




STUDY PROTOCOL

REVISED **A protocol for a systematic review and meta-analysis of tuberculosis care around the time of pregnancy [version 2; peer review: 1 approved, 2 approved with reservations]**

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Abstract

Background

Tuberculosis is estimated to cause 1.5 million deaths annually and is most common during the reproductive years. Despite that fact, we found that tuberculosis screening, prevention or care recommendations for people around the time of pregnancy were absent from some national policy recommendations and varied in others.

Objectives

To address the apparent gaps and inconsistencies in policy, we aim to design a systematic review and meta-analysis of the original research evidence informing tuberculosis care around the time of pregnancy.


Methods

With assistance from librarians at the Biomedical library of the University of Gothenburg, Pubmed, CINAHL and Scopus databases will be searched. Search terms will aim to identify studies generating original research evidence informing care for tuberculosis around the time of pregnancy. Evidence may include: the outcome of TB and/or of

Open Peer Review

Approval Status

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- Marian Loveday**, University of KwaZulu-Natal, Durban, South Africa
- Alexandra J Zimmer** , McGill University, Montreal, Canada

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pregnancy; the cost-effectiveness or acceptability of any intervention; the sensitivity and specificity of any assessment, selection, diagnostic or test criterion. The output from these literature searches will be screened by two independent reviewers to select the eligible studies for inclusion. Discrepancies will be resolved with a third reviewer. Firstly, publications that provide contextual data will be tabulated, summarising their main contributions. Secondly, studies that provide evidence directly guiding patient care will be our focus and will be considered to be key. The key studies will be subject to quality assessment, data extraction and when possible, meta-analysis.

Conclusions

This systematic review and meta-analysis aims to guide policy, practice and future research priorities concerning tuberculosis care around the time of pregnancy.

Plain language summary

Tuberculosis is a leading infectious cause of death and is most common during the reproductive years. To address gaps and inconsistencies in policy, we aim to review original research evidence informing tuberculosis care around the time of pregnancy. Evidence may include: the outcome of TB and/or the outcome of pregnancy; the cost-effectiveness or acceptability of any intervention; the reliability (sensitivity and specificity) of any assessment, selection, diagnostic or test criterion. First, publication databases (Pubmed, CINAHL and Scopus) will be searched to identify evidence. The output from these literature searches will then be screened to select eligible studies. Next, publications that provide contextual data will be tabulated, summarising their main contributions. After this, studies that provide evidence directly guiding patient care will be our focus and will be considered to be key. The key studies will be subject to formal quality assessment, data extraction and when possible, meta-analysis to assess and summarise their findings. In conclusion, this systematic review and meta-analysis aims to guide policy, practice and future research priorities concerning tuberculosis care around the time of pregnancy.

Keywords

systematic review, meta-analysis, tuberculosis, pregnancy

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Author roles: **Carlsson C:** Conceptualization, Funding Acquisition, Methodology, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Lönnermark E:** Conceptualization, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Review & Editing; **Datta S:** Conceptualization, Formal Analysis, Methodology, Project Administration, Supervision, Writing – Review & Editing; **Evans CA:** Conceptualization, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Visualization, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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Tuberculosis is a leading infectious cause of death and is most common during the reproductive years. To address gaps and inconsistencies in policy, we aim to review original research evidence informing tuberculosis care around the time of pregnancy. Evidence may include: the outcome of TB and/or the outcome of pregnancy; the cost-effectiveness or acceptability of any intervention; the reliability (sensitivity and specificity) of any assessment, selection, diagnostic or test criterion. First, publication databases (Pubmed, CINAHL and Scopus) will be searched to identify evidence. The output from these literature searches will then be screened to select eligible studies. Next, publications that provide contextual data will be tabulated, summarising their main contributions. After this, studies that provide evidence directly guiding patient care will be our focus and will be considered to be key. The key studies will be subject to formal quality assessment, data extraction and when possible, meta-analysis to assess and summarise their findings. In conclusion, this systematic review and meta-analysis aims to guide policy, practice and future research priorities concerning tuberculosis care around the time of pregnancy.

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REVISED Amendments from Version 1

In this revised, second version of our manuscript we have made multiple improvements, all responding to the reviewers' recommendations. These changes are all fully detailed in our responses to each of the three reviewers. In summary, we have: clarified, better referenced, emphasised the limitations of and better justified [Table 1](#); clarified and standardised the review question, objectives, and 'PICO' (Population, Intervention/exposure, Comparison, and Outcome) statement including the acceptable comparators; improved the explanation of the eligibility criteria for and criteria to be met for a meta-analysis to be performed; improved our text to state that topics recently published as systematic reviews and meta-analyses will be included in our planned systematic review and meta-analysis; better defined the meaning of the phrase 'around the time of pregnancy'; clarified the grant information and updated the references cited in order to accommodate the aforementioned improvements. We thank the reviewers for their suggestions that led to these improvements to our manuscript.

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

Introduction

The World Health Organisation (WHO) estimates that tuberculosis (TB) disease causes 1.5 million deaths annually ([WHO, 2022](#)) and that approximately half a million of these deaths are in women ([WHO, 2018](#)). As data on pregnancy are not routinely collected in most TB surveillance programs ([Mathad & Gupta, 2012](#)), the exact number of TB disease cases in pregnancy is poorly characterised. However, in women TB disease is more common during reproductive age and the number of pregnancies affected by TB disease was estimated to be over 200,000 in 2011 ([Sugarman *et al.*, 2014](#)). More up to date estimates are urgently needed.

