STUDY PROTOCOL

Preventing deaths due to tuberculosis: An assessment of global targets with a protocol for a systematic review and meta-analysis [version 1; peer review: 3 approved with reservations, 2 not approved]

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Abstract

Background: Tuberculosis (TB) is believed to have caused more deaths than any other infection since records began. The "Sustainable Development Goals", previous "Millennium Development Goals", World Health Organisation "End TB Strategy" and the second and third "Global Plans to Stop TB" all prioritise(d) key targets to reduce deaths due to TB. However, there seems to be limited research evidence available to inform how this may best be achieved. We therefore aim to summarise, critically appraise, and synthesise the trial evidence that interventions decrease deaths due to TB.

Methods: We will follow the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We will search the PubMed, Scopus and Web of Science databases for peer reviewed English/Spanish language publications focused on evaluating interventions to reduce deaths due to TB as primary or secondary trial outcomes. We plan to use the following search terms: tuberculosis OR TB; death OR mortality OR fatality OR survival; prevent* OR reduce* OR decrease*; AND trial. Eligible publications will be selected by two independent reviewers and a third will resolve any discrepancies. Key information will be extracted using a shared cloud-based spreadsheet, publications categorised and summarised and critically appraised. Key data will be extracted and synthesised. Meta-analysis will be carried

Open Peer Review

Approval Status ? ? ✗ ✗ ?

	1	2	3	4	5
version 1 23 Nov 2023	? view	? view	✗ view	✗ view	? view

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out if there are three or more studies investigating similar interventions with a similar outcome. The quality of trial evidence and any risk of bias will be formally assessed using the Cochrane tools.

Conclusions: We report a protocol for a systematic review of the published literature involving trial evidence assessing whether interventions reduce deaths due to TB and a meta-analysis of the quantitative evidence. We aim to clarify research gaps and to synthesise evidence in order to guide future policy and research.

PROSPERO registration: Record number CRD42023387877

Keywords
tuberculosis, TB, mortality, survival, death

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Quevedo Cruz L: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Carballo-Jimenez PP**: Writing – Original Draft Preparation, Writing – Review & Editing; **Datta S**: Methodology, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Evans CA**: Data Curation, Formal Analysis, Methodology, Supervision, Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

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Background

Tuberculosis (TB) is believed to have killed more people than any other infectious disease and in 2022, the World Health Organisation (WHO) estimates that TB killed 1.6 million people, mostly among people who were not co-infected with HIV. Estimated trends in deaths due to TB decreased between 2015 and 2019, but then increased during the COVID-19 pandemic. The WHO estimates that one third of cases of TB disease are undiagnosed or not formally treated and deaths due to TB are often considered likely to be underestimated by operational definitions[1,2]. Additionally, apparently successful TB treatment is followed by a marked increase in all-cause mortality, often attributed to cancer or heart disease, and this "post-TB" mortality is under-reported or potentially unreported in current estimates of deaths due to TB[3–5].

In 2001, global efforts to address the TB pandemic included a new "Global Plan to Stop TB 2001–2005", which was associated with the UN Millennium Development Goals (MDG). A major purpose of this new global plan was to expand the previous "Directly Observed Treatment Short Course" (DOTS) strategy to better encompass the emerging challenges of HIV and drug-resistant TB. The global targets proposed aimed to prioritise detecting, treating, and curing TB disease. However, deaths due to TB were not given the highest prominence in this period, despite death rates increasing at these times in the African and European regions (see Table 1)[6].

In contrast in 2006, reducing deaths due to TB was included as a priority in the subsequent "Global Plan to Stop TB 2006–2015"[6]. This second global plan used deaths due to TB in 1990 as a baseline comparator. During 2006–2015, this target was almost achieved, so that between 2000 and 2015 the rate of deaths (not numbers of deaths) due to TB was estimated to have fallen by 34%, although this decline was slowest in the WHO African Region (2.2% per year)[6].

Consequently in 2010, a third plan called the "Global Plan to Stop TB 2011–2015" was published. This was an interim evaluation of the Global Plan to Stop TB (2006–2015) which proposed new complementary objectives that focused more on the development of new technologies and diagnostic tests, involving improving the use of TB research into policy and practice[6].

