Author's response to reviews

Title: Evaluating the impact of a novel restricted reimbursement policy for quinolone antibiotics: A time series analysis

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Version: 2 Date: 13 April 2012

Author's response to reviews: see over
Reviewer 1’s report

It is a well written and interesting paper about a new antibiotic policy implemented in a Canadian ambulatory care setting with the aim of keeping quinolone use in bay. As the readership will not only come from Canadians health care people but from all around the world, sometimes more precise descriptions are needed.

Major Compulsory Revisions
1) More than 4/5 of visits belonged to OSA+ doctors. Than how can you give a reliable estimate about differences of prescribing behaviours of different kind of doctors? And why do you differentiate these two groups anyway? both of them had new restrictive policy with small differences.

Thank you. We agree that both groups of physicians were subject to changes in the way in which their patient’s could access quinolones. However, the program of interest was the optional special authorization program, since the other program (requiring a paper-based intrusive application process on a patient by patient basis) was felt to be too resource intensive to maintain in the longterm.

2) Segmented regression models use two parameters to describe changes: the level change (value at the beginning of the time intervals, describe sudden change) and slope changes (measure change during a time step: e.g. one month, describe gradual change). You have to explain this to readers in the methods section and than use these two parameters consequently in the results section to describe your findings. (Than it will be more clear that: e..g there was only a sudden decrease in quinolone use for UTIs and URTIs after the implementation of the programme). To write on the figures the slopes and intercepts of the pre and post intervention regression lines would be also useful.

See also:

Thank you. This is an excellent suggestion. Below we have appended the results of the analyses that you suggest (Appendix 1). The absolute differences were estimated using the models, with comparisons being made between ‘no OSA program’ and ‘with OSA program’ at 12 months post OSA.

With respect to adding this information to the figures themselves, we felt the figures became too cluttered when we added this information to the figures themselves, but instead have added the information to the text of the results.

Minor Essential Revisions
1) For UTI the change in FQ ue was – 3%, while for URTI itwas – 1.6 %, I think it is clinically insignificant. Secondly, this was a level change (change between the first month’ use of before and after policy). But was this change stable over
We apologize for the misunderstanding. We reported these results using units of “per 1000 people with UTI”, but it appears that the interpretation was taken as percentage changes. To clarify, both of the level changes (-33.6 per 1000 and 116.1 per 1000) were estimated from the most parsimonious segmented regression model after dropping the non-significant changes in slopes. For UTI, the slope was not significant in the full model (p = 0.4192). For URTI, the slope was not significant in the full model (p = 0.2642). We do agree that the changes we observed were not clinically significant, and in the first sentence of the discussion, we reiterate this: “we found no change in prescription of the overall quinolone class of antibiotics for four common infections after implementation of a new restricted reimbursement policy for quinolones”.

2) I think you should more carefully phrase about the implemented changes (new policy). OSA was only one main pillar of it, so I would retain to use of this acronym alone as the synonym of the implemented changes. Basically it was formulary change with the following main elements:
- new restriction policy for quinolones (OSA OR traditional prior authorisation)
- adding to formulary two new quinolones (these could not be prescribed with reimbursement at all?)

Thank you. We agree that this was a multifaceted intervention, which also involved an educational pamphlet mailed to physicians. We have clarified this.

3) Nothing is known about the new therapeutic guideline (aimed at restricting the use of FQ)- what has been changed compared to the previous version of the guideline?

Thank you. We have now clarified this by adding the following statement to the methods:
“Prior to November 15, 2005, four quinolones (ciprofloxacin, levofloxacin, norfloxacin and ofloxacin) were a general benefit on the AHW formulary (meaning that they would be reimbursed without restriction).”

4) Could you give an example how this 'restricted' reimbursement policy worked? How was the system before? All antibiotics in formulary were reimbursed? At same scale ? And in the new system?

We have clarified this. As requested, we also have appended a new Appendix 1, which includes all of the details of this program (rather than simply providing the web link).

