobial use in Ontario. It adds important new observations to the literature about antibiotic prescribing among seniors and should see the light of day.</p> <p>Minor changes should be considered along the following lines:</p> <p>The proportion of seniors getting a prescription in a year (40%) and the rate (30 DID) should be contextualized against the best available estimates for the full Ontario population structure - CIPARS data. This would help give a reader a better sense of the scale of use against a comparator."</p> <p><b>In response to this comment, we have compared our results against the Canadian Antimicrobial Resistance Surveillance System Report 2016 (reference 1) in the Interpretation. The comparison is as follows:</b></p> <p><b>[...] A national report on antimicrobial use in Canada found a similar rate of use among seniors (23.0 defined daily doses per 1000 person days per year), but a higher proportion receiving a prescription (86%) (1).</b></p> <p>Similarly, while family physicians do prescribe a majority of scripts for this population, that majority (around 70%) is far lower than others have reported for FP contributions to all scripts. Ergo, discussion may want to touch on the growing importance of specialist prescription in this age group"</p> <p><b>In response to this comment, we have edited the Interpretation to emphasize that specialists are an important source of antimicrobial prescriptions to seniors. We have added the following:</b></p> <p><b>[...] Interventions should be directed to family physicians, who accounted for more than 70% of antimicrobial prescriptions to Ontario's seniors. However, prescriptions from specialists remain common, and dermatologists and internists have previously been identified as high-frequency prescribers (1).</b></p> <p>If possible, seniors should not be looked at simply as one homogeneous group as there is evidence that the rate of prescribing increases by decade. Please consider a breakdown of prescribing rate by age strata within the senior group.</p> <p><b>In response to this comment, we divided seniors into five age strata: 65 to 69, 70 to 74, 75 to 80, 80 to 84, and over 85. We found that rates of prescribing increase with age, with 49.2% of residents over 85 years prescribed an antibiotic in 2015, compared to 34.2% of residents 65 to 69 years. Prescribing rates for antivirals and antifungals increased with age as well. We added the new analysis to the first paragraph of the Results section (Antimicrobial prescriptions):</b></p> <p><b>[...] Prescriptions for antibiotics, antifungals and antivirals increased with age. In 2015, 49.2% of residents age 85 years or older were prescribed an antibiotic, compared to 34.2% of residents age 65 to 69 years (p&lt;0.001). Similar increases between the two age strata were seen for antivirals (14.7% vs. 1.8%, p&lt;0.001) and antifungals (2.2% vs. 1.3%, p&lt;0.001).</b></p> <p>There is not much detail on the linkage strategy. Some studies have used strict linkage with infectious diagnostic codes, which I suspect has been the approach here. However, others have developed algorithms accepting anatomically specific diagnostic codes (e.g.. Disorder of the urinary tract) that are associated with prescription - and then check back against the stricter linkage strategy to assure the picture is similar. I do not suggest this for the paper but recommend the authors explore it to see if linkage rates can be improved.</p> <p><b>We agree that linking diagnoses and prescriptions with anatomically specific diagnostic codes, rather than specific infectious diseases diagnostic codes, would be of interest to determine whether linkage rates could be improved. We have addressed this in the Limitations section of the Interpretation:</b></p> <p><b>[...] Diagnoses were identified with infectious disease-specific diagnostic codes; broader systems-based codes may have improved our linkage rates.</b></p> <p>The recommendation for outpatient stewardship is welcome but not sufficiently specific. Can we say more about the indications that should be highest priority? (e.g. acute bronchitis, asymptomatic bacteriuria which will most likely be</p>