Active TB disease during pregnancy is associated with an increased risk of prematurity, low birth weight and perinatal death ([WHO, 2018](#)), and is normally treated with the same regimens as for non-pregnant individuals ([WHO, 2010](#)). However, a recent study has demonstrated that pregnant women have an increased risk of hepatotoxicity and temporary treatment interruptions ([Beck-Friis *et al.*, 2020](#)), possibly indicating a need for closer monitoring of this population as well as for further investigation of the pregnancy-specific safety of TB medications ([NHS, 2023](#)).

To counteract the risks imposed by active TB disease during pregnancy, early TB detection and treatment is important. Most women access antenatal care at least once during pregnancy ([UNICEF, 2019](#)), and the integration of TB and antenatal care is recommended by the WHO ([WHO, 2018](#)). Integration could facilitate active TB case finding to increase early detection of the disease, while also helping ensure that the care for concomitant active TB disease and pregnancy is more easily accessible to patients. Another important aspect to include in integrated TB care around the time of pregnancy is family planning, as conception often occurs during TB treatment, and TB medications impair the efficacy of some oral contraceptives. An integrated and holistic approach to TB care around the time of

pregnancy may contribute to seeing the pregnant person in the context of their family and extending services further to include family members and household contacts, potentially increasing the impact and reach of interventions within antenatal and TB care.

Early detection and treatment of TB is largely dependent on an efficient screening process. However, there has been recent debate regarding the sensitivity of the often-used method of largely restricting TB diagnostic testing to people with symptoms suggestive of TB. This debate may be particularly important during pregnancy, when symptoms of TB can potentially be masked by or confused with physiologic changes in pregnancy ([Lacourse *et al.*, 2018](#)).

The treatment of active TB disease (regardless of HIV-status) and also for HIV-positive individuals the administration of TB preventive therapy (TPT) for treating latent TB infection to reduce the risk of progression to active TB disease are generally considered to be necessary, irrespective of whether the patient is pregnant. In contrast, there is uncertainty concerning the risks versus benefits for TPT administration during pregnancy for HIV-negative women. It is not yet certain if pregnancy and its immune changes increase susceptibility to progression from latent TB infection to active TB disease. However, some studies have demonstrated an increase in TB incidence in the postpartum period ([Gilks *et al.*, 1990](#); [Jonsson *et al.*, 2020](#); [Mathad & Gupta, 2012](#); [Zenner *et al.*, 2012](#)), possibly indicating TB progression during pregnancy and an unmasking of symptoms during the postpartum immune-restitution phase. Whether to recommend TPT during or shortly after pregnancy is still an issue of debate and is a balance between preventing the risks associated with active TB disease during pregnancy and the risks of possible medication side effects. A recent study in HIV-positive women demonstrated greater risks associated with the initiation of isoniazid preventive therapy (IPT) during pregnancy than with initiation postpartum ([Gupta *et al.*, 2019](#)), whereas a systematic review from 2020 concluded that current evidence does not support systematic deferral of IPT until postpartum ([Hamada *et al.*, 2020](#)).

Further adding to the complexities of both active TB disease and latent TB infection around the time of pregnancy are psychological factors intimately associated with pregnancy. These may manifest as an unwillingness to take medications, or to undergo a chest x-ray during pregnancy for fear of harming the foetus. Moreover, they could also cause feelings of guilt in both parents and healthcare personnel if an unfavourable pregnancy event takes place during TB treatment.

The complex interactions between TB and pregnancy outlined above highlight the need for research evidence, and it is therefore regrettable that pregnant women are frequently excluded from research studies.

Funding

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Figure 1. IRIS-stipendiet logo.

United Kingdom Research and Innovation Medical Research Council Skills Development Fellowship, The United Kingdom Research and Innovation Quality-Related Strategic Priorities Fund, a Wellcome Trust fellowship, CONCYTEC/FONDECYT, The Joint Global Health Trials Scheme funding from the Wellcome, UK Foreign, Commonwealth and Development Office, the UK Medical Research Council, and the UK Department of Health and Social Care through the National Institute of Health Research, and IFHAD: Innovation For Health And Development.

Survey of current policy documents

We observed that international and national guidelines seemed to lack clear and consistent guidance concerning TB care around the time of pregnancy. Reasons for this may include the lack of data on TB in pregnant and postpartum women as well as the lack of evidence that has resulted from the exclusion of pregnant women from most research studies. With the intention of testing the veracity of our observation, we made a convenience sample of the global, international and national guidelines on TB care around the time of pregnancy that were most relevant to the settings where the co-authors of this protocol manuscript work. The results of our investigation are shown in [Table 1](#). The table illustrates the fact that in many settings where TB screening and/or preventive therapy are recommended for various high-risk groups, pregnancy-specific recommendations are lacking. Furthermore, international and national guidelines that do include pregnancy-related TB screening or preventive therapy recommendations propose strikingly diverse approaches. Although the findings from our survey of these guidelines summarised in [Table 1](#) are clear, the global scope is limited. In possible future work, it would be valuable to add guidelines from several high-burden TB countries such as India, South Africa, Indonesia, and Kenya to add depth to our findings. Notwithstanding this limitation, the apparent gaps and inconsistencies in policy prompt us to undertake a systematic review and meta-analysis to address the following review objective.

Review objective

This systematic review and meta-analysis aims to summarise and critically appraise the evidence informing how best to provide tuberculosis care for people with TB around the time of pregnancy.