Around the end of the MDG and their transition to the Sustainable Development Goals (SDG) era, the global plans were superseded by the ambitious "End TB Strategy 2016–2022"[6]. In this new policy, prevention of deaths due to TB is the top priority and is the first ever policy to discuss the elimination of all TB-related deaths as a potential target. By 2025 the End TB strategy target aimed to decrease the number of deaths due to TB by 75%, but from 2016 to the start of 2020 when the COVID-19 pandemic started, only a 14% reduction had been achieved. This slow progress was reversed because of the COVID-19 pandemic, which has been associated with an increase in deaths due to TB[7].

The End TB Strategy includes three pillars in the fight against TB[7]. The following is a description of each of these pillars discussed in the context of deaths due to TB:

1. Integrated, patient-centred care and prevention are emphasised, but there seems to be a lack of tools to identify those with high risk of death due to TB, who might benefit from additional care.

2. Bold policies and supportive systems are prioritised, but many low-and-middle income countries do not have good vital registration systems, thus death is assessed by diverse processes that are often considered to be unreliable.

3. Intensified research and innovation are also emphasised, but most research is funded by international institutions, philanthropists and grants that do not necessarily follow the priorities of the recipient country and do not appear to explicitly prioritise preventing deaths due to TB.

In conclusion, global policies including the current SDG and WHO End TB Strategy prioritise reducing deaths due to TB but do not appear to be clear how this should be achieved, beyond improving all aspects of TB care. We therefore aimed to summarise, critically appraise, and synthesise the evidence that interventions may reduce death due to TB.

Review objectives

Review and synthesise the evidence that interventions decrease deaths due to TB.

Review question

How can deaths due to TB be prevented?

Methods

The planned methods for this systematic review and meta-analysis are published in the PROSPERO database with registration number CRD42023387877 that is available at this link: PROSPERO registration/387877. The review will use the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 Checklist[8].

Due to the diversity of the published literature, the breadth of potentially relevant interventions and the difficulty defining deaths due to TB in the setting of multimorbidities, we anticipate that it may be appropriate to do a scoping review of publications focused on deaths due to TB in order to ensure that we have accessed all relevant literature; if so then this will use the PRISMA extension for Scoping Reviews (PRISMA-ScR) Checklist. The possible scoping review is not further considered in this protocol[9].

Inclusion criteria

For the systematic review and meta-analysis, we will include peer reviewed publications in Spanish and English language, which include clinical trials that considered deaths caused

Table 1. Global targets concerning deaths due to tuberculosis. The table shows targets that include deaths due to tuberculosis (TB) that have been published as part of the principal global priorities to control TB since 2001. This table only focuses on TB mortality targets and current associated targets; thus, unrelated targets from different priorities such as HIV co-infection are not included in the table.

Organisation	Strategy	Year	Current PRIMARY target: reduction in number of deaths due to TB		Current SECONDARY target: % reduction in TB incidence rate		Current TERTIARY target: % of TB-affected households facing catastrophic costs due to TB	
			Indicator and target	Results achieved	Indicator and target	Results achieved	Indicator and target	Results achieved
World Health Organisation (WHO Global TB report)[6]	The first Global Plan to Stop TB (2001–2005).	Target 2005	-	-	-	-	-	-
	The second Global Plan to Stop TB: The Stop TB Strategy (2006–2015 and 2011–2015)	Target 2015	The global burden of TB disease (deaths) reduced by 50%	47%*	The global burden of TB disease (disease prevalence) reduced by 50%	42%	-	-
		Target 2050	Eliminate TB as a public health problem	Awaited+	Eliminate TB as a public health problem	Awaited+	-	-
	Global plan to end TB: End TB Strategy (2016–2022 and 2023–2030)	Mile-stone 2020	35%	9.2%	20%	11%	zero	47%
		Mile-stone 2025	75%	5.9%**	50%	10%**	zero	48%**
		Target 2035	95%‡‡	Awaited+	90%	Awaited+	zero	Awaited+
United Nations (MILLENNIUM DEVELOPMENT GOALS, MDGs, 2000–2015)[6]		Target 2015	Incidence, prevalence and death rates associated with TB (indicator 6.9).	Replaced by the End TB Strategy	Incidence, prevalence and death rates associated with TB (indicator 6.9).	Replaced by the End TB Strategy	-	-
United Nations (SUSTAINABLE DEVELOPMENT GOALS, SGD, 2016–2030)[6]		Target 2030	90%	Awaited+	80%	Awaited+	zero	Awaited+

‡ Values compares to 1990 levels.