	<p>miscoded as UTI).</p> <p>In response to this comment, we have elaborated in the Interpretation that stewardship interventions should prioritize upper respiratory tract infections and urinary tract infections, which were the most common indications in our study:</p> <p>[...] Our findings suggest that antibiotic prescribing has not been curtailed by existing interventions. Since more than 90% of antimicrobials are prescribed in outpatient care, community-based efforts are urgently needed, particularly targeting upper respiratory tract and urinary tract infections, the most common diagnostic indications in our study.</p> <p>Specific codes (eg. Acute bronchitis) can be used to infer something more about appropriateness - as prescribing is generally not recommended for many specifically coded disorders in the URTI category that still draw drug therapy.</p> <p>We have addressed this comment in the Limitations section of the Interpretation:</p> <p>[...] Another limitation is our categorization of diagnoses. Disease-specific diagnoses, such as acute bronchitis and acute rhinosinusitis, would have allowed us to better assess antimicrobial appropriateness.</p> <p>Nitrofurantoin growth in Ontario is welcome but it is disappointing that it is not already the most frequently prescribed drug for UTI. Discussion on this would be welcome.</p> <p>After updating our analyses, we found that ciprofloxacin was the most commonly prescribed antibiotic for UTI in 2006 (0.296 DDDs per 1000 person days), while nitrofurantoin became most common in 2015 (0.341 DDDs per 1000 person days). Trimethoprim/sulfamethoxazole use declined significantly, from 0.215 to 0.14 DDDs per 1000 person days.</p> <p>If possible, it would be better to speak to the full therapeutic area of skin and soft tissue infection (SSTI) like the authors did to URTI, LRTI and UTI. Cellulitis is a narrower category. Even though skin abscesses should be treated locally, they still drive a lot of prescribing.</p> <p>In response to this comment, we have replaced all instances of "cellulitis" with "skin and soft tissue infection." Given some very recent studies suggesting systemic antibiotics may confer additional benefit beyond incision and drainage for suppurative cellulitis and skin abscess, we have not commented on this less common and more controversial soft tissue infection scenario in this manuscript.</p> <p>The rate of increase in antiviral use is notable and I encourage the authors to draw out a second paper breaking down whether this is due to influenza drugs, anti-herpes/zoster drugs or some other class.</p> <p>We plan on looking into use of the other antimicrobial classes in future research. Since the focus of this study is on antibiotics, we have not made any changes to this manuscript.</p> <p>The first paragraph of the discussion is a bit too much of a restatement of findings just exposed in results and could be trimmed.</p> <p>In response to this comment, we have shortened the first paragraph of the Interpretation and reframed it as a discussion of the importance of studying outpatient antimicrobial use.</p> <p>"Antimicrobial" should appear in the key words.</p> <p>In response to this comment, we have added "Antimicrobial" as a key word.</p>
<b>Reviewer 2</b>	Susan Baxter
<b>Institution</b>	
General comments (author response in bold)	<p>Descriptive research is tricky - a bit like a blurry photograph of a moving person. One has no idea who it is, what they're doing or why. So it's up to you - the authors - to explain what's what and contextualize the picture, especially since this is a field rife with descriptive data and very little clinical research.</p> <p>In this case you've explained your methods well and given quite exhaustive detail about the drugs, graphed it all and ably focused on the data. In my view you either need to simplify your perspective, present your data and leave it at that. Or, if you want to emphasize the importance of your data then you need calm the rhetoric and explain how your data fits into the bigger picture.</p>

As it stands, if you are going to introduce your piece using scare tactics about antimicrobial resistance as an "urgent" health concern then you need to provide some details. For one thing, what is the incidence of antibiotic resistant bacterial disease in Ontario (since that is where you are concentrating your research)? What is morbidity/mortality as a result? It is all very well to refer to urgent public health issues but it would seem important to back that up with some evidence.

In actual fact I found your data quite reassuring, insofar as over the ten year period you cover antibiotic use did not increase and the use of broad-spectrum drugs declined.

Some questions/issues:

What was antimicrobial use in the decade prior to 2005? Has it gone up or down? Stayed the same? Any ideas as to why? Have the Choosing Wisely and other such messages had an impact? It would seem relevant since you are fairly certain this is a major public health issue. And therein lies a bit of a problem: Public health discourse has a tendency to over-focus on disastrous scenarios, many of which never materialize. The use of emotive language ("the burden" antimicrobial use" when what you mean is simply "the majority" of antimicrobial use was antibiotics (abstract, para 2, Methods, last line) and so on simply serve to distract from your primary message, which, in this case, are your data which indicate there was little change over a decade."