Review question

The review question is intentionally broad in order to capture all the published evidence that can directly guide policy, practice and future research priorities: How should TB care be modified for current or recent pregnancy?

PICO

Population

People of any age around the time of pregnancy (i.e. who are pregnant or were recently pregnant), with or without comorbidities such as HIV infection, who have TB or are considered to be at high risk of TB infection or disease. Most relevant research has focused on pregnancy, but some important research evidence also includes the postnatal period that will be included in our review in order to include all the relevant diverse evidence available.

Intervention/exposure

Any interventions and/or exposures will be included if they provide evidence informing how best to provide care for people with TB around the time of pregnancy.

Comparison

Evidence concerning interventions will be assessed relative to the any control group that did not receive the intervention. However, no comparison group is required by our inclusion criteria.

Outcome

Outcomes may include: the outcome of TB and/or of pregnancy; the cost-effectiveness or acceptability of any intervention; the sensitivity and specificity of any assessment, selection, diagnostic or test criterion. . Outcomes may be categorised as 1) maternal/pregnant person outcomes and 2) infant outcomes.

Methods

The systematic review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Ethics

We do not plan to apply for ethical approval for this systematic review and meta-analysis because no human subjects nor individual participant research data will be involved.

Inclusion criteria

Original peer reviewed publications in English and/or Spanish, presenting research evidence informing care for TB around the time of pregnancy will be included. Evidence outcomes may include: the outcome of TB and/or of pregnancy; the

Table 1. Guidelines for TB screening and treatment during pregnancy.

Guideline	Region	TB screening		TB treatment	
		TB infection	TB disease	TB infection	TB disease
WHO	Global	None	Partial*	None	Universal
CDC	USA	None	None	None	Partial**
ECDC	Europe	None	None	None	None
MinSa	Peru	None	None	None	Universal
FHM/ILF	Sweden	Partial***	Partial***	Partial****	Universal
NICE	UK	None	None	None	None

Legend	Explanation
None	We were unable to identify recommendations specific to pregnancy.
Partial	The recommendation is only applicable if a certain condition is met (as specified by the asterisked statement below)
Universal	The guideline included recommendations without requirements for further conditions to be met

*May be conducted in settings with TB prevalence >100/100 000

**If probability of disease is moderate to high

***If patient is from setting with TB incidence >100/100 000/year or suspected exposure

****During pregnancy if exposed within last 2 years, otherwise deferred to post-partum

Note:

WHO indicates World Health Organisation, Geneva, Switzerland, see <https://www.who.int/publications/i/item/9789240001503>;

CDC indicates Centers for Disease Control, Atlanta, USA, see <https://www.cdc.gov/tb/publications/guidelines/default.htm>;

ECDC indicates the European Centres for Disease Control, see <https://www.ecdc.europa.eu/en/publications-data/programmatic-management-latent-tuberculosis-infection-european-union#globan-dropdown-gb1vrnv6b9e>;

FHM indicates The Public Health Agency of Sweden and ILF indicates the Swedish Society for Infectious Diseases, see <https://www.folkhalsomyndigheten.se/contentassets/92e06754e3464636b1bdbb980378bcf3/rekommendationer-for-preventiva-insatser-mot-tuberkulos.pdf>;

MinSa indicates Ministerio de Salud (in Spanish, Ministry of Health in English), Peru, see <http://www.tuberculosis.minsa.gob.pe/portaldpctb/recursos/20190404114640.PDF>; and

NICE indicates National Institute for Health and Care Excellence, UK, see <https://www.nice.org.uk/guidance/ng33/chapter/recommendations#diagnosing-latent-tb-in-all-age-groups>.

cost-effectiveness or acceptability of any intervention; the sensitivity and specificity of any assessment, selection, diagnostic or test criterion. There will be no date restrictions on the searches that will include all publications since records began in each database until the date that the searches are last updated, which will be stated in the systematic review publication.

Exclusion criteria

Publications that do not present original peer reviewed research evidence such as reports, abstracts, editorials, reviews or case reports and studies that cannot inform any aspect of patient care will be excluded. Case series may be eligible if they provide research evidence by including statistical comparison with one or more control groups.

Publication triage

The included publications will be triaged into three categories. Firstly, publications providing contextual data that is not likely to have an impact on current clinical practices will be tabulated, summarising main findings. Secondly, publications that provide evidence directly informing clinical practice and patient care will be our focus and will be considered key publications. These key publications will be subject to quality assessment, data extraction and summary of key data and if possible, meta-analysis.

Information sources

With assistance from librarians at the Biomedical library of the University of Gothenburg, the following bibliographic database information sources will be searched: [Pubmed](#), [CINAHL](#) and

Scopus. The information sources will not include grey literature.