‡‡ Values compares to 2015 levels.

*The target of a 50% reduction was achieved in three WHO regions – the Region of the Americas, the South-East Asia Region and the Western Pacific Region – and in nine high TB burden countries.

**Achievement reached until 2022 from WHO Global report 2022.

+ Achievement is not measurable until now.

by *Mycobacterium tuberculosis* as a primary or secondary outcome. We will include studies of TB affecting any part of the human body (pulmonary or extra-pulmonary), with or without any comorbidities (*e.g.* COVID-19, HIV, diabetes), with or without treatment, in people of any age (*e.g.* children or adults), with any TB antibiotic susceptibility (*e.g.* resistant or susceptible to rifampicin).

Exclusion criteria

Non-human studies.

Population
People with TB disease.

Intervention (or exposure)
Interventions may include any strategies that aimed or were observed to affect deaths due to TB. The exposure being studied is death due to TB.

Comparisons
These may include the population without TB, or for interventions aiming to reduce deaths due to TB these may be control groups receiving standard of care and/or placebo.

Outcome
Deaths due to TB (whether confirmed, suspected, or estimated).

Information sources
For the systematic review and meta-analysis, we will use the PubMed, Scopus, and Web of Science databases, supplemented by identification of relevant studies by searching the citations of key publications. The "grey literature" will not be included.

Search strategy for article screening
We plan to include the following keywords:

(1) tuberculosis OR TB;

(2) death OR mortality OR fatality OR survival;

(3) prevent* OR reduce* OR decrease*;

(4) trial.

The term 'survival' appears to have high sensitivity but low specificity for identifying publications related to TB mortality, so may be excluded from some searches.

Data screening will be done with the support of the Rayyan tool following the inclusion and exclusion criteria reported. The selection process will be done by two independent reviewers (LQ/CE), and if there is any discrepancy then a third reviewer (SD) will be invited to review and reassess.

Measures of effect
For the systematic review and meta-analysis, the main measure of effect will be the time-to-event until death due to TB. We will focus on hazard ratio and 95% confidence intervals. Depending on the research evidence identified, we may also need to summarise and/or perform data synthesis of incidence, odds ratios, or relative risk of death due to TB.

Data extraction
Data extraction of the included studies will be done and recorded using a shared cloud-based spreadsheet that logs all edits and who made them. Sociodemographic data and quantitative data will be extracted. Also, we will extract detailed information characterising the interventions included such as doses.

Type of studies
For the systematic review and meta-analysis, all types of trials will be included.

Risk of bias (quality) assessment
Risk of bias will be assessed using the Cochrane tool[10]. These plans may be modified, if necessary, as adaptations to the progress of the systematic review.

Strategy for data synthesis
The selected studies will be summarised in a detailed table and with descriptive statistics using the PRISMA checklist. Mortality will be presented as percentages. Other variables considered will be presented as percentages, means or medians.

Meta-analysis
Meta-analysis will be carried out if there are three or more studies investigating similar interventions with a similar outcome and we will calculate pooled estimates of effect and calculate their respective weighted means.

Ethics and dissemination
Ethical approval is not relevant to this protocol because the planned research will only use publicly available anonymous unlinked summary reports of research data. We intend to publish our findings in an international peer-reviewed open-access journal and disseminate them in at least one national (Peru) and at least one international conference.

Discussion
This protocol describes plans for a systematic review and meta-analysis that aims to rigorously assess the trial evidence that interventions reduce deaths due to TB, aiming to inform policy, practice, and future research.

Data availability
No data are associated with this article.

