

Dear Prof. Higgins

Manuscript ID BMJ.2015.028142.R2 entitled "Impact of BCG, DTP and measles-containing vaccines on childhood mortality: a systematic review"

Thank you for sending us your paper. We sent it again to our statistical advisor prof. Riley for external peer review and discussed it internally. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below and in the report from prof. Riley, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

dr. Wim Weber  
European editor, The BMJ  
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Our discussions were about the following:

1. The DTP studies were considered to have been seriously at risk of bias and showed a great deal of heterogeneity in their results - Is averaging the results, even when the worst of the studies were removed, appropriate and safe?

RECOMMENDATION 1: Can you please clearly note the limitation of studies being at high risk of bias when making any conclusions. For example, at the moment the abstract conclusions do not mention the high risk of bias when mentioning the conclusions about DTP. So, please go through and just check that any conclusions about positive or negative effects of the vaccines are always accompanied with a note on risk of bias.

2. The RR for DTP quoted in the abstract is 1.38, but the text says that removing a particularly poor study brought this down to 1.36. Is thus 1.36 the more appropriate figure to highlight ?

We realized that this is subjective. According to your risk of bias criteria, it is hard to exclude this one poor study over and above other poor studies that were labelled at 'high risk of bias'. You already removed 7 other studies at VERY high risk of bias, but this was not in that category.

RECOMMENDATION 2: Given that excluding the study is post-hoc and gives a more dramatic effect (as it increases significance, with CI now excluding 1) about increased mortality risk, we would prefer we stick to the 1.38 one.

3. We wondered about mentioning indicative absolute risks in the paper, in the text and the abstract for all three vaccines.

RECOMMENDATION 3: We felt that it is important to put the results in context of absolute risks. But we also realized that this may be difficult, as the baseline risk may vary considerably across populations, and so you may need to link the 'average' RRs to some 'average' baseline risk. But a paragraph in the discussion would be welcome.

4. You responded generally satisfactorily to queries from Refs 1 and 2, but choose not to follow ref 3 (queries # 72-86). These mostly relate to the interpretation of the biases. You argue that this is rather speculative, while the ref feels that, once you know the direction, you can work with them.

RECOMMENDATION 4: We tend to agree with you, as it is difficult to be sure about the direction of bias. Even if on average one might expect bias in a particular direction, one cannot be sure that here (in this setting) that biases for a particular study are not in the other direction. One can see this in meta-epidemiological research, e.g. comparing effects from trials with effects from observational studies. Although, on average, effects from observational studies tend to inflate the effect, in some settings the effect can be deflated by the observational evidence.

5. Causal language

RECOMMENDATION 5: On re-review, we noticed that the language is at times slightly more causal than we would like. E.g. in the what this study adds box, you say: "We found evidence that receipt of BCG and measles-containing vaccines may reduce overall mortality by more than expected through their effects on the diseases they prevent, and evidence that receipt of DTP may increase all-cause mortality". Though some evidence is from trials and causality may be more likely, we think that in general it would be safer to use 'were associated with ..' throughout. Indeed, you already do this in most places, but there are some omissions.

First, please revise your paper to respond to all of the comments by prof. Riely. His report is available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

**\*\* Comments from the external peer reviewers\*\***

Reviewer: 1

Recommendation:

Comments:

This is an incredibly thorough and detailed revision / response to comments. The authors have addressed my statistical review in detail, and I am pleased to see that results are robust to the issues I raised. I therefore do not have any remaining concerns, and I think this article would be an excellent addition to the BMJ. This review is clearly a massive undertaking and a crucial, transparent summary of the evidence-based; the meta-analyses are exceptionally undertaken and reported, and the conclusions appear justified based on the results. My only remaining comment is for the authors to state, in their results section, that the sensitivity analyses did not change conclusions (if they agree). Currently, they say in the methods that "Sensitivity analyses using alternative meta-analysis approaches are presented in online supplementary material." but they never discuss the findings as far as I can tell. Finally, I must note that I agree with the authors their subgroup assessments of sex are done well. Reviewer 1 was very critical but the authors have correctly only pooled within-trial information (direct differences in the effect between males and females) and I also don't see why any risk of bias issues would affect boys differently to girls.  
Best wishes, Richard Riley

Additional Questions:

Please enter your name: Richard Riley

Job Title: Professor of Biostatistics

Institution: Keele University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Funds for a member of staff?: No

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vi) unanswered questions and future research

g. Footnotes and statements

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