PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and Safety of Available Preventive Tuberculosis Treatment Regimens for Children and Adolescents: Protocol for a Systematic Review and Network Meta-analysis.
AUTHORS	Sabella-Jiménez, Vanessa Hoyos Mendez, Yenifer Benjumea-Bedoya, Dione Estupiñán-Bohorquez, Andrés Felipe Acosta-Reyes, Jorge Florez, Ivan D D.

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Alexander Gonzalez Institution and Country: Instituto de Medicina Tropical Pedro Kouri, Cuba Competing interests: None
REVIEW RETURNED	03-Jun-2022

GENERAL COMMENTS	The protocol fits properly to the PRISMA statement (PRISMA- P) 2015, maybe the authors could consider to declare explicitly the PICO strategy was used for the construction of the research question and bibliographical search as we observed you when the authors declare (Participants, Interventions, Comparations and Outcomes) Also they could consider to use the updated of PRISMA 2020 statement for the final report

REVIEWER	Reviewer name: Dr. Hawult Taye Adane Institution and Country: Armauer Hansen Research Institute, Ethiopia Competing interests: None
REVIEW RETURNED	25-May-2022

GENERAL COMMENTS	Dear Authors First, I would like to thank Sabella-Jimenez et al for developing this interesting review protocol entitled as" Effectiveness and Safety of Available Preventive Tuberculosis Treatment Regimens for Children and Adolescents: Protocol for a Systematic Review and Network Meta-analysis." I found that the protocol has well define research question and all sections of the main document is well written, articulated and prepared as per the standard (PRISMA-P). Hence, I am very happy to see the published protocol and the Review and Network Meta-analysis papers as well. Thank you that I was very comfortable and really enjoy on reading this interesting protocol. I have no major comments, except the following minor issues for your consideration. INTRODUCTION • Line: 51-52. I think, instead of the word "determine", other alternative terms such as estimate/evaluate or provide summary of ….. is preferred to explain the aim of SRNMA protocol/ final report. • Though it is not mandatory, could you provide an explicit

statement of the question or hypothesis that can reflect the expected/possible Effect difference among the existing regimens (Intervention Vs comparator) .

METHODS AND ANALYSIS
• Subheading: Study design would be better to describe as Review method/approach and the specific method (PICO) should be mentioned. I would say "The protocol of this systematic review was developed based on PICO components of the review method and prepared according to the …. (PRISMA-P).
Participants
• Why you exclude studies with HIV infected children/adolescents. I think, at this stage, it is better to consider all possible target population who are eligible for TPT and then you can see the difference (effectiveness and safety) Or you may a room to perform subgroup analysis if you will find enough numbers of related studies.

Outcomes
• Are you rely on your own primary outcome definition for active TB as the disease caused by being infected with M.tuberculosis OR you will stick with the standard definition- I think all original articles use the same case definition for active TB. Alternatively, you can define based on your inclusion and exclusion criteria. Here please noted that you should include "Eligibility criteria" as an additional subheading

Searching strategies
• I think, it would be also good to present your searching strategies and study selection process using diagram (Figure)- preferably PRISMA flow chart-.

REVIEWER	Reviewer name: Yohhei Hamada
	Institution and Country: United Kingdom of Great Britain and Northern Ireland
	Competing interests: None
REVIEW RETURNED	24-May-2022

GENERAL COMMENTS	The protocol is well written and follows the standard methodology. I have several comments below that the authors may wish to incorporate.
	Regarding inclusion criteria, can you clarify if the review would include children without confirmed LTBI by LTBI tests? The authors state "regardless of the definition of LTBI" but it is not clear if this means young child contacts without confirmation by LTBI testscan also be included. A previous RCT of 3HP included such patients and thus the above point should be clarified. https://jamanetwork.com/journals/jamapediatrics/fullarticle/2089639
	The primary outcome is a bit unclear if it includes clinically diagnosed TB.
	I'm not sure if I understand "Treatment adherence/compliance is obtained when a patient was administered and took at least 80% of the doses of the corresponding drug within the period defined by the protocol (10). Regardless of the definition of treatment adherence/compliance, this outcome is included as described by the study authors". Are you saying you would include any definition of adherence as defined by the study authors? Then the preceding sentence is confusing.
	Can you clarify if ROB2 is used per outcome as recommended by Cochrane and for which outcomes?

