Author’s response to reviews

Title: Reduction of antibiotic prescriptions for acute respiratory tract infections in primary care: a systematic review

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Author’s response to reviews:

Dear Editor,

We would like to thank the reviewers for their thorough and critical review which helped us to improve our manuscript. Below you find a point by point response to the concerns and questions of the reviewers. We have clarified and rephrased the manuscript accordingly. For your ease we have highlighted all changes in yellow.

For all authors

Anna Köchling
Reviewer #1:

This paper addresses an important implementation question of how to reduce the overuse of antibiotic medication in those 13 and older. The authors have conducted a rigorous, although not exhaustive search of the literature and summarized findings from 13 randomized controlled trials, most but not all are group randomized. The paper should be of interest to Implementation Science readers, even readers like me who have a limited medical background.

• I would, however, suggest the authors add a few explanatory sentences about some of the terms that are used, e.g., POCT, which is mentioned on line 282 but does not describe the primary relevance that CRT - one of two POC tests described in the paper -- and hence infection can be tested and used in consultation in a single office visit.

• We explained the role of CRP POCT in line 270-275 and the importance of rapid strep testing in line 303 – 307.

The potential use of POCT during a single office visit has general relevance to implementation. Other approaches, such as those using a clinical decision support system (CDSS), delayed prescribing, and communication skills training are relevant to other settings besides treatment for respiratory tract infections.

One of the major challenges in improving the specificity of delivery of Abx prescriptions is that, although we know that the prescription rate currently is too high, we don't know what the optimum rate should be in practices. Indeed, the title of the paper is somewhat of a misnomer, as "optimization" of antibiotic treatment is not just dependent on reducing the percentage with RTI who are given antibiotics.

• We thank you for your helpful recommendation and changed the title from “Optimisation of antibiotic prescriptions for acute respiratory tract infections in primary care: a systematic review“ to „Reduction of antibiotic prescriptions for acute respiratory tract infections in primary care: a systematic review“.
There have been broad recommendations, such as Pew's 2016 report for the US that 30% of outpatient prescriptions were unnecessary and a 15% overall reduction in prescriptions would presumably meet the US plan of action to reduce this inappropriate use by half. The authors use an absolute 10% reduction in rates as their major criterion of success. However, the huge variation in base rates, where the lowest value is 24% and the highest is over 89% makes this an unsatisfactory single criterion for defining the number of trials that show a successful reduction. For example, under this criterion, the McGinn study, which found a 9% reduction from a 38% control condition would be considered a failure.

Can the authors make a better justification for using such a difference in rates? Is there not a bound where reduction the rate would be too high?

- This is a thoughtful reflection. Potentially harmful reductions of antibiotic prescription have rarely been addressed. We address this topic now and have added references. The range of 10 to 20% is probably appropriate (See lines 178 – 193).

The paper could do with some reorganization and adding some lead sentences to inform the reader what different parts of the paper are about.

- We reorganized the paper and added subheadings to make it easier to read, e. g. the chapter on “Secondary endpoints” (lines 496 – 546), the chapter on “Effects of multifaceted interventions” (lines 406 – 471), the chapter on “Relevance of intervention effects” (lines 472 – 495).

For example, the section starting in line 213 seems to summarize some of the individual level trial findings on the 3 trials that involve CDSS. In my reading it is unclear why just these 3 trials are discussed at this point, particularly before discussing what the interventions are around line 233.

- We updated the chapter “secondary endpoints”. It is now at the end of the “Results”.

 Aren't the two sentences starting on line 310 reversed? If not I don't understand the point.

- Thank you for your remark. We have updated this part and clarified the sentence.
Line 315 is this decayed effect after 6 weeks pertain to the Altiner trial (only)?

- Yes, in the trial by Altiner et al. the observed reductions after 6 weeks were not sustainable (lines 341-342).

Regarding a secondary endpoint, the authors' state (line 204) that the intervention groups' reduction in inappropriate prescriptions as 60% versus 27% in the control. The text is unclear to me whether this is based on a single trial, or a subset of the 17.

- The chapter about the secondary endpoints was rewritten – especially the part regarding inappropriate antibiotic prescribing.