Search strategy for article screening

The databases stated above will be searched with the following search terms:

PubMed:

(Tuberculosis[mesh] OR tuberculosis[tiab] OR tuberculoses[tiab] OR tb[tiab] OR ltb[tiab] OR ltbi[tiab]) AND (Pregnancy[mesh] OR pregnan*[tiab] OR pregnant women[mesh] OR pre-natal[tiab] OR prenatal[tiab] OR post-natal[tiab] OR postnatal[tiab] OR peri-natal[tiab] OR perinatal[tiab] OR postpartum period[mesh] OR post-partum[tiab] OR postpartum[tiab] OR obstetric*[tiab] OR peripartum[tiab] OR peri-partum[tiab]) AND (pregnancy outcome[mesh] OR Outcome[tiab] OR mortality[mesh] OR mortality[tiab] OR Premature Birth[mesh] OR pre-term[tiab] OR preterm[mesh] OR premature[tiab] OR miscarriage*[tiab] OR Abortion, Spontaneous[mesh] OR gestational age[mesh] OR gestational age[tiab] OR stillbirth[mesh] OR stillbirth[tiab] OR stillborn[tiab] still-born[tiab] OR still-birth[tiab] OR congenital[tiab] OR death[mesh] OR death[tiab] OR birth weight[mesh] OR birth weight[tiab] OR birthweight[tiab] OR pregnancy complication*[tiab] OR pregnancy complications[mesh] OR adverse pregnancy outcomes[tiab] OR adverse effect*[tiab] OR adverse event*[tiab])

Limit English, Spanish

The search will then be translated to use in CINAHL and Scopus in addition to Pubmed.

The citations identified will be exported into the systematic review tool [Rayyan](#), where they will be screened by two independent reviewers. Any disagreements will be resolved by discussion with a third independent reviewer. This process will be documented and presented through a flow chart diagram.

Measures of effect

Measures of effect addressing clinically important issues will be subjected to quality and bias assessment and, data extraction and meta-analysis provided that we find at least three similar studies measuring the same outcome of interest. An example of a measure of effect that may be eligible for quality and bias assessment and data extraction and meta-analysis is the reliability of symptom screening to select pregnant people who should undergo testing for TB disease.

Risk of bias (quality) assessment

Bias assessment will be undertaken for the key articles, using a standardised risk of bias assessment tool. The tool will be selected as the most suitable depending on the character of the key studies included in the final selection. We anticipate using a tool designed by the Cochrane group. The Cochrane effective practice and organisation of care (EPOC) risk of bias (RoB) tool may be most appropriate if the key studies on which we focus are all either randomised trials and/or non-randomised trials and/or controlled before-after (CBA) studies and/or interrupted time series (ITS) studies. Further information concerning how we plan to select the most appropriate risk of bias assessment tool is available from the Cochrane group's guide on

[how to prepare a risk of bias table for review that include more than one study design, suggested risk of bias criteria for EPOC reviews, and summary assessments of the risk of bias.](#)

Data extraction

Data will be extracted from the included key articles addressing clinically important information that has not recently been subjected to systematic review or meta-analysis. Data extraction will be done by two to three independent reviewers using a data extraction form in [Microsoft Excel](#) (Microsoft Excel for Mac Version 16.66.1). The data extracted will include (but will not necessarily be limited to) study characteristics, methodological characteristics and outcomes.

Strategy for data synthesis

Data extracted from the key studies will be summarised as follows. Count data will be summarised as proportions with their 95% confidence intervals and represented by bar graphs. Data with an approximately Gaussian distribution will be summarised by means and standard deviations and represented by simple error bar graphs. Strongly skewed data will be summarised by medians and interquartile ranges and may be represented by box plots.

Meta-analysis

In addition to the systematic review, provided that we find at least three similar studies measuring the same outcome of interest, then a meta-analysis will be performed with a random effects model in order to generate pooled results for presentation in a forest plot. We will assess the heterogeneity of the data with I^2 statistics. All data will be analysed using [Stata](#) Software version 16.0 (Stata Corporation LLC, College Station, Texas, USA). The meta-analyses will include pooled outcomes of comparable studies calculating their respective weighted means, including weighted confidence intervals.

Dissemination

The work will be published in an international peer reviewed open access journal, ensuring that anyone with internet access can make use of the results.

Discussion

Our clinical practice has highlighted apparent gaps and variability in TB-related care for people around the time of pregnancy. Consistent with these subjective observations, our summary of selected national and international guidelines identified apparent gaps and inconsistencies in policy. We aim to do a systematic review and meta-analysis of original research evidence informing TB care around the time of pregnancy in order to guide policy, practice and future research priorities.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Harvard database: PRISMA-P checklist for 'A protocol for a systematic review and meta-analysis of tuberculosis care around

the time of pregnancy'. <https://doi.org/10.7910/DVN/YD2G3I> (Carlsson & Evans, 2022).

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Current Peer Review Status: ? ? ?

Version 1

Reviewer Report 23 August 2023

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? **Alexandra J Zimmer** 

¹ McGill University, Montreal, Québec, Canada

² McGill University, Montreal, Québec, Canada

This is an interesting and important research topic. As the authors themselves mention, pregnant persons are often omitted from research studies when it comes to TB. Therefore, this review aims to highlight the knowledge already accumulated and paves the way for future studies, ensuring that this often-overlooked demographic receives appropriate TB care.

Please consider the following suggestions:

Abstract

- There's a mention of providing "evidence directly guiding patient care". It might be helpful if you could specify what constitutes "evidence" in this context. Are you referring to a particular intervention, policy, or both?
- The term "potential meta-analysis" is mentioned; however, it's not clear what you might "potentially" meta-analyze. If this hasn't been decided, perhaps consider providing some information about the meta-analysis.

Introduction

- With respect to the number of pregnancies affected by TB disease, consider using a more recent reference. The current reference pertains to data from 2011, which is outdated.
- A citation might be needed for the statement: "and TB medications impair the efficacy of some oral contraceptives."
- The mention of "other recent systematic reviews" appears throughout the protocol. It might be enlightening to discuss these reviews more deeply, focusing on the research questions they addressed and how this review plans to bridge any existing gaps.

Funding

- Figure 1's direct contribution to the article's content seems limited. Consider omitting it.

