STUDY PROTOCOL

REVISED Interventions aiming to eliminate catastrophic costs due to tuberculosis: a protocol for a systematic review and meta-analysis [version 2; peer review: 4 approved]

Previously titled: 'A protocol for a systematic review and meta-analysis of strategies to quantify or eliminate catastrophic costs due to tuberculosis'

Paula P. Carballo-Jimenez[1-3], Sumona Datta[1-4], Rubén Aguirre-Ipenza[5], Matthew J. Saunders[1-3], Luz Quevedo Cruz[1-3], Carlton A. Evans[1-3]

[1]IFHAD: Innovation For Health And Development, Department of Infectious Disease, Imperial College London, London, UK
[2]IPSYD: Innovación Por la Salud Y Desarrollo, Asociación Benéfica Prisma, Lima, Peru
[3]IFHAD: Innovation For Health And Development, Laboratory of Research and Development, Universidad Peruana Cayetano Heredia, Lima, Peru
[4]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK
[5]Universidad Continental, Lima, Peru

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Abstract

***Background*:** People with tuberculosis disease and their household members may suffer direct out-of-pocket expenses and indirect costs of lost income. These tuberculosis-related costs can worsen poverty, make tuberculosis treatment completion unaffordable, impair quality of life and increase the risk of death. Costs due to tuberculosis are usually defined as catastrophic if they exceed 20% of the pre-disease annual household income. The World Health Organisation strategy to "End TB" and the United Nations Sustainable Development Goals include the target that no households should face catastrophic costs due to tuberculosis. However, there is limited evidence and policy concerning how this global priority of eliminating catastrophic costs due to tuberculosis should be achieved. This systematic review and meta-analysis aims to address this knowledge gap.
***Methods*:** Publications assessing interventions that aimed to eliminate catastrophic costs will be identified by searching three electronic databases (PubMed, Scopus and Web of Science) together with reference lists from pertinent publications. We will screen eligible studies, extract data, and assess the risk of bias with the quality assessment tool from the National Heart, Lung, and Blood Institute. Discrepancies will be resolved by discussion between the reviewers. If we find sufficient comparable studies quantifying strategies to eliminate catastrophic costs then a meta-analysis will be performed. This systematic review and meta-analysis is registered with the

Open Peer Review

Approval Status ✓ ✓ ✓ ✓

	1	2	3	4
version 2 (revision) 03 Nov 2022	✓ view	✓ view	✓ view	✓ view
version 1 15 Mar 2022	? view			

1. **Sedona Sweeney**, London School of Hygiene & Tropical Medicine, London, UK
2. **Jane Rahedi Ong'ang'o**, Kenya Medical Research Institute, Nairobi, Kenya
3. **Bianca Sossen**, University of Cape Town, Rondebosch, South Africa
4. **Shweta R. Singh**, National University of Singapore, Singapore, Singapore

Any reports and responses or comments on the

PROSPERO database (CRD42022292410).
***Conclusion*:** This systematic review and meta-analysis aims to rigorously assess the evidence for strategies to eliminate catastrophic costs due to tuberculosis.

Keywords
systematic review, meta-analysis, catastrophic costs, tuberculosis

article can be found at the end of the article.

Corresponding author: Paula P. Carballo-Jimenez (paula.carballo@ifhad.org)

Author roles: Carballo-Jimenez PP: Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Datta S**: Conceptualization, Formal Analysis, Funding Acquisition, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Aguirre-Ipenza R**: Conceptualization, Writing – Review & Editing; **Saunders MJ**: Conceptualization, Writing – Review & Editing; **Quevedo Cruz L**: Writing – Review & Editing; **Evans CA**: Conceptualization, Formal Analysis, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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REVISED **Amendments from Version 1**

We thank the reviewer for their helpful comments on the first version of our manuscript. To address these comments, the second version of our manuscript includes the following changes.