I found it difficult to understand the descriptions of effects from multifaceted interventions, especially around line 397. "Two RCTs combined all three categories" - what categories are these?

- We have updated the chapter on effects of multifaceted interventions (lines 406-471) and used more subheadings to make it clearer and easier to read. We explained what these categories are and are confident that it is clear.

There is a description in the text regarding interventions, but the control condition descriptions are embedded in the tables; is there any explanation of why one of the control sites was able to reduce their rates 13% over time? That's as large as the overall intervention effect at T1.

- No specific explanation was given, beside Hawthorne effect. We specified that in the review (lines 624-625).

As to the methodology used to compare differences, the authors only used comparisons that came from the original studies, clustered into different types of interventions and countries. This makes it hard to absorb the material, and I found only one summary paragraph on page 513 to be an actual summary of the findings.

- Indeed summarizing the findings was a challenging task given the heterogeneity of designs and outcome measures which did not plotting the results as Forest or Abbé-plot. The in-between comparability of the RCTs is fairly limited. The best summaries are figure 3 and 4 which we believe give a good optical impression of the different baseline prescription rates and the
different effect sizes. This is to our knowledge the first attempt to display this result graphically. We provide a summary of the main results as a subsection at the beginning of the discussion which due to the aforementioned facts limit itself to provide summaries of ranges in reduction of Abx prescriptions rather than comparing trials directly.

I recognize that there are a limited number of trials and comparisons that are being made, but the authors could well have used meta-regression to check whether there are some predictive indicators that could be extracted from these studies.

• We apologize but the data available does not allow a meta-regression to examine moderators predicting e.g. successful interventions. An important point of our review is that definition of a meaningful reduction in antibiotic prescription is hard to define and we did not always agree with the authors conclusions.

There are sections that examine the distinguished effects of single element and multifaceted interventions. While the ranges of intervention differences are given, there is no overall point and confidence interval for these overall effects. This makes it impossible to compare the two sets of interventions.

• The available data from the RCTs published trial does unfortunately not always allow to give separate estimates or recalculate effects and confidence intervals of the components of multifaceted trial. Whenever available we reported the confidence intervals.

Line 149: Define times T1 and T2. I presume T2 is over one year based on line 192 but it is not clear.

• Time points for T1 and T2 are very heterogeneous among included RCTs. Therefore, we are referring to our tabular summary of study characteristics in the text (line 161-164).

I wasn't able to find footnotes to the figures in the version that I received, included the downloaded figures. These footnotes are essential to understanding the differences in all the colored diamonds and circles, please check that they are available.

• Footnotes and legend were at the end of the manuscript. We corrected that and added the figure keys in the graphic. The legends for the figures are in the main manuscript.
Reviewer #2:

This systematic review attempts to better define a challenging problem in primary care - that is, improving antibiotic prescriptions for common infections (in this case respiratory tract infections). This is a difficult issue to study, as the authors note, due to the extreme heterogeneity in both practice as well as study designs.

At times, as written, it is unclear if the participants are the primary care practices or the patients in these practices.

• The direct recipient of the interventions where sometimes physicians and sometimes patients, the main outcome was prescription. Therefore this is indeed complex. We have tried to rephrase.

It is unfortunate that your scope of review could not be broadened beyond the databases specified as this would have strengthened your results and conclusions, and may also have increased the generalizability of your findings.

• We agree it is a pity that due to lack of funding we could not search EMBASE and other databases. However, with regard to the interpretation of our findings, we believe that the inclusion of few trials we have missed by not having access to more databases, would not have changed our conclusion.

The manuscript does require further proofreading by someone fluent in written English (there are minor grammatical, punctuation and formatting errors throughout

o e.g. use of abbreviations without defining them at the first use, e.g. POCT, CRP, RADT;

❖ We checked the abbreviations.

o using numerals vs. spelling out numbers below ten [e.g. six vs. 6];
We checked and corrected the systematic review.
- starting sentences with numerals [e.g. 17 instead of seventeen];

We checked and rephrased.
- formatting of references as they are cited in the text;

We checked the systematic review and added references when individual RCTs were mentioned.
- use of "und" instead of "and").