Reporting guidelines
Figshare database: PRISMA-P checklist for 'Preventing deaths due to tuberculosis: an assessment of global targets with a protocol for a systematic review and meta-analysis', https://doi.org/10.6084/m9.figshare.24003807[11].

Acknowledgements
We would like to thank members of the IFHAD: Innovation for Health And Development team in Lima, Peru, many of whom made valuable contributions this project but who do not meet the rules to qualify as co-authors.

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PubMed Abstract | Publisher Full Text | Free Full Text

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6. **Previous Global Plans.** Stop TB Partnership. [cited 2023 Apr 24].
Reference Source

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Reference Source

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http://www.doi.org/10.6084/m9.figshare.24003807.v1

Open Peer Review

Current Peer Review Status: ? ? ✗ ✗ ?

Version 1

Reviewer Report 13 May 2024

https://doi.org/10.21956/wellcomeopenres.21523.r74017

?

Anthony Danso-Appiah
Centre for Evidence Synthesis and Policy; School of Public Health, University of Ghana, Accra, Greater Accra Region, Ghana

In spite, of sustained investment in TB control over decades, the number of clinical cases and deaths remain high. Therefore, any attempts to assess effectiveness of interventions aimed at reducing deaths should be given a priority. The authors aim to conduct a systematic review and meta-analysis to distil evidence at the highest level that could inform global policy and practice. A background to the review describing mainly WHO strategic plans and targets has been provided and the methods describe the inclusion/exclusion criteria, search for studies, study selection, data extraction, quality assessment and plan of data analysis. The review when conducted well be innovative and policy relevant. However, a number of issues have been raised which need to be addressed before protocol could be considered acceptable.

Title:
The title is less well-formulated, lacks clarity, and unable to capture the essence of the study or highlight pertinent issues in the background. Turning the title into question, it is not clear what exactly the systematic review aims to do and achieve. The authors should take a careful look, formulate the title incorporating the PICOS elements and rewrite the background to highlight key messages relating to the object of the study.

Background:
The background needs to have a section on existing preventive interventions for TB and how the interventions might work to prevent deaths, in sufficient details.

There should be a section of the background to justify the need for this systematic review in the context of existing systematic reviews that this study will not duplicate existing systematic reviews unnecessarily. The authors should also clearly state the specific SDGs the review is focusing on.

It will help if the 1990 baseline numbers are provided so that the 34% reduction will have a scientific meaning (page 3, paragraph 3, line 7).

The authors should cite the following sentence 'Consequently in 2010, a third plan called the "Global Plan to Stop TB 2011–2015" was published' (page 3, paragraph 4, lines 1-2).

"In conclusion" is misplaced and should be deleted so the sentence starts from "Global policies...." (page 3, conclusion).

The sentence "We therefore aimed to summarise, critically appraise, and synthesise the evidence that interventions may reduce death due to TB" repeats itself in the sentence under the "Review objectives" (see marked-up document for further comments).

The review question "How can deaths due to TB be prevented" has not been touched on in the background. If this is the object of the systematic review, then this should be described in sufficient details as part of the background, and the title revised in respect of this (see earlier comment).

Methods:

The authors state "Due to the diversity of the published literature, the breadth of potentially relevant interventions and the difficulty defining deaths due to TB in the setting of multimorbidities, we anticipate that it may be appropriate to do a scoping review of publications focused on deaths due to TB in order to ensure that we have accessed all relevant literature; if so then this will use the PRISMA extension for Scoping Reviews (PRISMA-ScR) Checklist. The possible scoping review is not further considered in this protocol[9]". If scoping review is no longer on the table, there is no need to mention it here to cause confusion, the authors should already know the type of review they are planning to do so that the review process and methods are chosen accordingly.

The sentence starting as "For the systematic review and meta-analysis" is confusing as it suggests more than one study is being considered in this protocol. "For the systematic review and meta-analysis" should be deleted so the sentence starts with "We will ....." (main methods, inclusion/exclusion criteria, line 1). The rest of the sentences "We will include peer reviewed publications in Spanish and English language, which include clinical trials that considered deaths caused by *Mycobacterium tuberculosis* as a primary or secondary outcome. We will include studies of TB affecting any part of the human body (pulmonary or extra-pulmonary), with or without any comorbidities (*e.g.* COVID-19, HIV, diabetes), with or without treatment, in people of any age (*e.g.* children or adults), with any TB antibiotic susceptibility (*e.g.* resistant or susceptible to rifampicin)" should be put under "Type of studies", which should form the first PICOS element (see marked-up document).