1. The wording of the title and abstract and research question have been clarified to increase their consistency with the unchanged wording of our primary objective.
2. These changes make the absence of overlap with previous systematic reviews clearer.
3. The background information in the 'Introduction' section is now more detailed.
4. The description of plans for data extraction is more detailed, now including specific examples for each type of data.
5. The protocol for data synthesis is now described in more detail.
6. In the 'Risk of bias' section, the link has been clarified.

We believe that these improvements from the first to the second version of our manuscript have enhanced clarity and increased detail, without involving any fundamental change.

Any further responses from the reviewers can be found at the end of the article

Introduction

Since records began, tuberculosis (TB) has killed more people than any other infectious disease globally. TB is strongly associated with poverty because TB principally affects poorer people in poorer regions and TB disease, diagnosis and treatment related costs can all worsen poverty[1].

Costs due to TB are usually assessed at the level of the household and include direct out-of-pocket expenditures and also the indirect costs of lost income due to TB, including before TB was diagnosed or treated. These costs due to TB have been quantified using diverse strategies including[2]:

- prospective recording of costs versus retrospective recall over brief periods or retrospective recall over prolonged periods;
- characterisation of actual costs throughout the TB illness versus assessing costs over one short period (usually one month) at one randomly selected time during treatment and then extrapolating these costs to the duration of the entire illness;
- paper versus electronic data collection;
- locally developed cost data collection tools versus internationally standardised data collection instruments; and
- diverse strategies to assess pre-disease household income as the denominator for assessing whether costs due to TB were catastrophic.

As costs due to TB increase, the risk of adverse TB treatment outcomes (principally treatment non-completion) increases. Indeed, we found that in Peruvian shantytowns when costs due to TB exceeded 20% of the pre-illness income of that household, then treatment outcomes were more likely to be adverse (treatment non-completion, treatment failure or death during treatment) than favourable (cure or treatment completion)[3]. Similar findings have been reported in Brazil and Moldova[4,5]. Consequently, costs due to TB are usually considered to be catastrophic if they exceed a threshold of 20% of the pre-illness household annual income[6], although other thresholds have been used occasionally[7,8].

In 2011 the World Health Organisation (WHO) together with the Japan Anti-Tuberculosis Association (JATA) developed an international tool to estimate costs due to TB over a recent brief period (e.g. one month) and then extrapolate these costs to the entire TB disease and treatment duration. This venture led to the creation of a standardised handbook using this approach for conducting TB patient cost surveys that has been used in several countries[2].

The WHO "End TB Strategy" has three principal targets to be achieved by 2035: a 95% reduction in the number of TB deaths; a 90% reduction in TB incidence rate; and 0% of TB-affected families facing catastrophic costs due to TB[9]. The United Nations "Sustainable Development Goals" (SDG) describe similar targets to be achieved by 2025: a 90% reduction in the number of TB deaths; an 80% reduction in TB incidence rate; and 0% of TB-affected families facing catastrophic costs due to TB[9]. Thus, both WHO and SDG global objectives prioritise eliminating catastrophic costs due to TB. This is generally believed to require sufficient political action that TB-affected patients and their TB-affected households can:

- reduce direct costs of out-of-pocket expenditures due to TB;
- reduce indirect costs by maintaining their income as much as possible despite TB; and also where necessary
- receive socioeconomic support to reduce the impact of costs due to TB.

Preventing catastrophic costs due to TB has been prioritised in global policy in order to:

- mitigate the adverse effects of TB on quality of life[10];
- reduce the impoverishing effects of TB[1]; and
- increase the likelihood that patients with TB will be able to afford to complete TB care sufficiently to be permanently cured and return to good health[11].

Despite the consensus that catastrophic costs due to TB should be prevented, there is remarkably little clarity concerning how

this may best be achieved. For example, from first principles it seems logical that interventions including the following may reduce catastrophic costs due to TB.

Earlier TB case-detection

- Improved health systems and active case finding searching for people with TB disease (instead of passive case finding, waiting for them to present to and be diagnosed by health facilities) may more often diagnose TB earlier in the disease, whilst it is less severe and has caused less costs.

