Author’s response to reviews

Title: Cannabis use and the risk of tuberculosis: A systematic review

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Version: 1 Date: 03 May 2019

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We would like to thank the editor and the reviewers for taking the time to review our manuscript and for the positive feedback. Please find our point-by-point response to each of the reviewers’ comments below.

Reviewer reports:

Jakob Manthey (Reviewer 1): This systematic review is well written and presents the available literature in a concise and balanced way. I appreciate that the authors make their decision transparent to include studies without comparator groups as these studies are of low quality. However, given the lack of high-quality studies I think it is reasonable to include these studies in this review.

My professional expertise does not allow to comment on the TB part of the review, but the cannabis and epidemiological aspects are well covered and discussed.
Author response: Thank you for your positive feedback on our manuscript. We are not completely sure whether you are indicating that you agree with our approach or are suggesting that we should have treated the studies without a comparator group in exactly the same way as those that do have a comparator group. We feel that our approach, of including papers without a comparator group in the review, but placing less emphasis on their findings in the way that we narratively synthesise the evidence, is most appropriate. The findings of all studies are fully reported in Table 1.

Stéphanie Baggio (Reviewer 2): This manuscript summarizes previous findings on the relationship between tuberculosis and cannabis use using a systematic review. This is a well-written study with a sound and well-described methodology. However, I have some concerns, as listed below.

My main concern is that the authors did not include a meta-analysis to provide further evidence on the relationship between tuberculosis and cannabis use. In the current version, the manuscript is inconclusive, and a meta-analysis would help to achieve a better understanding of the findings of the studies included in the systematic review. The authors stated that the studies are too heterogeneous, but meta-analyses are designed to account for clinical heterogeneity (patients, outcomes, designs) and statistical heterogeneity.

Author response: In conducting this review we certainly did consider conducting a meta-analysis but after due consideration we concluded that it was not appropriate. The Cochrane systematic review guidelines help to explain our justification for this decision. The guidelines state that “there are situations in which a meta-analysis can be more of a hindrance than a help” and goes on to say that “if studies are clinically diverse then a meta-analysis may be meaningless, and genuine differences in effects may be obscured”. The studies in our review were certainly clinically diverse. For example, some looked at latent TB as the outcome, others looked at active disease. There were also differences in studies in terms of the definition of cannabis exposure – for example, some studies examined the risks associated with sharing a cannabis water pipe with a TB case, others examined people engaged in activities such as ‘hotboxing’, while others simply examined ‘cannabis use ever’ as the exposure of interest.

Furthermore, Cochrane states that “meta-analyses of studies that are at risk of bias may be seriously misleading. If bias is present in each (or some) of the individual studies, meta-analysis will simply compound the errors, and produce a ‘wrong’ result that may be interpreted as having more credibility.” This again is highly pertinent to our review in which all studies were assessed as being at high risk of bias.
We hope that we have adequately justified why we believe that it is not appropriate to conduct a meta-analysis in this review.

Reference to Cochrane guidelines on the topic: https://handbook-1.cochrane.org/chapter_9/9_1_4_when_not_to_use_meta_analysis_in_a_review.htm

Reviewer 2: Cannabis is increasingly used to (self-) treat chronic pain. How does cannabis worsen health condition of people with active tuberculosis? This question should be addressed in the discussion section.

Author response: Our review focuses on cannabis use as a risk factor for acquiring TB. The question as to how cannabis might worsen the condition of people who already have active TB disease is therefore outside the scope of the review. On consideration we therefore feel that to bring this point in, in the discussion, though important in its own right, would not reflect the evidence we have reviewed.

Reviewer 2: The abstract does not mention that most studies found a relationship between tuberculosis and cannabis use. At first read, I thought that there was no relationship, which was misleading.

Author response: We believe that the abstract gives an accurate reflection of the state of the evidence. We have been very careful to avoid overstating the findings, since, as we also note in the abstract, the quality of the evidence was low (all studies were at high risk of bias). It is true that four of the six comparative studies provided some evidence of an association but we feel that to simply state this in the abstract without providing some context (e.g. that only two of the four studies examining the association between cannabis and latent TB adjusted for confounding, and that neither of the two studies examining the association between cannabis and active disease found evidence of an association) may be a little misleading and risk over-stating the strength of the evidence.

Reviewer 2: To avoid publication bias, the authors should search for published protocols and registered trials. As the link between tuberculosis and cannabis use seems quite weak, such studies may change significantly the findings. Therefore, it seems crucial to include them.
Author response: We were careful in this review to search for both published and unpublished literature, including ongoing studies. Given the nature of the subject area registered clinical trials in this area would be highly unlikely. In addition to the electronic database searches we therefore used several other methods to detect relevant studies (including those that are ongoing):

i) We conducted a forward citation search in Web of Science to help identify follow-up studies or new research citing any of the study reports included in the review

ii) We searched the World Health Organization website and Google Scholar

iii) We hand-searched searched abstract lists for key conferences

iv) Experts in the field were contacted - again this would have helped to identify any planned (i.e. at the protocol stage) or ongoing studies

We believe that we have taken the most appropriate approach to identifying the relevant literature, given the subject area. We do comment in the discussion section that publication bias may be a concern because many outbreaks will simply never be reported.

Reviewer 2: Minor comments

Please use "tuberculosis" in the abstract. "TB" is not defined and the number of words is the same using the whole term or its abbreviation.

Author response: Thank you for noting this - we have now defined TB in the abstract and highlighted this change in yellow (Abstract, line 24, page 2).

That concludes our response to reviewers and we do hope it is satisfactory and that you do consider publishing this review.