The authors state they will include "...peer reviewed publications.....". The authors should state explicitly what type of studies in terms of design types will be included (RCTs, routine hospital data, cohort? etc). They should state study types that will not be eligible for inclusion.

The authors should provide a justification for planning to include only English and Spanish language articles (page 3, line 2, Inclusion/exclusion criteria).

The table is misplaced and should be removed from the methods (page 4). It should be summarized precisely and concisely as part of the background, and if possible, added as

"Additional/Supplementary material".

The heading “Exclusion criteria” and the sentence “Non-human studies” should deleted (page 4, last paragraph). Instead, the authors should move it to the “Types of studies”. Information about what will not be eligible for inclusion should be added to the respective PICOS elements.

The population should be described in sufficient details. For example, sufficient information about the case definition including diagnosis and the diagnostic tool/criteria used should be provided to define the population/participants, as case definition, which will differ across diagnostic tool/criteria employed, is important. Who will not be eligible for inclusion should also be stated.

Given that no or only little information about the interventions being assessed has been provided in the background, the authors should provide a comprehensive information describing the interventions being assessed under the “Intervention (or exposure)”. "(or exposure)" should be deleted so the heading is "Intervention". This section should align with the suggested section to be added to the background to describe how the interventions might work.

The authors state "The exposure being studied is death due to TB". Death is an outcome and exposure (see marked-up document for further comments).
Also, the authors state that the comparisons may include the population without TB. How then can the effectiveness of the interventions be compared? In fact, both the intervention and control groups should be TB cases. The only difference should be the intervention The authors should be explicit about what will constitute the controls for which the effect of the intervention will be assessed.

The authors state that the comparisons may include the population without TB. Epidemiologically, this group cannot be a good control/comparison group. This is because in order to be able to assess the efficacy/effectiveness of preventive interventions, both the intervention and control group should be TB patients. The only difference should be the intervention i.e. one group receives the intervention (intervention group) and another group receives the control (control group). There is lack of clarity, generally, and the authors should be explicit about what will constitute the control for which the effect of the intervention will be compared.

Under “Outcome” the authors state "Deaths due to TB (whether confirmed, suspected or estimated). This is not enough. They should state in sufficient details sources the deaths will be obtained, for example, routine data, trial data, autopsy reports, etc.?

It should be noted that a key objective of a systematic review is to capture every relevant study meeting the pre-specified eligibility criteria. Therefore, a comprehensive literature search is essential for a high-quality systematic review as failure to locate important studies can introduce a bias which can significantly affect the review findings and conclusions. The current section ‘Information sources’ is not comprehensive enough and also lacks rigour. As a minimum, all relevant electronic databases should be identified, and the period searched should be clearly stated. Given that this is intervention effectiveness systematic review, the authors, as a minimum, should include Cochrane CENTRAL. They should also include EMBASE, Google Scholar, LILACS, CINAHL, TB specific databases, just to mention a few. They should explain why they intend to exclude Grey literature or non-published studies, as exclusion can introduce publication bias.
The search terms are not comprehensive enough. The authors should create a tables of search

terms/concepts and search strategy to be added as supplementary materials.

The “Information sources” section needs attention and should be rewritten in line with the comments provided.

Before study screening/selection, the authors should provide information on how they plan to manage the search results/output.

The section on “Measures of effect” should be moved to the analysis.

The “Data extraction” section needs to be reported in sufficient details. The authors state they will extract sociodemographic and quantitative data as well as detailed information characterising the interventions included such as doses. This is not enough. They should state the specific data to be extracted (based on the PICOS, for example, characteristics of the population/participants, Interventions, Comparator(s) and Outcome), and provide information about whether there will be conversions/transformations of data and how missing data will be managed.