Reducing TB severity

- Reductions in TB drug-resistance and co-morbidities and optimisation of therapy can reduce the costs due to TB and therefore reduce the incidence of catastrophic costs due to TB.

Reduced costs during TB therapy

- Education, public health promotion, stigma reduction, laws and other measures may further reduce the indirect costs of lost employment due to TB.

- Information, improved health systems and universal health coverage may help to reduce the direct out-of-pocket expenditures caused by TB disease.

- Providing home-based care versus community-based clinic care versus hospital-based care in order to potentially reduce direct and indirect costs due to TB.

Supporting TB-affected households

- TB specific socioeconomic support for people with TB disease may mitigate and/or reimburse their direct and indirect costs due to TB.

- Existing socioeconomic support systems (such as microcredit or cash transfer interventions to reduce extreme poverty) may be sensitive to, or be made sensitive to people living with TB, for example by adding TB disease to their eligibility criteria.

Increasing pre-TB income

- Socioeconomic development may decrease poverty sufficiently to reduce the risk that costs due to TB reach the threshold for catastrophic costs.

Reducing TB cases

- Reductions in poverty, under-nutrition, HIV, and other factors together possibly with improved public health systems may reduce the incidence of TB and hence indirectly reduce the incidence of catastrophic costs due to TB.

We have modelled the potential global effects of TB-specific versus TB-sensitive interventions[12] and have in Peru been prospectively evaluating the health and economic effects of TB-specific socioeconomic interventions for TB-affected households[13–17]. Related findings have been reported in other settings[18]. Ecological analyses[19] and modelling[20] studies have further assessed the impact of social protection interventions on TB. For the current research, in order to inform public health policy, we aim to complete a systematic review and meta-analysis of these and other approaches to eliminate catastrophic costs due to TB.

Objectives

The objectives of this study are to do a systematic review and meta-analysis of interventions aiming to eliminate catastrophic costs due to TB.

Review questions

The questions of this systematic review and meta-analysis are what:

- strategies have been used to eliminate catastrophic costs due to TB; and

- is the effectiveness of these interventions for eliminating catastrophic costs due to TB?

Methods

This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) checklist. The protocol is registered in the PROSPERO database 2022 CRD42022292410 available from: https://www.crd.york.ac.uk/. The individual link for this record is: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022292410).

The eligibility criteria for studies to be included in this study are as follows.

Inclusion criteria

Studies concerning the elimination of catastrophic household costs due to TB, including any type of TB (pulmonary or extrapulmonary; drug-susceptible or drug-resistant; whether or not complicated by comorbidities such as associated HIV-infection).

Exclusion criteria

Studies that could not inform strategies to achieve the WHO and United Nations SDG target of eliminating catastrophic costs due to TB because the study only quantified:

- out-of-pocket expenditure costs without considering indirect costs of lost income; or

- monetary costs without assessing these costs as a proportion of household income; or

- catastrophic costs at a population level without considering the proportion of individual households that experienced catastrophic costs.

Population

The population to be included in this systematic review and meta-analysis is TB-affected households i.e. patients with TB and the people living with them.

Intervention/Exposure
Interventions will include any strategies aiming to mitigate or eliminate catastrophic costs due to TB e.g. TB active case finding (versus standard of care passive case finding); socio-economic support (compared with standard of care without socio-economic support); or home-based care (compared with standard of care in hospital).

Comparison
The comparison / control condition will be standard of care (without any intervention).

Outcome
The proportion of households with catastrophic costs due to TB.

Information sources
Three electronic databases will be searched: PubMed, Scopus and Web of Science. We will also search reference lists from relevant publications.

