Author’s response to reviews

Title: Government policy interventions to reduce human antimicrobial use: protocol for a systematic review and meta-analysis

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Author’s response to reviews:

Dear Editors,

On behalf of myself and my co-authors, I am submitting a revised version of our paper entitled Government policy interventions to reduce human antimicrobial use: protocol for a systematic review and meta-analysis. We want to thank the reviewers for their thoughtful comments on our paper, which we have revised accordingly. Please find our specific responses below:

Reviewer #1: The following revisions required to improve quality of the manuscript;

1. Grey literature: Strategy for grey literature is not clear. How would you search that data from non-indexed journals? Kindly add to protocol.

   We have expanded our discussion of grey literature searching to clarify that we will identify non-indexed articles using web-searching with keywords, hand-searching reference lists, and contacting subject experts from around the world.

   The text now reads:

   To identify grey literature, we will use keywords to conduct targeted web searching to identify government and civil society reports, and hand-search reference lists of included studies to identify non-indexed articles. We will also use the ProQuest Dissertations and Theses database to
identify dissertations on this topic. After full-text screening, we will also contact six subject-matter experts – one from each WHO region – to identify any additional studies from their region that meet our inclusion criteria.

2. Agreement between review authors: How would you ensure the agreement between the two review authors? What will be the minimum cut-off of agreement and how would you measure and report? Kindly add all these information to the protocol.

   As noted in the text, “Any disagreements between reviewers will be resolved by consensus or in consultation with a third reviewer (SJH) if needed.” As such it is not necessary to measure reviewer agreement.

3. Contact with authors: It is important to mention that how many times you would contact to an author regarding to you queries.

   We have added the following sentence to the manuscript: “Authors will be contacted twice before data is marked as missing.”

4. Need reference: Kindly add reference to the I2-statistic and also add the common cut-off for heterogeneity [Line 264; Page 13].

   We have added the requested citations.

5. Meta-analysis: it would be better to add more on meta-analysis plans such as type of analysis, choice of model, small study effects and publication bias etc. as a priory.

   We have added additional paragraphs on our meta-analysis plans as requested.

6. Sensitivity analysis: There is a need to add sensitivity analysis plan as a priory. A plan for influential analysis may also be added.

   We have amended the protocol to note that sensitivity analyses will be carried out to consider the impact of dropping weaker study designs and studies at high risk of bias.
Reviewer #2:

This paper describes a protocol for a systematic review with the dual aim of identifying and describing evaluated government policy interventions to decrease antimicrobial use, and to estimate the effectiveness of these strategies.

The methodology for the review is in general well described.

Thank you!

However, I think that the eligible population and eligible intervention sections need clarifying, as I think that details which are relevant regarding the eligible population are under the intervention section and vice versa. For example, I think the fact that impact of the government policy can be assessed at any level should go under the population section, whereas details of what constitutes a 'government' should go under the intervention section.

We have made this change as requested.

In the eligibility criteria for the effectiveness review it states that to be included studies will need to meet the methodological requirements of the EPOC group. It would be preferable for these criteria to be explicitly reported. Does it, for example, include the requirement that controlled before-after studies have more than one intervention and control group?

We have clarified these requirements as requested; the text now reads:

Quasi-experimental designs will need to meet the minimum methodological requirements of the Cochrane Collaboration’s Effective Practice and Organization of Care (EPOC) Group. This means that controlled before-and after studies must have at least two intervention and two control sites, and interrupted time series studies must have at least three measures pre- and post-intervention to be included. Randomized controlled trials and non-randomized controlled trials will be included. Uncontrolled before/after studies with at least three measures pre- and post-intervention may also be included if is possible to re-analyse the data using an interrupted time-series analysis.

The researchers report that they will use the EPOC criteria for assessing risk of bias of the included studies. Although not a requirement of the tool, it would be nice if the baseline characteristics that will be assessed to look at comparability of populations could be pre-specified in the protocol.
We have made this change as requested by adding the line “For controlled studies, we will look for baseline imbalances in antibiotic prescribing levels, and population age and sex/gender distribution.”

In the methods, the first section should be modified to read "This systematic review protocol has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines."

We have made this change as requested.

I have primarily assessed the methodology of the review. However, I note that the authors concentrate heavily on the fact that reducing antimicrobial use is a method of reducing the risk of antimicrobial resistance. Therefore, it seems that levels of antimicrobial use are being used as a proxy for antimicrobial resistance, and that this should instead be the outcome of interest for this review? It may be that there are very few studies that have looked directly at how policy interventions affect antimicrobial resistance, or another reason for concentrating on this outcome. In any case, I think the protocol would benefit from reporting of the rationale for choosing levels of antimicrobial use as an outcome rather than antimicrobial resistance.

We have added an explanation of this choice to the “outcomes” section, which reads:

“Many countries do not collect sufficient regional or national surveillance data on AMR to allow analysis of the impact of policy level interventions on resistance, and surveillance definitions of resistance vary between countries[24]. As such, we chose to focus on antimicrobial use, which is an intermediary between policy interventions and AMR. Better data exists for this outcome, as prescribing and sales of antibiotics are often captured as routine health administrative data.”

Note that in Prospero there is a review registered that may overlap with this research question: Jane Lim, Shweta Singh, Minh Cam Duong, Clarence Tam, Li Yang Hsu, Mishal Khan, Johanna Hanefeld, Helena Legido-Quigley. Assessing the impact of policies and programs targeting antimicrobial resistance: a systematic review. PROSPERO 2017:CRD42017064629 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017064629

Thank you! We became aware of this protocol shortly after submitting our own protocol – while the research questions do partially overlap we still think there is value to completing our review, particularly as replication is becoming increasingly recommended in systematic reviews.