BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034821
Article Type:	Protocol
Date Submitted by the Author:	08-Oct-2019
Complete List of Authors:	Alene, Kefyalew; Curtin University Bentley Campus, Health Sciences Adane, Akilew; Telethon Kids Institute Jegnie, Alemken; University of Western Australia Faculty of Science, Agriculture and Environment
Keywords:	PUBLIC HEALTH, EPIDEMIOLOGY, Tuberculosis < INFECTIOUS DISEASES

Impact of multidrug-resistant tuberculosis and its medications on adverse maternal and perinatal outcomes: Protocol for a systematic review and meta-analysis

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Keywords: Multidrug-resistant tuberculosis, MDR-TB medications, adverse maternal outcomes, adverse perinatal outcomes, protocol, systematic review

Abstract

Introduction: Multidrug-resistant tuberculosis (MDR-TB) is a common public health problem, affecting pregnant women. However, the impacts of MDR-TB and its medication on pregnancy and perinatal outcomes has been poorly understood and inconsistently reported. Therefore, using the available literature, we aim to determine whether MDR-TB and MDR-TB medications during pregnancy impact maternal and perinatal outcomes.

Methods and analysis: This systematic review and meta-analysis will adhere to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Systematic searches will be conducted in PubMed, Scopus and Web of Science for studies reporting adverse maternal and perinatal outcomes due to MDR-TB and/or its medication. Adverse birth outcomes include miscarriage or abortion, stillbirth, preterm birth, low birth-weight, small and large for gestational age, and neonatal death. Two independent reviewers will screen search records, extract data and assess the quality of the studies. The Newcastle-Ottawa quality assessment scales will be used to assess the methodological quality of the included studies. In addition to a narrative synthesis, a random-effects meta-analysis will be conducted when sufficient data are available. I^2 statistics will be used to assess the heterogeneity between studies.

Ethics and dissemination: As it will be a systematic review and meta-analysis based on previously published evidence, there will be no requirement for ethical approval. Findings will be published in the peer-reviewed journal and will be presented at various conferences.

Strengths and limitations of this study

- As to our knowledge, this systematic review will be the first to synthesise and quantify the impact of MDR-TB and its medication on adverse birth and maternal outcomes.
- Databases will be searched without time restrictions and independent evaluation will be employed.
- A recently developed robust variance meta-analysis technique will be applied to detect and correct for publication bias.
- The potential limitation of this review could be the heterogeneity of studies in outcomes of interest.
- English language restriction is the other limitation.

Introduction

Tuberculosis (TB) is a common non-obstetric cause of death among pregnant women and one of the risk factors for adverse birth outcomes (1). It has been estimated that more than 200 000 pregnant women are affected by TB globally; with 41% and 31% of the cases occurred in African and South-East Asian countries, respectively (2). The emergence of multidrug-resistant tuberculosis (MDR-TB) with resistance to rifampicin and isoniazid (the two most important first-line therapeutic agents) and extensively resistant TB (XDR-TB), with additional resistance to a fluoroquinolone and a second-line injectable drug, has become a major global concern that poses additional challenges for the treatment of TB among pregant women (3). In 2017, globally, there were an estimated 490 000 incident MDR-TB cases, of which 9% were XDR-TB cases (4).

MDR-TB is common among pregnant women and may result in a higher risk of pregnancy-related complications and perinatal death (1, 5). It has also been suggested that MDR-TB during pregnancy could potentially trigger an increased risk of adverse birth outcomes such as spontaneous abortion, small for gestational age, and low birth weight (6-8). The impact of MDR-TB in pregnant women can be aggravated by several factors such as the severity of the disease, the site of infection and the treatment regimen, and substantially varies from mild symptoms to severe compilations and sometimes death (5, 9). Pregnant women with untreated MDR-TB are at increased risks of maternal and infant mortality, suggesting treatment with second-line TB drugs

(10). However, as the treatment of MDR-TB takes longer duration and is more toxic than DS-TB, the risk of adverse birth outcomes such as miscarriage, stillbirth, preterm birth, low birth-weight (LBW) is suggested to be higher in patients with MDR-TB than in patients with DS-TB (11). These adverse birth outcomes often occur as a result of the disease process itself or due to side effects related to second-line TB medications such as fluoroquinolones, aminoglycosides, ethionamide, and prothionamide. Some of these drugs have been identified to have teratogenic effects. For example, aminoglycosides including streptomycin, kanamycin, and amikacin have been shown to impact fetal birthweight and hearing capacity (6, 12, 13). As a result, some studies have recommended termination of pregnancy (8, 14) and others have suggested reducing the dose of teratogenic drugs or suspending the treatment during pregnancy (15, 16). On the contrary, some studies did not find an association between MDR-TB medications and the perinatal outcomes (17). However, previous studies have provided such conflicting evidence based on individual studies with a small sample size (8, 18, 19), and adequate data regarding the impact of second-line MDR-TB drugs in pregnant women are lacking (14).

As most previous studies revealed inconsistent results, mainly because of limited statistical power, a comprehensive systematic review including meta-analysis is required to have clarity regarding the impact of MDR-TB and second-line TB drugs on perinatal outcomes. Quantification of the effects of MDR-TB and its medication on birth outcomes is essential to inform service providers and policymakers in allocating resources and in the prevention of adverse birth outcomes in countries where MDR-TB is prevalent.