Survey of current policy documents

- For clarity, it might be helpful to specify that "co-authors" pertain to the co-authors of this particular manuscript.

Table 1

- It would be advantageous to include a column that indicates the country/region associated with each guideline.
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- Finally, include references for all guidelines in the table.

Objective / question

- Because the question is broad, the review might be better suited as a scoping review. That said, if other systematic reviews on this subject have already been done, then a scoping review may not be informative. Therefore, I suggest narrowing the research question so that the PICO categories are better defined.

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- You cannot exclude articles from your review because other reviews have already covered them. This comes back to my initial question about how this review differs from others that have already been done in this area, and also refining the research question to address research gaps.

Outcomes

- Consider categorizing outcomes as 1) maternal/pregnant person outcomes and 2) infant outcomes.

Measures of effect

- Even with the provided example, the measures being assessed remain a bit ambiguous. Please clarify.

Meta-analysis

- For greater clarity, please define what constitutes a "sufficient" number of studies for conducting a meta-analysis.

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

No

Is the study design appropriate for the research question?

Partly

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, tuberculosis, diagnostics, global 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.

Author Response 02 Jan 2024

Carlton Evans

IMMEDIATELY BELOW ARE ALL THE REVIEWER COMMENTS, EACH FOLLOWED BY OUR RESPONSE We thank the reviewer Dr Dione Benjumea-Bedoya for these comments, which we fully quote and reply to below. “This is a very interesting systematic review protocol to address the gaps in screening and treatment for latent and active tuberculosis in pregnant and postpartum women. Below are some comments that may help authors to improve their work. The IRIS Stipendiet logo is not necessary.”

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and also a meta-analysis provided that there are three or more studies investigating similar interventions with a similar outcome.

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“For ease of reading, if space permits, consider placing the recommendation directly within the table cell rather than as a footnote.” We agree and have explored various options. We believe that the new layout of Table 1 is much improved and thank the reviewer for this suggestion. **“Finally, include references for all guidelines in the table.”** Thank you we have made this change. **“Objective / question. Because the question is broad, the review might be better suited as a scoping review. That said, if other systematic reviews on this subject have already been done, then a scoping review may not be informative. Therefore, I suggest narrowing the research question so that the PICO categories are better defined.”** Thank you, we have clarified this throughout the manuscript. **“Publication triage. You cannot exclude articles from your review because other reviews have already covered them.”** Thank you, this statement has been deleted from the abstract and manuscript. **“This comes back to my initial question about how this review differs from others that have already been done in this area, and also refining the research question to address research gaps.”** Thank you, we have clarified this throughout the manuscript. **“Outcomes. Consider categorizing outcomes as 1) maternal/pregnant person outcomes and 2) infant outcomes.”** We have made this change. **“Measures of effect. Even with the provided example, the measures being assessed remain a bit ambiguous. Please clarify.”** This paragraph has been re-written, clarified and expanded. **“Meta-analysis. For greater clarity, please define what constitutes a “sufficient” number of studies for conducting a meta-analysis.”** Thank you this is now specified as three eligible studies. We have also updated the funding statement and references cited.

Competing Interests: None

Reviewer Report 23 August 2023

<https://doi.org/10.21956/wellcomeopenres.20042.r57890>

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Marian Loveday

¹ South African Medical Research Council, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

² South African Medical Research Council, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

Thank you for asking me to review this protocol for a systematic review and meta-analysis of tuberculosis care around the time of pregnancy. The authors are undertaking an important and urgently needed task in conducting a systematic review and meta-analysis of TB care around the time of pregnancy and I look forward to reading their paper in the future. The authors have done a great job and the concerns I have raised will described below will I hope improve the manuscript.

My first concern is the focus of the manuscript. Are you focussing on the care of TB during pregnancy or 'around the time of pregnancy?' Although 'around the time of pregnancy' is included in the title, the focus of the systematic review and meta-analysis is pregnancy and the research question is 'How should TB care be modified for current or recent pregnancy?' The focus of the manuscript needs to be clarified.

Under the PICO Population section the authors state that their population of interest is '*People of any age who are or were recently pregnant, with or without comorbidities such as HIV infection, who have TB or are considered to be at high risk of TB infection or disease.*' This needs to be clarified in line with the rest of the manuscript.

In your methods section you describe that your review and analysis will only include studies that provide evidence directly guiding patient care, but have not been the subject of recent systematic review and meta-analysis will be included. How are you going to identify these studies?

Also in your methodology you describe that studies that have recently been included in systematic reviews and meta-analysis will be excluded. Given the limited studies in this field, this may not be many studies and it might be worth considering including studies of maternal TB in the postpartum period.

Minor comments

- In the methods section the authors state '*With the assistance from librarians...*' As far as I am aware, we don't usually mention the inclusion of the librarians, but just name the databases that will be searched.
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number of pregnancies affected by TB disease was estimated to be over 200,000 in 2011.' I suggest you replace most with more and people with women.

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Partly

Is the study design appropriate for the research question?

Partly

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: TB, TB and HIV, DR-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.

Author Response 02 Jan 2024

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Competing Interests: None

Reviewer Report 08 August 2023

<https://doi.org/10.21956/wellcomeopenres.20042.r59443>

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Dione Benjumea-Bedoya

¹ Universidad Remington, Medellín, Colombia

² Universidad de Antioquia, Medellín, Colombia

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Results: TB prognosis, pregnancy outcome, cost-effectiveness, acceptability, sensitivity, and specificity should be well described and included as eligibility criteria.