	What are specific methods used to conduct random-effects meta-analysis? E.g. Are you going to use The Hartung-Knapp method? What are the continuous outcomes you have in mind? Can you clarify why year of publication can be an effect modifier? Isn't study year more relevant if the likelihood of TB infection is at play?

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	28-May-2022
GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. This is a proposal for a meta-analysis; its description of what the authors plan to do seems appropriate, and I recommend publication. Peter Flom

VERSION 1 – AUTHOR RESPONSE

June 23, 2022

Professor
Imti Choonara, MBChB, MD, FRCPCH, DTM&H
Editor-in-Chief
BMJ Paediatrics Open

Dear Dr. Choonara,

Please find attached the revised version of our protocol for a systematic review and network meta-analysis entitled Effectiveness and Safety of Available Preventive Tuberculosis Treatment Regimens for Children and Adolescents: Protocol for a Systematic Review and Network Meta-analysis. We confirm again that the present manuscript is not published elsewhere, nor is currently under consideration for publication in any other journal.

We thank you for the opportunity to revise our manuscript and provide responses to the reviewers' comments. Please find below the editor in chief's and the reviewers' comments to the authors and our point-by point responses with the corresponding corrections to the manuscript.

We thank you for your time and consideration.

Kind regards,

Ivan D. Florez, MD, MSc, PhD, On behalf of the authors
Department of Pediatrics, University of Antioquia, Medellin, Colombia

Editor in Chief Comments to the Authors:

1. Introduction last paragraph. Delete the last sentence. Journal policy is for authors to avoid describing their study as the first.

Response: We appreciate your comment. The last sentence was deleted from the introduction (page 4, paragraph 5).

2. RCTs are the gold standard for efficacy, but not for safety. If you want to comprehensively look at safety, you will need to expand your search to prospective cohort studies (see Zeng L, Wang C, Jiang M, et al Safety of ceftriaxone in paediatrics: a systematic review. Arch Dis Child Published Online First: 06 March 2020. doi: 10.1136/archdischild-2019-317950; Egunsola O, Choonara I, Sammons HM. Safety of levetiracetam in paediatrics: a systematic review. PLoS One 2016; 11 :e0149686.

Response: Thank you for your comment. Observational studies such as cohort and case-control studies may help determine if a harmful agent truly has deleterious effects without it being unethical to randomize patients to exposures that might result in harmful effects without benefit. Also, through observational studies, very rare adverse events may become evident with longer follow-up duration. However, randomized controlled trials provide less biased estimates of potentially harmful effects than other study designs because randomization ensures balance of known and unknown determinants of the outcome, which is the reason why we only sought to include RCTs in the present systematic review. (Levine M, Ioannidis JPA, Haines AT, Guyatt G. Chapter 14: Harm (Observational Studies). Users' Guides to the Medical Literature. Guyatt G, Rennie D, Meade MO, Cook DJ, JAMAevidence & McGraw Hill Education. 3rd ed, 2015, p 538 – 544.)

Reviewers' Comments to the Authors:

Reviewer 1: Yohhei Hamada

1. The protocol is well written and follows the standard methodology. I have several comments below that the authors may wish to incorporate.

Response: We appreciate your comment.

a. Regarding inclusion criteria, can you clarify if the review would include children without confirmed LTBI by LTBI tests? The authors state "regardless of the definition of LTBI" but it is not clear if this means young child contacts without confirmation by LTBI tests can also be included. A previous RCT of 3HP included such patients and thus the above point should be clarified.
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2089639

Response: Thank you for your comment. We will include studies evaluating "children and/or adolescents under 18 years of age, with LTBI, who were contacts of individuals with drug-susceptible TB, regardless of the definition the authors used for LTBI''. Therefore, we are considering the studies that defined LTBI, regardless of the criteria used. We decided to be flexible in this matter for several reasons. First, there is no gold standard for direct identification of M. tuberculosis infection in humans and authors could have used a positive tuberculin skin test (TST) and/or interferon gamma release assay (IGRA) as eligibility criteria. Second, definitions of LTBI could differ from mid 1900's to this day (RCTs of LTBI date back to that time). We are aware that this flexibility could influence the heterogeneity we could find. However, we think this approach may bring more external validity and, considering the expected low number of trials in children with LTBI, we are interested in obtaining as much evidence as possible. Considering this key comment, we have decided to explore the impact of this factor on the effect estimates. Therefore, we will run a sensitivity analysis excluding the studies that considered patients in which LTBI was not diagnosed through laboratory tests (IGRA or TST). Lastly, we are interested in close contacts of an infectious patient with TB, even in the case of a negative baseline TST. In the latter case, patients could have been included in some studies and LTBI confirmed when TST conversion occurs, or excluded if TST remains negative.

b. The primary outcome is a bit unclear if it includes clinically diagnosed TB.