5) As both kind of doctors (OSA+ and OSA -) could prescribe FQs with reimbursement than I cannot see any main difference between these two status. Maybe for OSA+ doctors this reimbursement was automatic, while for OSA- ones it took some time to receive the approval? Did the scale of their reimbursement
differed? (I mean could they prescribe medicines with the same price for patients?)

I apologize. Reading this section again, I realize that we did a poor job of describing the program. I have significantly modified this section to clarify your questions.

6) Was the traditional prior authorisation of OSA negative doctors only an administrative step? Or has it been rejected any time? What motivated the doctors to become a designated FQ prescribers (OSA+) ? To save time?

There were two motivations to become an OSA doctor – firstly, this reduced the administrative workload of physicians since they did not have to complete further paperwork when prescribing quinolones. Secondly, patients could receive reimbursement for their prescription immediately, rather than having to wait to see if their prescription qualified for reimbursement.

7) Chart review: over estimate quality as informed consent was required. How many invited doctors denied to participate?

We have added this information to the results, and acknowledge this as a limitation in the discussion section.

8) You found that guideline adherence was 42.5% and 58.5% before and after the policy change. What were the most common adherence problems? Does it changed over time? In which infection type out of the 4 the doctors ignored the recommendations?

These are excellent questions, to which we respond below. Given space limitations, we have added some of this information to the text of the paper, but not all of it.

What were the most common adherence problems?

The tables below show that most adherence problems were due to use of levofloxacin (75%) (with fewer problems due to misuse of other quinolones), and that adherence problems were most frequently observed for upper respiratory tract infections (74%).

Table  Guideline non-adherence by antibiotic type and by infections of Interest

<table>
<thead>
<tr>
<th>Antibiotic Type</th>
<th>non-adherence (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>130 (74.7%)</td>
</tr>
</tbody>
</table>
Did adherence to guidelines vary over time?

To address this, we looked at the appropriateness of prescribing in months 0-6 post OSA implementation and 6-12 months post OSA implementation separately (to see if the impact of the program wanes over time – and as well to assess for seasonable variations).

Four comparisons were made as below. We compared the 1st 6months vs. 3rd 6months noting appropriate prescribing 41% of the time in the 1st 6months vs. 59% of the time in the 3rd 6months (p=0.0123; diff = 18.47%). We then compared the 2nd 6months vs. 4th 6months noting appropriate prescribing 46% of the time in the 2nd 6months vs. 58% of the time in the 4th 6months (p = 0.0960; diff = 12.47%). Next, we compared the 1st 6months plus 2nd (i.e. 12 months prior to OSA implementation) vs. 3rd 6months noting appropriate prescribing 44% of the time in the 1st 12months vs 59% of the time in the 3rd 6months (p=0.0125; diff = 15.8%). Finally, we compared the 1st 6months plus 2nd (i.e. 12 months prior to OSA implementation) vs. 4th 6months noting appropriate prescribing 44% of the time in the 1st 12months vs 59% of the time in the 3rd 6months (p=0.0262; diff = 14.55%). Hence, while we did note some seasonable differences, overall, we conclude that the effect of the program did not appear to wane over the first year after the OSA program was implemented.

In which infection type out of the 4 the doctors ignored the recommendations?
We are limited by a small sample size to answer this question, but our exploratory analyses did not suggest that appropriateness of prescribing varied significantly across the four infection types comparing OSA physicians and nonOSA physicians.

9) Why adjustment for age was needed? The population was a narrow, homogenous age group (those above 65 yrs).

As age is a common confounder, and may impact treatment choice, this was included as an explanatory variable. Although age was restricted to >65 yrs of age, this includes a large range of ages across which treatment choices and outcomes would be expected to vary.

10) What was the fourth quinole (not reimbursed one)

Norfloxacin – to clarify, this medication was a general benefit before and after the introduction of the OSA program. This has been clarified.