**We agree that the use of overly emotive and "catastrophic" language is distracting, and have strived to refrain from such wording in this manuscript. In response to this comment, we have further softened our language throughout the manuscript, including the instances the reviewer mention above. We would be happy to make additional changes if the Editorial team prefers.**

2. Your references regarding the increase in (primarily) antibiotic use are American which seems problematic as the U.S. tends towards overtreatment and higher drug use generally. Also, large swathes of the U.S. tend to be warm year round while Canada is a northern country, cold for a fair part of the year. During the cold months people develop flu- and cold-like symptoms (and upper respiratory tract infections) which can morph into bacterial ones particularly in the cold. This would seem to make a somewhat higher antibiotic use during the winter months understandable.

**In response to this comment, we have directly compared our results with those from the Canadian Antimicrobial Resistance Surveillance System Report 2016 (reference 1), which is a national study on antimicrobial resistance and use. Unfortunately there is insufficient research on antimicrobial use in Canada; we therefore believe that our study makes a unique contribution to the current literature.**

3. It's somewhat unclear how you extrapolate from community prescriptions to the wider problem of antibiotic resistance, by which I assume you mean MRSA and C. difficile and so on, since these cluster in hospitals and nursing homes.

**In response to this comment, we have increased our discussion of the association between outpatient antimicrobial use and resistance in the Interpretation. We cite studies demonstrating the link (references 10-12, 36, 37), and evidence that in-hospital antimicrobial use is not strongly correlated with in-hospital resistance (reference 38):**

**[...] The evaluation of outpatient antimicrobial use is of pressing importance, as higher use has been associated with greater antimicrobial resistance, in both community and healthcare settings (10-12,36,37). Furthermore, the correlation between in-hospital antimicrobial use and resistance has been found to be poor, suggesting that outpatient prescribing drives much of inpatient resistance (38).**

4. Also, you refer to individuals being at greater risk after taking antibiotics yet your reference (9) indicates that this lasts a few months, possibly a year at most. Again, the rhetoric doesn't quite match the evidence.

**The ecological studies referenced (references 10-12) suggest that greater outpatient antibiotic use confers higher antimicrobial resistance rates in the community, suggesting a long-term impact. We would be happy to make additional changes if the Editorial team prefers.**

5. Simply tracking prescriptions is not always an indication of what drugs people take; how confident are you that your data reflect what patients actually took?

**We include as a limitation that the use of administrative databases may have led to misclassification of antimicrobial prescriptions and diagnoses. However, the Ontario Drug Benefit database had greater than 99% accuracy when compared against**

pharmacy dispensing data (reference 33). Although it is true that antimicrobial prescribing and dispensing may not correlate fully with actual antimicrobial administration, the focus of our study was on antimicrobial prescribing practices by physicians and identifying ways to improve them. We would be happy to make additional changes if the Editorial team prefers.

6. Finally, and this is perhaps a moot point, please don't overuse the term "stewardship". I realize it is a common term referring to the judicious use of antibiotics but it really doesn't mean very much and frankly after the fourth or fifth time it became rather irritating."

In response to this comment, we have removed several instances of the term "stewardship" from the manuscript.

7. Also, I suspect that many people in their mid-sixties and beyond would rather resent being classified as "elderly". Senior will do.

In response to this comment, we have replaced all instances of the term "elderly" with "older adults" or "seniors." We would be happy to only use the term "seniors" if the Editorial team prefers.

Data is not knowledge. Neither is it clinical care. Nevertheless your data show that things are perhaps not quite as bleak as so often presented; perhaps your tone could reflect this.

In response to this comment, we have softened our language throughout the manuscript. We would be happy to make additional changes if the Editorial team prefers.