Response: Thank you for your comment. In response to your observation, we have revised the manuscript accordingly. Please see page 5, paragraph 5: "We defined active TB as the disease caused by being infected with M. tuberculosis (19), confirmed bacteriologically or diagnosed clinically based on the TB diagnostic criteria of the American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines (20)".

c. I'm not sure if I understand "Treatment adherence/compliance is obtained when a patient was administered and took at least 80% of the doses of the corresponding drug within the period defined by the protocol (10). Regardless of the definition of treatment adherence/compliance, this outcome is included as described by the study authors". Are you saying you would include any definition of adherence as defined by the study authors? Then the preceding sentence is confusing.

Response: Thank you for your comment. We have revised the sentence and we have decided to remove the first sentence to avoid confusion (please see page 5, paragraph 5). We think the best approach is to consider treatment adherence/compliance as used and reported by the authors of the primary studies.

d. Can you clarify if ROB2 is used per outcome as recommended by Cochrane and for which outcomes?

Response: Thank you for your comment. According to Cochrane's recommendation, ROB2 will be evaluated for each of the primary and secondary outcomes (please see page 6, paragraph 5).

e. What are specific methods used to conduct random-effects meta-analysis? E.g. Are you going to use The Hartung-Knapp method?

Response: We appreciate your comment. You are correct. We are applying the Hartung-Knapp-Sidik-Jonkman method for our random effects meta-analysis. We have added this to the text. Please see page 7, paragraph 2: "Since we expect clinical and methodological heterogeneity among the studies, we plan to pool direct evidence for each treatment comparison using a frequentist random-effects (RE) model, applying the Hartung-Knapp-Sidik-Jonkman method (23)".

f. What are the continuous outcomes you have in mind?

Response: We appreciate your comment. Since there are no continuous outcomes, the sentence mentioning them has been deleted from the manuscript (page 6, paragraph 4; page 7, paragraph 2).

g. Can you clarify why year of publication can be an effect modifier? Isn't study year more relevant if the likelihood of TB infection is at play?

Response: Thank you for your comment. We agree. We have revised the manuscript accordingly. The study year, rather than the publication year, will be our potential effect modifier (page 7, paragraph 4).

Reviewer 2: Dr. Hawult Adane, Armauer Hansen Research Institute

1. First, I would like to thank Sabella-Jimenez et al for developing this interesting review protocol entitled as" Effectiveness and Safety of Available Preventive Tuberculosis Treatment Regimens for Children and Adolescents: Protocol for a Systematic Review and Network Meta-analysis." I found that the protocol has well define research question and all sections of the main document is well written, articulated and prepared as per the standard (PRISMA-P). Hence, I am very happy to see the published protocol and the Review and Network Meta-analysis papers as well. Thank you that I was very comfortable and really enjoy on reading this interesting protocol.

Response: We appreciate your comment. No changes have been made to the manuscript.

2. I have no major comments, except the following minor issues for your consideration.

a. INTRODUCTION: Line: 51-52. I think, instead of the word "determine", other alternative terms such as estimate/evaluate or provide summary of ….. is preferred to explain the aim of SRNMA protocol/ final report.

Response: Thank you for your comment. We have revised the manuscript accordingly (please see page 4, paragraph 5). "We aim to evaluate the effectiveness and safety of all the different regimens available for the treatment of LTBI for children and adolescents less than 18 years of age, contacts of drug-susceptible TB, without human immunodeficiency virus (HIV) infection."

b. Though it is not mandatory, could you provide an explicit statement of the question or hypothesis that can reflect the expected/possible Effect difference among the existing regimens (Intervention Vs comparator).

Response: We appreciate your comment. Due to the availability of different regimens and durations for LTBI (which is the reason why we have designed a network meta-analysis) it is not practical nor feasible to elicit a hypothesis in terms of intervention vs comparator. In fact, authors have described how null hypothesis generation should be avoided for a number of statistical factors (Efthimiou et al 2019). Therefore, no changes are applied.

c. METHODS AND ANALYSIS: Subheading: Study design would be better to describe as Review method/approach and the specific method (PICO) should be mentioned. I would say "The protocol of this systematic review was developed based on PICO components of the review method and prepared according to the …. (PRISMA-P).