Although it has been stated the Cochrane Risk of Bias (RoB) tool will be used for quality assessment of risk of bias in the included studies, the authors should provide details on how the assessment will be done and risk of bias judged. As a minimum, quality domains to be assed and how each domain will be judged should be provided. How disagreements/conflicts will be resolved should also be provided.

The authors should move "Measures of effect" here and provide a comprehensive analysis plan. The following should be reported:

- Measures of effect to be used and the assumptions for selecting them.
- Software for the analysis
- Model (fixed-effect or random-effects) that will be employed
- How the effect estimates will be presented, with their 95% confidence intervals?
- Anticipated sources of heterogeneity, heterogeneity assessment and any planned subgroup analysis
- If sensitivity analysis is planned, it should be reported
- The section “Meta-analysis” can be merged with "Strategy for data analysis".

The authors state they will conduct as meta-analysis if there are three or more studies investigating similar interventions with a similar outcome and we will calculate pooled estimates of effect and calculate their respective weighted means. In fact, a meta-analysis can be conducted with two or more studies.

The references are too few for a systematic review of this nature.

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

No

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: Epidemiology, evidence synthesis and evidence-based public health.

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.

Reviewer Report 09 May 2024

https://doi.org/10.21956/wellcomeopenres.21523.r80668

Sophie Huddart
Center for Tuberculosis, University of California San Francisco, San Francisco, California, USA

The authors propose a systematic review of mortality-averting interventions for TB. While this is an important area of research, the research question is too broad for a single systematic review. Additionally, critical details are missing from this protocol. My suggestions are as follows:

Major:
- Targeting all types of mortality-averting interventions is too broad a question for a systematic review. I suggest the authors identify 1) a period of the cascade of care of interest ie pre-treatment, treatment, or post-treatment mortality, and 2) a type or types or intervention of interest and refocus the research question. As written the research question appears to incorporate mortality at any phase of TB experience and any possible intervention, including those as fundamental as anti-TB therapy. "How can deaths due to TB be prevented?" is not an adequately focused research question for a review. The authors should have a PICO (population, intervention, comparator, outcome) format review question
- the introduction should motivate the *specific* research question of this review and how the resulting review will inform future research and/or policy and programmatic action
- inclusion and exclusion criteria need to be more specific. How are the authors defining a clinical trial? Does it need to be randomized or will you consider observational studies? What outcomes must the study report?
- Similarly, the population should be more specific. If the included population does include all ages, countries, HIV, and comorbidity statuses, this should be stated explicitly.
- In the exposure section, the authors state, "The exposure being studied is death due to TB," this

is incorrect; TB death is the proposed outcome of interest.
- In the comparison section, comparison to non-TB populations does not sound like a relevant comparison group. The authors should adjust or justify this.
- The search strategy would benefit from input from an academic librarian. Will the authors include MeSH terms? The full database-specific search strategies should be published with this protocol
- If survival is going to be excluded from "some searches" this should be specified explicitly.
- If there are specific outcome measures that are going to be considered, these should be specified in the inclusion and exclusion criteria
- The meta-analysis section should specify which meta-analytic model will be used for each extracted outcome. How will the authors decide whether pooling is appropriate, ie how will they measure and interpret statistical heterogeneity? Will low-quality studies be included in meta-analyses? Will subgroup analyses be conducted?

Minor:
- in the opening sentence, remove the word "believed."

Is the rationale for, and objectives of, the study clearly described?
No

Is the study design appropriate for the research question?
No

Are sufficient details of the methods provided to allow replication by others?
No

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

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, Biostatistics, TB

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 09 May 2024

https://doi.org/10.21956/wellcomeopenres.21523.r80667

Courtney Yuen

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The proposed systematic review attempts to answer an important question of what intervention strategies are effective for reducing global TB mortality. However, the methodology of the review is inadequately conceptualized, and without more definition around the scope of the interventions being assessed, I think that a systematic review may not be appropriate.