11) In the abstract you wrote: „impact on economical consequence“: this topic was not touched in the manuscript. Deleit it please.

Thank you. This has been done.

12) Figure 1 and 2: In all years in October the index visits which were followed by NO antibiotic use were outstanding (and this were the months with lowest FQ use). What is the explanation for that?

This is an astute observation that we noted was due to a substantial increase in claims for code 487 (Influenza). We presume that these claims related to influenza vaccination given in the fall (October) – for which no antibiotic was required. We have highlighted this in Appendix 2 of this response. We have added this to page 12 of the paper.

„Of note, Figure 1 displays a seasonal drop in the use of antibiotics in October of each year – this corresponds to physician claims for influenza which we postulate relates to visits for influenza vaccination.”

13) Levofloxacin use Figure: levo use dropped substantially before the introduction of the new reimbursement policy. Why?

It is possible that this related to physicians receiving the education package slightly before the program implementation date.

The reviewer wondered about several typos:
Possible calculation problems/typing errors:
1) mortality risk: in the text: 0.3% in the Table 1: 0.8%

Both numbers were correct, and are based on different denominators. In Table 1: 0.8%, the denominator was the overall study population. In the text: “For patients presenting with any of the four infections used to define unique index visits, the thirty day mortality risk was stable before (0.3%) and after (0.3%) implementation of the optional special authorization program (p=0.54)”, the “0.3% and 0.3%” were among the patients with four infections of interest. We have clarified these points.

2) in the text: 3856 patient visits vs. in Table 1: 3846 patient visits

Thank you. This is a typo, with the 3846 being correct. This has been corrected.

3) any AB use within 30 days post index visit: in the text: 49.5%, in the table 50.8%

This relates to us not being clear on our denominator in the Table. Apologies. Both numbers were correct. One number was for Study Population and the other one was for “Unique Index Visits”. This has been clarified in the text and the table.

4) In table 1. Quinolone use was 29.4 % while in the Figure 1: the monthly quinolone use was always below 20% (200/1000 index visit). In Figure 2 it was even lower. Any explanation?

You refer to the numbers provided in Table 1, which as noted, refers to quinolone use following a unique index visit:

<table>
<thead>
<tr>
<th>First Line Antibiotic Use Followed Unique Index Visits</th>
<th>n = 397,534</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolones</td>
<td>57,823 (29.4%)</td>
</tr>
</tbody>
</table>

In the text and Figure 1, we refer to the rate of quinolone use, other antibiotic use and no antibiotic use post index visit for the infectious conditions of interest. This explains the observed difference. We have clarified this in the paper.

5) In the chart review cohort, the proportional distribution of the 4 infections and consequently the AB use rates) differed substantially from the administrative data cohorts’ data. Therefore the chart review sample was not representative. The
other interesting thing that in the chart review cohort the share of URTI was much higher (69.6% vs. 46.8% in Table 1) but NO antibiotic use ocurred in smaller proportion (31.9% vs. 50.5 %). This finding is strange (I would expect the opposite) as URTI is the only infection type from the 4 one that do not require AB use due to its mainly viral origin. Could you explain this finding?

As we acknowledged in the limitations section, diagnosis information provided within physician claims is not always accurate. However, there is no reason to believe that the accuracy of claims information differs before and after the introduction of OSA, or for physician who join / do not join the OSA program. As such, while we acknowledge this as a limitation, we do not feel it is a major limitation given that we are interested in overall quinolone prescribing. We believe that this also explains the finding that is noted by the reviewer.

6) levofloxacin not levafoxacin
Thank you. This has been corrected.

7) Durbin-Watson not Durbin-Wason
Thank you. This has been corrected.

8) …with abilling claim for an infection of interest in fact had one of the…..
I am uncertain what this referred to. I could not find this typo.

9) In table : not ofloxacin but gatifloxacin was added to the formulary as a new.
Thank you. This has been corrected.