Search strategy
We will use the following search terms:

Pubmed: ((tuberculosis[MeSH Terms]) OR (tuberculosis OR koch disease* OR TB[Title/Abstract]))

AND (catastrophic cost* OR catastrophic household cost*[Title/Abstract])

Scopus: TITLE-ABS-KEY ((tuberculosis OR "koch disease" OR tb) AND (catastrophic AND cost*))

Web of science: (tuberculosis OR Koch disease* OR TB) AND (catastrophic AND cost*) (All Fields)

Measures of effect
The main measure of effect will be the proportion of households with catastrophic costs due to TB. For continuous or categorical data outcomes, we will use mean or rate differences between the catastrophic cost intervention group versus the control group. For dichotomous data outcomes, odds ratio, relative risk, and/or absolute risk will be used. For data measured on the same scale and the same unit, weighted mean differences will be used, otherwise standardised mean differences will be used. The 95% confidence intervals of these measures will also be assessed.

Data extraction
Data will be extracted from studies selected from the electronic databases using the search strategy. We will also review the references cited by these publications to find other relevant articles. Two reviewers will independently review potentially relevant publication titles, then abstracts and finally full-text publications for eligibility. Discrepancies will be resolved by discussion and when necessary independent consideration by another reviewer. The following data will be extracted from each publication:

- the proportion of households with catastrophic costs due to TB;
- the proportion of households with frequently-occurring study characteristics e.g. sociodemographic factors, TB diagnostic test used, TB treatment administered first-line versus second-line, type of TB pulmonary versus extra-pulmonary;
- the proportion of studies using frequently-reported strategies for quantifying out-of-pocket direct costs e.g. a one-time questionnaire versus a monthly questionnaire versus a questionnaire applied three times (at the beginning of treatment, the end of intensive phase and the end of treatment);
- the proportion of studies using frequently-reported strategies for quantifying indirect cost of lost income e.g. self-report versus calculation using the human capital approach;
- the proportion of studies using frequently-reported strategies for quantifying pre-illness household income e.g. self-report versus using the World Bank poverty headcount;
- the proportion of studies reporting strategies for quantifying whole illness costs and their timing e.g. prospectively by repeated questionnaires versus extrapolation from a one-month period using the WHO approach;
- the proportion of studies reporting variables known to be related to catastrophic costs (e.g. more versus less poor);
- the proportion of studies reporting each type of intervention aiming to eliminate catastrophic costs e.g. active case finding versus passive case finding; economic and social support versus standard of care;
- the proportion of studies reporting each methodology used to assess the impact of interventions aiming to eliminate catastrophic costs e.g. randomised controlled trial versus observational studies;
- the magnitude of impact and statistical significance of interventions aiming to eliminate catastrophic costs due to TB.

The data will be extracted in CSV format that will be uploaded to the Rayyan software to screen for duplicate documents as well in a Microsoft Excel spreadsheet document. The study selection process will be documented using the PRISMA flow diagram. Heterogeneity of data will be assessed if there are enough suitable data to perform a meta-analysis. A shared cloud-based spreadsheet will log all edits and who makes them.

Type of studies
We will include all types of studies that inform the review objectives, without any restriction. For example: observational quantitative, qualitative, and mixed methods studies; intervention studies including randomised controlled trials; reviews; editorials; perspectives; and mathematical modelling studies will be extracted.

Risk of bias (quality) assessment

We anticipate that the quality assessment tool for case control studies from the National Heart, Lung, and Blood Institute (NHLBI) may be most appropriate to generate an overall rating for the quality of each study of "good", "fair", or "poor". This tool is available from the "Quality Assessment of Case-Control Studies" tool at the following link:

https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

Depending on pilot work after the data have been extracted, an alternative tool may be used such as Version 2 of the Cochrane risk-of-bias tool for randomised trials. These plans may be modified if necessary, as adaptations to the progress of the systematic review.