The most important issue is that the type of intervention being searched for is highly vague. In the PICO framework, under "intervention (exposure)" it says, "The exposure being studied is death due to TB," but this is actually the outcome. It also says, "interventions may include any strategies that aimed or were observed to affect deaths due to TB." This presumably would include any form of TB treatment, which would mean that all TB treatment trials (which typically assess death as an outcome) would be included. But there is no scientific question around the effectiveness of TB treatment for reducing mortality, and there are existing meta-analyses of the effectiveness of different TB treatment regimens. Similarly, antiretroviral therapy for people living with HIV is known to reduce TB mortality, and there are existing meta-analyses around this.
A systematic review should fill a knowledge gap, but the lack of specificity in the "Intervention" part of the PICO framework makes it unclear what types of studies the authors are looking for, and hence what knowledge gap will be filled. We do not need another systematic review on TB treatment or ART, but without a more specific description of the interventions being included, these are the obvious trials that will be identified."

Moreover, the purpose of a systematic review is to collate the evidence around a single specific question, which is why some variation of the PICO framework is normally applied to narrowly define the population, intervention, and outcome. If the question is broader and seeks to capture the breadth or diversity of approaches in a field, then a scoping review is likely more appropriate (the distinction is summarized well in this publication: Munn et al BMC Medical Research Methodology 2018; 18:143). The authors in fact acknowledge the challenge in answering their research question via a systematic review and suggest the possibility of a scoping review, but then lay out the protocol for the systematic review anyway. This seems inappropriate to me – either the research question is specific enough for a systematic review or it is not, and in its current version, it seems to me that it is not.

There are other issues with the search strategy and the types of studies being included, but I think these are secondary if the lack of definition around the intervention makes a systematic review inappropriate to begin with. But briefly: By including "prevent," "reduce," and "decrease" as terms, I think bias would be introduced because trials with negative results would be less likely to be identified. The justification for only including trials is unclear to me. This would be appropriate if the authors are interested in identifying clinical trials of treatments (like TB treatment or ART), but studies that look at whether programmatic intervention approaches reduce TB-associated mortality at a population level are likely to have quasi experimental designs, and most systematic reviews of population-level interventions include these.

In conclusion, I do not think that the research question is well enough defined to accept this as a proposal for a systematic review. I am not sure exactly what type of literature the authors are looking for, but I suspect that a scoping review may be more appropriate. Regardless of what type of review is planned, I think that it is important to articulate better what gaps in knowledge are going to be filled by this review, which requires acknowledging what is already well known (e.g. TB

treatment saves lives, ART saves lives) and then focusing the literature search on better understanding what is not known.

References

1. Munn Z, Peters MDJ, Stern C, Tufanaru C, et al.: Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach.*BMC Med Res Methodol*. 2018; **18** (1): 143 PubMed Abstract | Publisher Full Text

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

No

Is the study design appropriate for the research question?

No

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

No

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Tuberculosis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 08 May 2024

https://doi.org/10.21956/wellcomeopenres.21523.r80664

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Basilea Watson
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The specifics of the demographic variables studied are not mentioned. The detailed analytics of the meta analysis is not provided.
Please expand on the methodology section with details of the analytics that will be used. Also mention in detail the kind of studies that will be included, instead of vaguely mentioning it as trials.

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: Biostatistics, TB epidemiology, Data management

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.

Reviewer Report 16 February 2024

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Dear Authors.
Thank you for an excellent plan to conduct a systematic review of interventions to prevent TB death.

It is concerning that you have attempted to combine the summary of global targets with the SR&MA of clinical trial data.
The background and rationale provide substantive information on the global targets and this is extremely relevant to TB mortality but is very different to the study focus which is mortality observed in clinical trials. The submission appears disjointed as you should either:

- Follow the existing background with a SR&MA of progress towards those targets and an analysis of TB mortality as reported in routine data, OR
- Introduce this SR&MA with additional background to what has been happening with trials that evaluated TB outcomes.

Additional details:

- In your exclusion criteria, you should specify the exclusion of epidemiological studies or analyses of routine data (this seems implied by inclusion of clinical trials only).
- In the Meta-analysis section it is stated that it will be conducted if similar interventions or outcomes. I think it is correct to conduct the MA if there are 3 or more studies of the same interventions BUT i do not think you should specify the same outcome as you should already only be including studies with the same outcome (death).
- The WHO is spelt with a z not an s as ".... Organi**z**ation...."

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?

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, TB

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.