

Response to comments from reviewers and editors

Response to scientific editor

Many thanks for your helpful comments. We have revised the manuscript according to suggestions and comments from you and reviewers.

To highlight the methodological focus of the manuscript, we have revised the title as: “Antibiotics for eradicating meningococcal carriage: network meta-analysis and investigation of evidence inconsistency” (page 1).

Following are our point-by-point response and descriptions of related changes.

SE-1 Funding source: Please offer the support certificate.

Response: A certificate document is provided.

SE-2 Conflict of interest: Please offer signed pdf files.

Response: The signed files are attached. – All authors!

SE-3 Biostatistics: Any manuscript describing a study (basic research and clinical research) that used biostatistics must include a statement in the Materials and Methods section affirming that the statistical review of the study was performed by a biomedical statistician. Statistical review is performed before the submission or after peer-review. The author invites an expert in Biomedical Statistics to evaluate the statistical method(s) used in the study, including but not limited to the t-test (group or paired comparisons), chi-square test, ridit, probit, logit and regression (linear, curvilinear, or stepwise) modeling, correlation, analysis of variance, and analysis of covariance. The review by the biomedical statistician is conducted with respect to the following points: (1) Statistical methods are adequately and appropriately described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. The number of observations and subjects (n) is given. Losses in observations, such as drop-outs from the study, are reported; (4) Values, such as ED50, LD50 and IC50, have the 95% confidence limits calculated and have been compared by weighted probit modeling (using the functions described by Bliss and Finney); and (5) The word “significantly” is replaced by its synonyms (if it indicates extent) or the P value (if it indicates statistical significance). In addition, a copy of any approval document(s)/letter(s) or waiver should be provided to the BPG in PDF format.

Response: A sentence is added in the method section: “All statistical analyses were conducted and results checked by the corresponding author (FS) who has training and experience in statistical methods.” (page 7). Although this may not be really applicable, as request, I (Prof Song) have also signed a statement.

SE-4 AIM (no more than 20 words): The purpose of the study should be stated clearly and with no or minimal background information, following the format of: “To investigate/study/determine...”

Response: Many thanks and it has been revised as: “To compare different antibiotics for eradicating the carriage of *Neisseria meningitidis*, and to investigate heterogeneity and evidence inconsistency.” (Page 2)

SE-5 Please offer the audio core tip, the requirement are as follows: In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications: Acceptable file formats: .mp3, .wav, or .aiff. Maximum file size: 10 MB. To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

Response: The requested audio core tip is provided. Asmaa – could you do this, please?

SE-6 Please write the comments. Writing requirements for each subsection (1) Background To summarize concisely and accurately the relevant background information so that readers may gain some basic knowledge about your study’s relevance and understand its significance for the field as a whole. (2) Research frontiers To introduce briefly the current hotspots or important areas in the research field as related to your study. (3) Innovations and breakthroughs To summarize and emphasize the differences, particularly the advances, achievements, innovations and breakthroughs, as compared to other related or similar studies in the literature, which will allow the readers to assimilate the major points of your article. (4) Applications To summarize the practical applications of your research findings, so that readers may understand the perspectives by which this study will affect the field and future research. (5) Terminology To describe concisely and accurately any terms that may not be familiar to the majority of the readers, but which are essential for understanding your article.

Response: The requested Comments are provided (page 13-14).

SE-7 Would you please provide the decomposable figure 1, whose parts are movable and words can be edited.

Response: New Figure 1 is provided as requested, which could be easily edited. (Page 20)

SE-8 Tables: Please offer references number for all study.

Response: Thank you for this suggestion. We have added references to studies in Table 1 and Table 2.

Response to Reviewer-1 (02508408)

Response: We appreciate very much Reviewer-1’s positive comments on the manuscript.

Response to Reviewer-2 (02976990)

R2.1 The greatest weakness of this work is the heterogeneity between studies that has made comparisons very difficult. The meta-analysis combines very divergent groups and attempts to make comparisons some of which are not ideal. In this meta-analysis we have young people, military, and

contacts of cases from different regions in terms of disease burden and the study quality also varies a lot. This is the most “tricky” bit of this analysis. This also takes away from the “richness of information” readers will be expecting from this article. I however commend the authors for highlighting these weaknesses and pointing out the causes of inconsistencies such as effect modifiers that would be responsible for some observed results. To deal with the above-mentioned shortcoming, the authors should consider doing sub-group analyses comparing similar studies, groups or doses (where applicable). This will yield more reliable, easily interpretable estimates.

Response: We thank Reviewer-2 for these interesting comments. We agree that the RCTs included in the analysis were diverse in terms of participants and interventions, so we have attempted to investigate heterogeneity and evidence inconsistency in the network meta-analysis. As Reviewer-2 noticed, our investigation of heterogeneity and evidence inconsistency has produced some interesting findings. The methods we have used to investigate heterogeneity and evidence inconsistency are actually providing results similar to subgroup analysis. For example, results shown in Table 4 are differences between subgroups defined by types of carriers and study quality characteristics. Results shown in Table 5 and Figure 4 are based on subgroups of trials defined by direct or indirect evidence. Due to the relatively small number of trials included, further subgroup analyses could not be appropriately conducted.

R2.2 I agree with the authors that some of the indirect comparisons may not be valid. I will defer the decision on whether to keep these or exclude them to the authors.

Response: Thank you for this positive comment.

R2.3 Funnel plots are very crucial in meta-analysis. The authors have more than 20 studies, which should be adequate for a funnel plot. I would recommend that they do the funnel plot and include it in the article so that readers can interpret the findings of this meta-analysis with that in mind.

Response: Thank you for this suggestion. We have added a funnel plot using data from 14 placebo-controlled trial (new Figure 2). Corresponding changes are also made in Method (page 7), Results (page 8), and Discussion (page 13). Funnel plot could not be appropriately used to assess trials that compared different antibiotics, due to the small number of relevant trials.

R2.4 On Figure 2 Rifampin is spelt as “Rfampin”. kindly rectify this.

Response: Thank you very much for your careful checking. We have corrected this spelling error (Figure 3 in the revised manuscript).