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

Partly

Is the study design appropriate for the research question?

Partly

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 of infectious diseases, especially tuberculosis, and evidence-based medicine

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 02 Jan 2024

Carlton Evans

IMMEDIATELY BELOW ARE ALL THE REVIEWER COMMENTS, EACH FOLLOWED BY OUR RESPONSE We thank the reviewer Dr Dione Benjumea-Bedoya for these comments, which we fully quote and reply to below. “This is a very interesting systematic review protocol to address the gaps in screening and treatment for latent and active tuberculosis in pregnant and postpartum women. Below are some comments that may help authors to improve their work. The IRIS Stipendiet logo is not necessary.” Thank you for this point. Including this logo in the publication is required by the funder and has been agreed with the journal.

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Thank you we regret the previous inconsistency of our wording. We have now standardised our wording to "around the time of pregnancy" in order to accommodate the diverse evidence available. We now clarify that the most relevant research has focused on pregnancy, but that some important research evidence (that should be included in our review) also includes the postnatal period. **"Under the PICO Population section the authors state that their population of interest is 'People of any age who are or were recently pregnant, with or without comorbidities such as HIV infection, who have TB or are considered to be at high risk of TB infection or disease.' This needs to be clarified in line with the rest of the manuscript."** Thank you, we have clarified and made this consistent throughout the manuscript. **"In your methods section you describe that your review and analysis will only include studies that provide evidence directly guiding patient care, but have not been the subject of recent systematic review and meta-analysis will be included. How are you going to identify these studies? Also in your methodology you describe that studies that have recently been included in systematic reviews and meta-analysis will be excluded. Given the limited studies in this field, this may not be many studies and it might be worth considering including studies of maternal TB in the postpartum period."** Thank you, this statement has been deleted from the abstract and manuscript. **"Minor comments. In the methods section the authors state 'With the assistance from librarians...' As far as I am aware, we don't usually mention the inclusion of the librarians, but just name the databases that will be searched."** Thank you. The library team have been remarkably helpful and involved in the development of this protocol. We therefore prefer to keep this wording (which has been

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Competing Interests: None

Comments on this article

Version 1

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Competing Interests: None

Open Peer Review

Current Peer Review Status: ? ✓ ?

Version 2

Reviewer Report 17 January 2024

<https://doi.org/10.21956/wellcomeopenres.23067.r72390>

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Marian Loveday

South African Medical Research Council, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

The authors of the protocol have addressed the concerns I raised satisfactorily.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TB, TB and HIV, DR-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.

Version 1

Reviewer Report 23 August 2023

<https://doi.org/10.21956/wellcomeopenres.20042.r64921>

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Alexandra J Zimmer

McGill University, Montreal, Québec, Canada

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that this often-overlooked demographic receives appropriate TB care.

Please consider the following suggestions:

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- Consider categorizing outcomes as 1) maternal/pregnant person outcomes and 2) infant outcomes.

Measures of effect

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- For greater clarity, please define what constitutes a "sufficient" number of studies for conducting a meta-analysis.

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

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, tuberculosis, diagnostics, global health

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We regret that we are unable to find a more recent reliable estimate and note that recent publications also quote this estimate without any more recent ones. We now comment on this in this section of the manuscript. **“A citation might be needed for the statement: “and TB medications impair the efficacy of some oral contraceptives.”**

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“I notice that the selected countries are those with which the authors have affiliations. Consider the inclusion of guidelines from several high-burden TB countries like India, South Africa, Indonesia, and Kenya might add depth.” Thank you. We agree, but have instead decided to explicitly mention this limitation and we propose this as being potential future research.

“For ease of reading, if space permits, consider placing the recommendation directly within the table cell rather than as a footnote.” We agree and have explored various options. We believe that the new layout of Table 1 is much improved and thank the reviewer for this suggestion. **“Finally, include references for all guidelines in the table.”** Thank you we have made this change. **“Objective / question. Because the question is broad,**

the review might be better suited as a scoping review. That said, if other systematic reviews on this subject have already been done, then a scoping review may not be informative. Therefore, I suggest narrowing the research question so that the PICO categories are better defined. Thank you, we have clarified this throughout the manuscript. **“Publication triage. You cannot exclude articles from your review because other reviews have already covered them.”** Thank you, this statement has been deleted from the abstract and manuscript. **“This comes back to my initial question about how this review differs from others that have already been done in this area, and also refining the research question to address research gaps.”** Thank you, we have clarified this throughout the manuscript. **“Outcomes. Consider categorizing outcomes as 1) maternal/pregnant person outcomes and 2) infant outcomes.”** We have made this change. **“Measures of effect. Even with the provided example, the measures being assessed remain a bit ambiguous. Please clarify.”** This paragraph has been re-written, clarified and expanded. **“Meta-analysis. For greater clarity, please define what constitutes a “sufficient” number of studies for conducting a meta-analysis.”** Thank you this is now specified as three eligible studies. We have also updated the funding statement and references cited.

Competing Interests: None

Reviewer Report 23 August 2023

<https://doi.org/10.21956/wellcomeopenres.20042.r57890>

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Marian Loveday

South African Medical Research Council, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

Thank you for asking me to review this protocol for a systematic review and meta-analysis of tuberculosis care around the time of pregnancy. The authors are undertaking an important and urgently needed task in conducting a systematic review and meta-analysis of TB care around the time of pregnancy and I look forward to reading their paper in the future. The authors have done a great job and the concerns I have raised will described below will I hope improve the manuscript.