Strategy for data synthesis

As defined above, the principal measure of effect for this study will be to compare the proportion of households with catastrophic costs due to TB for intervention versus control groups. All proportions will be presented as percentages. Firstly, the raw data actual proportion of households with catastrophic costs due to TB will be compared in graphical and/or tabular form for both the intervention and also for the control group in each study. Secondly, the analysed data i.e. the odds ratios (and/or relative risks) of households experiencing catastrophic costs due to TB in intervention versus control groups will be compared in graphical and/or tabular form for each study. Proportions (and whenever possible odds ratios and/or relative risks) will be presented with their 95% confidence intervals. Whenever possible, comparisons will be reported as statistically significant ($P<0.05$) or not.

Meta-analysis

If we find sufficiently similar and suitable intervention studies, then we will assess the heterogeneity of the data with I^2 statistics and a Forest plot graph. All data will be analysed using Stata Software version 16.0 (Stata Corporation LLC, College Station, Texas, USA). The meta-analyses will include pooled odds ratios of comparable studies calculating the respective weighted means of these ratios, including weighted confidence intervals.

Ethics and dissemination

Approval from an Ethics committee will not be required for this systematic review and meta-analysis because it will include analysis of only anonymous unlinked data. We intend to present this work at conferences and to publish it in an international peer-reviewed open-access journal.

Discussion

The COVID-19 pandemic is believed to be markedly increasing TB disease, adverse TB outcomes, catastrophic costs due to TB and poverty[21], whilst impairing TB case finding and cure. We hope that this systematic review and meta-analysis will help to inform strategies for reducing or potentially eliminating catastrophic costs due to TB, towards ending TB.

Data availability

Underlying data

No data are associated with this article.

Reporting guidelines

The PRISMA-P checklist for "A protocol for a systematic review and meta-analysis of strategies to quantify or eliminate catastrophic costs due to tuberculosis" is available from the Harvard Dataverse:

https://doi.org/10.7910/DVN/JS3GVY/DKK8LN21

It is also available with a CC BY 4.0 licence from the IFHAD: Innovation For Health And Development data repository:

http://www.ifhad.org/wp-content/uploads/2021/12/Catastrophic_costs_search_strategy.pdf

Acknowledgements

The authors would like to thank other members of the IPSYD: Innovación por la Salud y Desarrollo team in Perú who made important contributions to this research but did not meet the rules to qualify to be co-authors, including exceptional support from Jonathan Gomez and Rosario Montoya.

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Reference Source
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Open Peer Review

Current Peer Review Status: ✔ ✔ ✔ ✔

Version 2

Reviewer Report 06 June 2023

https://doi.org/10.21956/wellcomeopenres.20392.r56506

✔ **Shweta R. Singh**
Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore

Overall, a meaningful pursuit of finding interventions aimed at eliminating catastrophic costs. A few methodological clarifications and consistency (in the Prospero protocol and this manuscript) can help the systematic review.

A few of the concerns are raised below:

1. The paper has many bullet points, which I am not sure are conventional in scientific papers. It would perhaps be better to put these together in a paragraph format.

2. The protocol registered in the PROSPERO database seems not updated compared to this version.

3. There is no plan for data synthesis from qualitative and mixed-methods articles.

4. Also, the data extraction parameters from reviews, editorials, and mathematical modelling studies are not stated.

5. For Risk of bias (quality) assessment, do you mean you will use separate tools for observational (cross-sectional, case-control and cohort) studies and controlled trials?

6. The PRISMA-P checklist link is not working in the data availability section.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, Antimicrobial resistance, epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 17 May 2023

https://doi.org/10.21956/wellcomeopenres.20392.r56279

Bianca Sossen
Department of Medicine, Faculty of Health Sciences, University of Cape Town, Rondebosch, Western Cape, South Africa

Carballo-Jimenez and colleagues have presented a study protocol for a systematic review that will summarise all published interventions that aim to eliminate catastrophic costs due to tuberculosis, and the effectiveness of these interventions. The protocol is clearly written and plans to follow PRISMA guidelines.

I have the following minor recommendations for consideration:

1. As part of data extraction, when the authors say "first-line versus second-line" (TB treatment), do they mean drug-susceptible versus drug-resistant?