10) Tables and Figures should be understandable without reading the text. So please write the full term of acronyms (IQR, AECB, abx, etc…) under the tables/figures.
Thank you. This has been done.

11) There is only 3 figure legend but there are 4 figures. Therefore the legends do not pass to the figures. Figure 2 is probably Figure 1, panel B.
Thank you. You are correct that there are two panels within Figure 1. We have clarified this point.

Discretionary Revisions
1) I would recommend to standardize for 100 unique index visits instead of 1000. Then you see the changes in %. Also the figures would be more easy to follow.

Although we understand the concern raised by the reviewer, we have elected to use conventional metric and provided results per 1000 unique index visits.

2) Would be a good quality indicator to see in how many % of visits for URTIs resulted in AB prescription. Stratification by infection type in Table 1 would be nice.
We have provided this information within Table 1. Given potential issues with the accuracies of diagnostic codes, we have not stressed these results in the text.

3) There were 436,888 doctor visit and 397,534 unique index visit, meaning that the difference (39,354 cases, ~10%) a repeated visit with the same condition (infection type) happened within 30 days. As all this nearly 39500 re-visits followed an AB prescribing visit (20% of 196,740) means that revisiting mainly occurred due to ineffective first AB treatment (not due to the watchful waiting behaviour of doctors when not prescribe AB at the first visit but call-back the patient - good practise in case of URTI). This should be emphasized in the text.

I apologize that we were not clear on this point. We have clarified the text within this paragraph.

Reviewer's report
Title: Evaluating the impact of a novel restricted reimbursement policy for quinolone antibiotics: A time series analysis
Version: 1 Date: 12 January 2012
Reviewer: Christopher Graber

Reviewer's report:
This is a well-written, concise, logical report on the effect of implementation of an optional special authorization program had on quinolone utilization in the population studied. Though the authors were not able to demonstrate an overall reduction in the use of quinolones upon implementation of the OSA program, I do think it is important that there were significant level changes in quinolone prescription for UTI and URTI because these are prime indications where quinolones are frequently overused (this should be highlighted in the manuscript more).

Thank you. We have highlighted this further within the first paragraph of the discussion.

I only have discretionary revisions/suggestions:
1. Abstract/Methods: I think it might be useful to give quantitative numbers on how many patient courses were analyzed in each phase of the study in this part of the abstract. For example, I would mention that there were 397,534 total unique index visits analyzed with regard to overall antibiotic utilization and that 1681 charts of patients with infections of interest were reviewed for indications for quinolone usage.
   **This has been done.**

2. Abstract/Results: For the second-to-last sentence, I would add the phrase "identified through chart review" after "Among quinolone prescriptions."
   **This has been done.**

3. Page 7: Methods/Optional Special Authorization Policy: I think it would be
useful for the authors to list the criteria for use set out by the OSA directly in the manuscript (either as text in the Methods or as a table) rather than just referring to the online document. 

**We have included this in Appendix 1 of the paper.**

4. Page 7: Study Population: I am interested as to why the authors only limited their analysis to AECB, pneumonia, URTI, and UTI. I would think that the effect of the OSA on indications for use that do not fall into one of these four categories would be of great interest as well, since such use may be more likely to be "off-label" and potentially inappropriate.

**While this may be of interest, we restricted our sample to people with one of the four diagnostic claims of interest, since quinolones are most commonly used for these four conditions. Unfortunately, as we made this decision a priori, and then requested the administrative data from Alberta Health and Wellness using these criteria, we do not have information on the use of quinolones outside of these diagnostic prescribing categories.**

5. Page 13: Results/Overall antibiotic and quinolone antibiotic use before and after implementation of the OSA program: I think it would be useful to determine how much of the reduction in levofloxacin usage for AECB, pneumonia, and URTI was due to replacement by moxifloxacin. Furthermore, I would expand Figure 3 into multiple panels to show individual fluoroquinolone use for each indication (i.e. graph cipro/levo/moxi for UTI, AECB, pneumonia, URTI).