My first concern is the focus of the manuscript. Are you focussing on the care of TB during pregnancy or ‘around the time of pregnancy?’ Although ‘around the time of pregnancy’ is included in the title, the focus of the systematic review and meta-analysis is pregnancy and the research question is ‘How should TB care be modified for current or recent pregnancy?’ The focus of the manuscript needs to be clarified.

Under the PICO Population section the authors state that their population of interest is '*People of any age who are or were recently pregnant, with or without comorbidities such as HIV infection, who have TB or are considered to be at high risk of TB infection or disease.*' This needs to be clarified in line with the rest of the manuscript.

In your methods section you describe that your review and analysis will only include studies that provide evidence directly guiding patient care, but have not been the subject of recent systematic review and meta-analysis will be included. How are you going to identify these studies?

Also in your methodology you describe that studies that have recently been included in systematic reviews and meta-analysis will be excluded. Given the limited studies in this field, this may not be many studies and it might be worth considering including studies of maternal TB in the postpartum period.

Minor comments

- In the methods section the authors state '*With the assistance from librarians..*' As far as I am aware, we don't usually mention the inclusion of the librarians, but just name the databases that will be searched.
- This sentence in the abstract is not wrong, but editing will increase its readability: '*Two independent reviewers will screen and select for inclusion the eligible studies.*'

Introduction

- **First paragraph:** '*However, TB disease is most common in people of reproductive age and the number of pregnancies affected by TB disease was estimated to be over 200,000 in 2011.*' I suggest you replace most with more and people with women.
- **Third paragraph:** 'case findings' should be 'case finding'
- **Fifth paragraph:** '*...preventive therapy (TPT) for latent TB infection*' This sentence is not completely correct. TPT is really for the prevention of TB and not the treatment of sub-clinical TB.
- **The section entitled 'Survey of current policy documents.'**
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- **Study status**
From the rest of the text I understood I was reviewing a study protocol, but in the study

status it appears the study has already started. This needs to be clarified.

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

Partly

Is the study design appropriate for the research question?

Partly

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: TB, TB and HIV, DR-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.

Author Response 02 Jan 2024

Carlton Evans

IMMEDIATELY BELOW ARE ALL THE REVIEWER COMMENTS, EACH FOLLOWED BY OUR RESPONSE We thank the reviewer Dr Dione Benjumea-Bedoya for these comments, which we fully quote and reply to below. **“This is a very interesting systematic review protocol to address the gaps in screening and treatment for latent and active tuberculosis in pregnant and postpartum women. Below are some comments that may help authors to improve their work. The IRIS Stipendiet logo is not necessary.”** Thank you for this point. Including this logo in the publication is required by the funder and has been agreed with the journal.

“Survey of current policy documents: the intention of Table 1 is not clear, especially because the guidelines included are intentionally selected...” The intention of Table 1 was explained by the statement “The lack of evidence possibly caused by the exclusion of pregnant women from research studies seems to be reflected in international and national guidelines for TB care around the time of pregnancy, as demonstrated by Table 1.”. We have clarified and extended this explanation in the revised version of the manuscript. **“..., there are names of institutions, but there is no specific reference for the documents reviewed.”** We have added detailed citation references and weblinks for all these reports in the footnote to Table 1. **“The review question “How should TB care be modified for current or recent pregnancy?” looks different from the objective, and does not follow the PICO question structure.”** Thank you. We have clarified this statement, and we believe that the breadth of our research question is a strength. The detailed PICO question

structure immediately follows, in the lines immediately below the research question.

“The Intervention/exposure is very unspecific.”

Thank you we agree and consider the breadth of our inclusiveness of interventions/exposures to be a strength of our approach: “Any interventions and/or exposures will be included if they provide evidence informing how best to provide care for people with TB around the time of pregnancy.”

“The comparison is not well developed as it should be the comparator of the intervention rather than the population.”

We have clarified this statement. **“Results: TB prognosis, pregnancy outcome, cost-effectiveness, acceptability, sensitivity, and specificity should be well described and included as eligibility criteria.”** Thank you. We have described these in more detail and also added them to the eligibility inclusion criteria.

“If this review is so unspecific it should be a scoping review rather than a systematic review and potential meta-analysis.” We have clarified this important issue by removing mention of a “potential meta-analysis” and clarified that we will perform a systematic review and also a meta-analysis provided that there are three or more studies investigating similar interventions with a similar outcome.

“Triage of publications: in a systematic review, it is not possible to focus only on publications with new evidence, excluding publications that were already included in previews systematic reviews and meta-analyses, as described in the second triage.”

Thank you, this statement has been deleted from the abstract and manuscript.

“The information sources did not include grey literature.” This has been added explicitly to the information sources section.

“The screening process was not fully described.” Thank you. We have added more detail to our description of the screening process.

We thank Marian Loveday for their comments, which we fully quote and reply to below.

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Competing Interests: None

Reviewer Report 08 August 2023

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Dione Benjumea-Bedoya

¹ Universidad Remington, Medellín, Colombia

² Universidad de Antioquia, Medellín, Colombia

This is a very interesting systematic review protocol to address the gaps in screening and treatment for latent and active tuberculosis in pregnant and postpartum women. Below are some comments that may help authors to improve their work.

The IRIS Stipendiet logo is not necessary.

Survey of current policy documents: the intention of Table 1 is not clear, especially because the guidelines included are intentionally selected, there are names of institutions, but there is no specific reference for the documents reviewed.