2. In light of the fact that the protocol only plans to review published articles, suggest including a planned review for any publication bias with a funnel plot as part of your data synthesis strategy

3. The link to the PRISMA-P checklist does not work

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Tuberculosis diagnostics and natural history

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 09 May 2023

https://doi.org/10.21956/wellcomeopenres.20392.r56508

Jane Rahedi Ong'ang'o
Centre for Respiratory Disease Research, Kenya Medical Research Institute, Nairobi, Kenya

Thanks for the opportunity allowing me to review this protocol. The title is clear and it indicates that this is a protocol for systematic review. There is a clear definition of what type of studies will be included in the review based on the catastrophic experience and whether this exceeds a threshold of 20% of the pre-illness household annual income as recommended by WHO. Various strategies (interventions) to eliminate catastrophic expenditure have been described in the introduction as well as the control group and the primary study outcome. Search strategies and data management is described clearly. Measures for taking care of risk for bias for individual studies has been stated. Well written protocol.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health/Epidemiology Research in tuberculosis/HIV with a focus in supporting health system strengthening

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 01 December 2022

https://doi.org/10.21956/wellcomeopenres.20392.r53176

Sedona Sweeney
Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, UK

I have had a look and the paper looks much improved, I have no further comments. I look forward to reading the results of this very interesting literature review!

Is the rationale for, and objectives of, the study clearly described?
Not applicable

Is the study design appropriate for the research question?
Not applicable

Are sufficient details of the methods provided to allow replication by others?
Not applicable

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: health economics with a focus on tuberculosis in low-income and middle-income settings

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 04 August 2022

https://doi.org/10.21956/wellcomeopenres.19373.r50128

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Sedona Sweeney
Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, UK

Thank you for the opportunity to review this protocol for a systematic review on catastrophic costs due to TB. This is an important topic for which there is still very little existing evidence.

- I would recommend clarifying the research question as described in the study. The objective of the study is described as 'to assess the evidence for strategies to quantify or eliminate catastrophic costs due to TB'. Given this description, it is unclear to me whether the primary focus of the review will be on quantifying the prevalence of catastrophic costs, or on the impact of interventions aiming to reduce or eliminate catastrophic costs (such as active case finding, home-based care, or socioeconomic support).

- If the main aim is to quantify the prevalence of catastrophic costs, this may not be a substantial addition to the literature as this question has recently been addressed by other authors (see Ghazy, R.M *et al.*, 2022)[1].

- I would therefore recommend considering focusing this paper on the impact of interventions aiming to reduce or eliminate catastrophic costs, an important and interesting question for which there is very little existing evidence. I would recommend including some further background describing any existing evidence on this topic in the introduction, to justify the rationale for the study.

- This study is planned as a systematic review and meta-analysis. The search strategy for this review is well-described. The description of plans for data extraction could be improved with further detail, for example by describing which study and methodological characteristics will be extracted, and which variables known to be related to catastrophic costs will be considered.

- The description of the risk of bias is clear, however the link to the NHLBI study quality assessment tool is broken and needs amending. The description of methods for data synthesis should describe synthesis methods for all measures of effect included in the study.

References

1. Ghazy R, El Saeh H, Abdulaziz S, Hammouda E, et al.: A systematic review and meta-analysis of the catastrophic costs incurred by tuberculosis patients. *Scientific Reports*. 2022; **12** (1). Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: health economics with a focus on tuberculosis in low-income and middle-income settings

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Sep 2022

Carlton Evans

Thank you for these helpful suggestions.
Precisely as the reviewer suggested, we have clarified the wording of the title, focus and research question of the protocol to increase their consistency with the unchanged wording of our primary objective. These changes make the absence of overlap with previous systematic reviews clear.

As the reviewer suggested, we have also: included additional background information in the 'Introduction' section; our description of plans for data extraction and data synthesis have been improved; the risk of bias link has been clarified.

We believe these improvements fully address the reviewer's observations and will be pleased to make any other necessary changes.

Competing Interests: None