**In appendix 3 to this response (see below), we provide the figures which you suggest. You are correct since these figures show that reductions in the use of levofloxacin was offset by increased use of moxifloxacin. Given that we have several figures already, rather than adding these figures, we have simply added a sentence to the results reflecting this.**

**Editorial suggestions:**

Please make the following formatting changes during revision of your manuscript. Ensuring that the manuscript meets the journal’s manuscript structure will help to speed the production process if your manuscript is accepted for publication.

1. Acknowledgements

Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made
significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Thank you. We can confirm that no medical writer or language editor was used. We have added the following statement to the acknowledgements section: The study funders had no role in the design, collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

2. Structure

Please check the instructions for authors on the journal website to ensure that your manuscript follows the correct structure for this journal and article type.

Done

3. Tables

Please note that we are unable to display vertical lines or text within tables, no display merged cells: please re-layout your table without these elements. Tables should be formatted using the Table tool in your word processor. Please ensure the table title is above the table and the legend is below the table. For more information, see the instructions for authors on the journal website.

WE have made this requested change.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 24 March 2012. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.
Appendix 1:

Table 1. Segmented regression models predicting change of adjusted rate of quinolone use pre and post OSA program (per 1000 people with an infection of interest)

<table>
<thead>
<tr>
<th>Model</th>
<th>Estimate</th>
<th>95% CIL</th>
<th>95% CIU</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolone use <strong>before</strong> OSA program (<strong>baseline level</strong>)</td>
<td>184.1</td>
<td>172.1</td>
<td>196.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Slope</strong> of quinolone use per month <strong>before</strong> OSA program (<strong>baseline trend</strong>)</td>
<td>-0.8</td>
<td>-1.6</td>
<td>0.1</td>
<td>0.0870</td>
</tr>
<tr>
<td>Change in quinolone use immediately after OSA program (<strong>level change</strong>)</td>
<td>-3.5</td>
<td>-24.3</td>
<td>17.3</td>
<td>0.7449</td>
</tr>
<tr>
<td><strong>Slope change</strong> per month in quinolone use after OSA program (<strong>trend change</strong>)</td>
<td>0.1</td>
<td>-2.4</td>
<td>2.6</td>
<td>0.9510</td>
</tr>
<tr>
<td><strong>Absolute difference in quinolone use at 12 months post OSA program</strong></td>
<td>-2.5</td>
<td>-53.5</td>
<td>48.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Segmented regression models predicting change of adjusted rate of levofloxacin use for AECB pre and post OSA program (per 1000 people with an infection of interest)

<table>
<thead>
<tr>
<th>Model</th>
<th>Estimate</th>
<th>95% CIL</th>
<th>95% CIU</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin use before OSA program (<strong>baseline level</strong>)</td>
<td>260.0</td>
<td>248.2</td>
<td>271.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Slope</strong> of Levofloxacin use per month <strong>before</strong> OSA program (<strong>baseline trend</strong>)</td>
<td>-0.1</td>
<td>-0.9</td>
<td>0.7</td>
<td>0.787</td>
</tr>
<tr>
<td>Change in Levofloxacin use immediately after OSA program (<strong>level change</strong>)</td>
<td>-72.6</td>
<td>-93.0</td>
<td>-52.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Slope change</strong> per month in Levofloxacin use after OSA program (<strong>trend change</strong>)</td>
<td>0.1</td>
<td>-2.4</td>
<td>2.5</td>
<td>0.959</td>
</tr>
<tr>
<td><strong>Absolute difference in levofloxacin use at 12 months post OSA program</strong></td>
<td>-71.8</td>
<td>-121.9</td>
<td>-21.7</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2: The red spikes relate to claims for “influenza” – likely relating to vaccination, not requiring antibiotic claims
Appendix 3: Prescribing of levofloxacin, moxifloxacin and other antibiotics after unique visits for the different infections of interest