The review question “How should TB care be modified for current or recent pregnancy?” looks different from the objective, and does not follow the PICO question structure.

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The comparison is not well developed as it should be the comparator of the intervention rather than the population.

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The information sources did not include grey literature.

The screening process was not fully described.

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

Partly

Is the study design appropriate for the research question?

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

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

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of infectious diseases, especially tuberculosis, and evidence-based medicine

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.

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Survey of current policy documents. For clarity, it might be helpful to specify that "co-authors" pertain to the co-authors of this particular manuscript.” We have made this clarification. **“Table 1. It would be advantageous to include a column that indicates the country/region associated with each guideline.”** Thank you we have added this to the first column of the table.

“I notice that the selected countries are those with which the authors have affiliations. Consider the inclusion of guidelines from several high-burden TB countries like India, South Africa, Indonesia, and Kenya might add depth.” Thank you. We agree, but have instead decided to explicitly mention this limitation and we propose this as being potential future research.

“For ease of reading, if space permits, consider placing the recommendation directly within the table cell rather than as a footnote.” We agree and have explored various options. We believe that the new layout of Table 1 is much improved and thank the reviewer for this suggestion. **“Finally, include references for all guidelines in the table.”** Thank you we have made this change. **“Objective / question. Because the question is broad, the review might be better suited as a scoping review. That said, if other systematic reviews on this subject have already been done, then a scoping review may not be**

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Competing Interests: None

Comments on this article

Version 1

Author Response 02 Jan 2024

Carlton Evans

IMMEDIATELY BELOW ARE ALL THE REVIEWER COMMENTS, EACH FOLLOWED BY OUR RESPONSE We thank the reviewer Dr Dione Benjumea-Bedoya for these comments, which we fully quote and reply to below. **"This is a very interesting systematic review protocol to address the gaps in screening and treatment for latent and active tuberculosis in pregnant and postpartum women. Below are some comments that may help authors to improve their work. The IRIS Stipendiet logo is not necessary."** Thank you for this point. Including this logo in the publication is required by the funder and has been agreed with the journal.

"Survey of current policy documents: the intention of Table 1 is not clear, especially because the guidelines included are intentionally selected..." The intention of Table 1 was explained by the statement "The lack of evidence possibly caused by the exclusion of pregnant women from research studies seems to be reflected in international and national guidelines for TB care around the time of pregnancy, as demonstrated by Table 1.". We have clarified and extended this explanation in the revised version of the manuscript. **"..., there are names of institutions, but there is no specific reference for the documents reviewed."** We have added detailed citation references and weblinks for all these reports in the footnote to Table 1. **"The review question "How should TB care be modified for current or recent pregnancy?" looks different from the objective, and does not follow the PICO question structure."** Thank you. We have clarified this

statement, and we believe that the breadth of our research question is a strength. The detailed PICO question structure immediately follows, in the lines immediately below the research question.

“The Intervention/exposure is very unspecific.”

Thank you we agree and consider the breadth of our inclusiveness of interventions/exposures to be a strength of our approach: “Any interventions and/or exposures will be included if they provide evidence informing how best to provide care for people with TB around the time of pregnancy.”

“The comparison is not well developed as it should be the comparator of the intervention rather than the population.”

We have clarified this statement. **“Results: TB prognosis, pregnancy outcome, cost-effectiveness, acceptability, sensitivity, and specificity should be well described and included as eligibility criteria.”** Thank you. We have described these in more detail and also added them to the eligibility inclusion criteria.

“If this review is so unspecific it should be a scoping review rather than a systematic review and potential meta-analysis.” We have clarified this important issue by removing mention of a “potential meta-analysis” and clarified that we will perform a systematic review and also a meta-analysis provided that there are three or more studies investigating similar interventions with a similar outcome.

“Triage of publications: in a systematic review, it is not possible to focus only on publications with new evidence, excluding publications that were already included in previews systematic reviews and meta-analyses, as described in the second triage.” Thank you, this statement has been deleted from the abstract and manuscript.

“The information sources did not include grey literature.” This has been added explicitly to the information sources section.

“The screening process was not fully described.” Thank you. We have added more detail to our description of the screening process.

We thank Marian Loveday for their comments, which we fully quote and reply to below.

“Thank you for asking me to review this protocol for a systematic review and meta-analysis of tuberculosis care around the time of pregnancy. The authors are undertaking an important and urgently needed task in conducting a systematic review and meta-analysis of TB care around the time of pregnancy and I look forward to reading their paper in the future. The authors have done a great job and the concerns I have raised described below will I hope improve the manuscript. My first concern is the focus of the manuscript. Are you focussing on the care of TB during pregnancy or ‘around the time of pregnancy?’ Although ‘around the time of pregnancy’ is included in the title, the focus of the systematic review and meta-analysis is pregnancy and the research question is ‘How should TB care be modified for current or recent pregnancy?’ The focus of the manuscript needs to be clarified.” Thank you we regret the previous inconsistency of our wording. We have now standardised our wording to “around the time of pregnancy” in order to accommodate the diverse evidence available. We now clarify that the most relevant research has focused on pregnancy, but that some important research evidence (that should be included in our review) also includes the postnatal period.

“Under the PICO Population section the authors state that their population of interest is ‘People of any age who are or were recently pregnant, with or without comorbidities such as HIV infection, who have TB or are considered to be at high risk of TB infection or disease.’ This needs to be clarified in line with the rest of the manuscript.” Thank you, we have clarified and made this consistent throughout the manuscript. **“In your methods section you describe**

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