Response: We appreciate your comment. The manuscript was revised according to the observation noted. Please see page 5, paragraph 1: "The protocol of this systematic review was developed based on PICO (Participants, Interventions, Comparators and Outcomes) components of the review method and prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (16)."

d. Participants: Why you exclude studies with HIV infected children/adolescents. I think, at this stage, it is better to consider all possible target population who are eligible for TPT and then you can see the difference (effectiveness and safety) Or you may a room to perform subgroup analysis if you will find enough numbers of related studies.

Response: We appreciate your comment. HIV infection is a high-risk condition where children do not need to be contacts of an active TB case to receive prophylaxis (and would not apply to our question). Due to their diagnosis and as part of their medical assessment, children with HIV receive preventive treatment regardless of exposure to an active TB case. At the same time, systematic reviews of TB preventive treatment in children with HIV (exclusively) have been published recently (Zunza et al, 2017).

e. Outcomes: Are you rely on your own primary outcome definition for active TB as the disease caused by being infected with M.tuberculosis OR you will stick with the standard definition- I think all original articles use the same case definition for active TB. Here please noted that you should include "Eligibility criteria" as an additional subheading

Response: We appreciate your comment. The subheading was included before the PICO components (page 5, paragraph 2). We included the most recent definition of active tuberculosis and the diagnosis of active TB from the World Health Organization, and the American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines, which is a general statement that can include the original articles' own definition. Please see page 5, paragraph 5: " We defined active TB as the disease caused by being infected with M. tuberculosis (19), confirmed bacteriologically or diagnosed clinically based on the TB diagnostic criteria of the American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines (20)."

f. Searching strategies: I think, it would be also good to present your searching strategies and study

selection process using diagram (Figure)- preferably PRISMA flow chart-.

Response: We appreciate your comment. The manuscript was revised and rewritten according to your observation (please see page 6, paragraph 2). "The full search strategies and study selection process will be presented in a PRISMA flow diagram."

Reviewer 3: Dr. Peter Flom, Peter Flom Consulting
1. I confine my remarks to statistical aspects of this paper. This is a proposal for a meta-analysis; its description of what the authors plan to do seems appropriate, and I recommend publication.
Response: We thank you for your comment. No changes have been made to the manuscript.

Reviewer 4: Dr. Alexander Gonzalez, Instituto de Medicina Tropical Pedro Kouri
1. The protocol fits properly to the PRISMA statement (PRISMA- P) 2015, maybe the authors could consider to declare explicitly the PICO strategy was used for the construction of the research question and bibliographical search as we observed you when the authors declare (Participants, Interventions, Comparations and Outcomes) Also they could consider to use the updated of PRISMA 2020 statement for the final report.
Response: Thank you for your comment. Following your suggestion and Dr. Hawult Adane's observation (Reviewer 2), the manuscript was revised accordingly. Please see page 5, paragraph 1: "The protocol of this systematic review was developed based on PICO (Participants, Interventions, Comparators and Outcomes) components of the review method and prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (16)."

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Alexander Gonzalez Institution and Country: Instituto de Medicina Tropical Pedro Kouri, Cuba Competing interests: None
REVIEW RETURNED	05-Jul-2022

GENERAL COMMENTS	I am very grateful for the opportunity provided to review this valuable protocol, reiterating that it is written in accordance with the recommended methodology for systematic reviews and meta-analyses. At the same time, I am satisfied with the changes made to the manuscript that will strengthen a better understanding for the scientific community. Thanks to the authors and we will be waiting for the publication of the protocol and its results. So, I recommend the publication of this appreciable protocol.

REVIEWER	Reviewer name: Dr. Hawult Taye Adane Institution and Country: Armauer Hansen Research Institute, Ethiopia Competing interests: None
REVIEW RETURNED	29-Jun-2022

GENERAL COMMENTS	I have no comments and confirmed that the authors fully addressed my previous comments. Now the protocol is well revised and ready for publication

REVIEWER	Reviewer name: Yohhei Hamada Institution and Country: United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	01-Jul-2022

GENERAL COMMENTS	The authors addressed my comments well.

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	25-Jun-2022
GENERAL COMMENTS	I had no problem with the first version of this paper, and I recommend publication.