Author's response to reviews

Title: Systematic Literature Review Assessing Tobacco Smoke Exposure as a Risk Factor for Serious Respiratory Syncytial Virus Disease Among Infants and Young Children

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Author's response to reviews:

Dear Editor:

Our prior submission to BMC Public Health was rejected because we had not followed systematic review criteria, so we selected the PRISMA criteria and reformatted our paper to include everything that is needed for a systematic review including an assessment of bias for every article. Additionally, we addressed the reviewers’ concerns as follows.

Reviewer 1

This is a scientifically sound but relatively limited study. The meta analysis suffers from a poor number of existing studies. Therefore, conclusions base on solely one - three studies. i.e. the results section of the abstract: "One study reported increased risk of death from bronchiolitis. Two studies found an increased risk of RSV lower respiratory tract infection in children presenting in the office setting, while three did not." Since the authors can not improve this but need to wait for further studies, the manuscripts is not able to reach a high priority even after revision.

There was only one outcome for which there were only 3 studies. We revised the abstract to remove reference to outcomes for which there were few studies. Our review is based on 30 studies which we feel is adequate to make the review worthwhile.

Reviewer 2

Needs some language corrections before being published.

We have edited the entire manuscript and it has been proof read by three individuals who are not the authors.
1. Is the question posed by the authors well defined?
The author highlights the known risk factors for RSV among children under five and clearly points that the role of environment tobacco smoking as risk factor for RSV was less known or uncertain. Though it implies equivocal evidence existed there was no a clear description and analysis of the evidence i.e citing magnitudes of evidences, the studies and validity of such evidence.

This section was revised: “Although exposure to environmental tobacco smoke (ETS) is a risk factor for asthma, wheezing, decreased pulmonary function, otitis media, cough, and lower respiratory tract infections (LRTIs) in general [13], its role in the development of serious RSV disease among infants and young children is less clear and has been a topic of interest among the healthcare community [14].” The rest of the manuscript then provides a detailed description of the existing evidence.

2. Are the methods appropriate and well described?

a) Whereas it is important to present valid evidence on ETS exposure and RSV severity, there is a need of including a section in the methodology justifying using literature review methodology but not primary data collection to produce evidence of the association.

This is difficult to address. Investigators use many different research methods to address a particular problem, and while in a grant proposal an investigator is expected to justify using one research approach rather than another, when the results are published, authors are not expected to justify why they did not conduct a different study.

b) The authors clearly show that they used several engines to search for the varieties of the exposure and outcomes of interest. The search terms were very clear and relevant to the issue being studied.

c) However if they also searched for unpublished/grey literatures it should be stated so, if not it should also be stated. Thus one should be able to get an opinion of the extent of publication bias inherent in this publication.

We have added the following to the methods to address this request: “We did not search for unpublished studies or reports.”

d) Readers would like to get to know the extent of comparability of the publications reviewed its reliability, validity and design. Thus the method/criteria for inclusion and exclusion of paper should be described in more detail for repeatability. Otherwise a clear description of the critical appraisal tool needs to be made for the readers to understand it.
In response to this request we have added an entire page describing our use of the Cochrane risk of bias tool starting on page 8.

e) That notwithstanding the statements “Each relevant article was read by several authors, study details were extracted into tables, and table content was verified by a second reviewer not involved in the data extraction. The authors discussed each article to reach consensus regarding the study details” should be backed by more objective methods of assessing the papers.

See the previous comment.

3. Are the data sound?
The study gives a very clear description of the various studies included, an analysis of the papers has to be done and more importantly how does it contribute to the evidence being sought.

We have added more than a page of text to the results summarizing our bias assessment and have added a large table providing a detailed assessment of each paper in regard to potential biases.

4. Are the discussion and conclusions well balanced and adequately supported by the data?
The aim of the study was to evaluate the evidence of an association between ETS exposure and increased risk of serious RSV disease. Authors made statements that there was evidence supporting that there was an association between ETS and RSV. This evidence was deduced from the narration, there was no objective assessment of the evidence like results of meta-analysis and thus it could be added to add more strength to the study.

We agree that had it been possible to conduct a meta-analysis it would strengthen the argument. But for reasons explained in the manuscript, the many different designs employed by the authors of the primary studies preclude a meta-analysis.

5. Are limitations of the work clearly stated?
There is a mention of the limitation in ascertaining of exposure and outcome, however none was clear about the analysis.

Given the nature of the primary literature, we did not conduct a formal analysis in this paper. We have presented the literature in a format that allows readers to make their own judgment based on the breadth and quality of evidence. We have added the following to the discussion: “This review has several limitations. The search was limited to studies published from 1990 to April 2009 in the English
language. We searched only Pubmed and Embase and did not attempt to locate unpublished studies. The nature of the primary studies precluded a meta-analysis.”

6. Do the title and abstract accurately convey what has been found?
A title and a structured abstract are presented; all accurately convey what has been found.

7. Competing interest and acknowledgements.
Authors presented acknowledgements as well as a statement on competing/conflict of interest.

8. Is the writing acceptable
It is acceptable if authors will address issue raised in this review.

Reviewer 3

Thank you for giving me the opportunity to review the manuscript. Overall, the manuscript is well written. There are a few comments I would like to make:

1. There is no record as to which internationally agreed to convention of systematic reviewing was adhered to eg. MOOSE;
We followed the PRISMA criteria and used the Cochrane Review Tool. We have made these points in the methods section.

2. The limitation to this study by searching on Pubmed and Embase may need to be highlighted and is if there were any language limitations;
We have indicated that only English articles were considered and that our search was limited to these two search engines.

3. The authors may need to report their assessment on publication bias in so far as the forest plots are concerned.
We have eliminated the forest plots. We have added a supplementary chart listing all of the potential biases of each article using the Cochrane bias assessment protocol.

Reviewer 4

Reviewer’s report:
Discretionary revisions:
1. In the Background/Introduction, it would be beneficial to delve into pathophysiology, to lay scientific basis for the causation of the respiratory tract infections by RSV especially in premature infants in the presence of ETS.
We found nothing in our search that provided insight into the pathophysiology of this association, so we are unable to added the requested information.

2. In the Background paragraph1, the author states “Risk factors for RSV
infection include .......... older siblings................. young chronological age”. It is not clear what is meant by “older siblings”. A little restatement will be welcome to make the sentence more coherent.

We have changed this to “having older brothers or sisters in the household.”

Minor essential revisions:
3. The referencing ought to be uniform, preferably put the number at the reference and not at the end of the sentence eg Marbury[32]....... rather than Marbury stated.................. [32].

We have addressed this in the rewrite. Generally, all references are placed at the end of the sentence except when the sentence makes more than one point, in which case the reference appears after the point that it supports.

4. On page 14, the statement starting “ETS exposure is associated with ..........” needs referencing.

We have added three references for this statement.

5. The statement in the paragraph following “It is difficult to interpret results from 3 studies ......”, these 3 studies need to be referenced for identification.

This sentence no longer appears in the manuscript.

Thank you for considering our new submission for publication in BMC Pediatrics.

Sincerely

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