We corrected that.

Methods

Lines 128-132 belong in the Results
- We added a new chapter “study selection” at the beginning of the “Results” (line 299 - 208).

Methods should include a more detailed description of the types of participants (e.g. patients, practices) and types of interventions that were eligible for inclusion.
- We delivered a more detailed prescription of participating patients (line 132 – 135), physicians and practices (135 – 137).
- We specified the eligible interventions in line 119 – 124.

Some of these details are included in the Results section rather than the Methods section. Outcomes, both primary and secondary, should be defined in the Methods section (they are first mentioned in the Results, lines 185-202);
- We clarified the primary and secondary outcomes in the Methods (line 126- 131).
for the primary outcome of 10% reduction in prescribing, how was this determined / why is this felt to be clinically important/significant? (from the Discussion it seems that 10% reduction was selected only after review of eligible studies);

• The problem of a meaningful clinically important difference has been well studied for comparison of performance between physicians and for clinical outcomes, e.g. pain. What constitutes meaningful clinically important difference has not been established either by consensus or biometric methods based on observed variations in performance. This is stated in the method section, we have expanded this section. We used as we clearly state an arbitrary cut off of 10%. This corresponds well e.g. with the threshold for small change in pain or functional capacity chosen in the recent ACP guidelines for back pain.

the Results also refer to rates of "inappropriate" antibiotics but how inappropriateness was assessed or defined is not clear

• The secondary outcome “Inappropriate antibiotic prescriptions” is explained in lines 526 – 541.

Please comment on handling of missing data in the Methods

• We address missing data which was not reported in the method section (line 149 – 153).

Was this systematic review registered?

• It was not registered (line 97). PROPERO refused to register this review since we already started the review when we tried to register.

• Results

Line 186: I am not clear about the meaning of the word "registered" in this context - could this be better defined or explained for the reader? (it is not a word that is commonly used when describing antibiotic prescriptions)

• We rephrased the sentence (line 229).

Line 204, re: inappropriate antibiotics - see comment above
• The secondary outcome “Inappropriate antibiotic prescriptions” is explained in line 526 – 541.

Lines 213-219 are a bit confusing to read; similar to use of the term "inappropriate antibiotics" it is not clear exactly what is meant by "non-indicated" antibiotics and, later, "inadequate" antibiotic prescribing

• We updated the chapter “secondary outcomes” (lines 496 – 546) and explained the term “inappropriate”.

Results of many secondary outcomes (as stated in the Methods) are not described

• We updated the chapter “secondary endpoints”.

Discussion

please elaborate on possible limitations / bias due to omission of other papers in other databases. Given that you have observed such variable differences in prescribing rates in the studies that were included, I would wonder how inclusion of papers from other world regions might have influenced your findings.

• We have rephrased and expanded the limitation section. However, our main point is unchanged. Even if we would have identified few additional RCTs on the subject this would not have changed our conclusion regarding the comparability and the lack of standards for measuring success in trials aiming to reduce antibiotic prescriptions (line 649 – 653).

Minor Comments:

Perhaps write out the inclusion and exclusion criteria (lines 111-121) rather than listing these with bullets (it would read more fluently, in keeping with the remainder of the manuscript)

• We have written out the inclusion and exclusion criteria (lines 115 – 139).
The paragraph starting on line 143 might be better titled "Data Analysis" (?)

- We beg to disagree. We believe the content of the section following line 152 (formerly 145) is better reflected by the “Summary of Abx prescription rates for acute upper/lower RTI”.

  e.g. line 310, line 348, line 498 - would include the reference in brackets when referring to specific studies

  - We added the references.

Lines 344, 345 - "significantly" is written twice

  - We corrected that sentence.

Consider replacing "percentage points" with "percent"

  - We replaced “percentage point” with “percent”.

Tables: add definitions for T0, T1, T2 to Table legends;

  - Footnotes and legend were at the end of the manuscript. We corrected that and added the figure keys in the graphic. The legends for the figures are in the main manuscript

  - Thank you for your remark, we corrected it.