The objective of the study

The aim of this systematic review and meta-analysis is to assess the impact of MDR-TB and MDR-TB medications during pregnancy on adverse maternal and birth outcomes.

Methods

Search strategy

This systematic review and meta-analysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (20). Systematic searching will be

conducted in PubMed, Scopus, and Web of Science databases to identify all potential studies that reported adverse maternal and perinatal outcomes among pregnant women who had MDR-TB diagnosis or exposure to MDR-TB medications during pregnancy. The search will be conducted from inception of each database to November 2019, with an English language restriction. The Medical Subject Headings (MeSH) term and combination of keywords related to pregnancy, MDR-TB and MDR-TB medications, and pregnancy outcomes will be used for the search. A complete searching strategy for the PubMed database is available in the supplementary file (Table S1). The reference lists and citations of the retrieved articles will be checked manually for additional studies. The authors of the papers will be contacted through email when there is a need for additional information.

Eligibility criteria

Inclusion criteria: Studies will be included in the systematic review if they evaluate any maternal morbidity and mortality as well as perinatal adverse outcomes among pregnant women with MDR-TB (with or without MDR-TB medications). The selection criteria to identify potential studies will be study population (pregnant women), intervention (MDR-TB and/or its medication during pregnancy), comparator (pregnancies with no MDR-TB, pregnancies with MDR-TB not receiving treatment), and outcomes (adverse perinatal outcomes, and maternal morbidity and mortality). MDR-TB medications will be defined, according to the recent WHO guideline on drug-resistant tuberculosis treatment, as second-line TB agents that are recommended for the treatment of drug-resistant TB (21).

Exclusion criteria: we will exclude correspondence, reviews, editorials, and conference abstracts. Studies conducted only on drug-susceptible TB or on animals will be also excluded. When multiple studies used the same data, we will include the study with the most detailed clinical data, with the largest sample size or with the longest follow-up period to avoid duplication.

Outcomes of the study

The review includes both perinatal adverse outcomes, and the maternal morbidity and mortality. Table 1 shows the definition of the perinatal adverse outcomes and the maternal morbidity and

mortality outcomes of the study. The outcomes of the study will be recorded as prevalence, incidence, relative risks or odds ratios, as reported in the individual papers.

Table 1: definitions of adverse maternal and perinatal outcomes of the systematic review

Outcomes	Definitions of outcomes
Preterm	Birth before 37 completed weeks' gestation
Low birth-weight (LBW)	Birthweight less than 2 500 g
Small for gestational age (SGA)	Birthweight <10th percentile for gestational age
Severe growth restriction (SGR)	Birthweight <3rd percentile for gestational age
Stillbirth	An infant born with no signs of life at 20 or more weeks' gestation
Abortion	Termination of a pregnancy before 20 weeks' gestation
Congenital anomalies	Any major birth defect or as defined by individual studies
Neonatal mortality	Death of a liveborn infant in the first 28 days of life
Maternal morbidity	Any pregnancy and birth complications reported in the original studies
Maternal mortality	Death while pregnant or within 42 days of the end of the pregnancy

Data extraction

All identified articles from the systematic searching will be uploaded into Rayyan (https://rayyan.qcri.org). Two researchers (KAA and AJ) will independently screen the titles and abstracts of the studies and will then review the full text based on the eligibility criteria. The two researchers will compare the results and disagreements will be resolved through discussion. If consensus is not reached between these two researchers, disagreements will be resolved by discussion with a third investigator (AAA).

Data from the included studies will be extracted and compiled using a standardised excel spreadsheet. We will extract information from each study on the last name of first author, year of data collection and publication, report type (grey literature v published studies), study country, study design, and data source. Information will be also collected on maternal age, sample size, effect size as reported by a study, multiple pregnancies, type of pregnancy outcomes, and number of cases with adverse birth outcomes. When available, the following additional information will

be also extracted from the primary studies: percentage of resistance to particular TB medicines, duration of MDR-TB treatment in months, percentage of pregnant women with HIV infection, and percentage of pregnant women with diabetes mellitus. Moreover, we will make an effort to include relevant information unavailable to the original study such as socio-economic setting (e.g., poor or rich country, income level for each country, WB member or not), geographical dimension (the state/province where the study is conducted). A data extraction sheet is available in the supplementary information (Table S2).

Quality and bias assessment

The methodological quality of the included studies will be assessed independently by the same two investigators (KAA and AJ), using a modified version of the Newcastle-Ottawa Quality Assessment Scales (22). This tool has scores ranging from zero to nine; scores between one and four will be defined as low quality, scores between five and seven will be defined as medium quality, and scores between eight and nine will be defined as high quality. Publication bias will be assessed graphically by a funnel plot and statistically using a recently developed Robust Variance Estimation (RVE) technique (23, 24).

Data analysis

A systematic narrative synthesis will be conducted to describe the outcomes of the study. When two or more studies are available, a random-effects meta-analysis will be used to obtain a pooled estimate value for each of the outcomes of interest. Heterogeneity between studies will be examined using the Cochran's Q test and quantitatively measured by the index of heterogeneity squared (I^2) statistics and its 95% confidence interval (CI) (25). Heterogeneity will be considered low, moderate and high when I^2 values are below 25%, between 25% and 75%, and above 75%, respectively (25). When there is evidence of significant heterogeneity, the sources of this will be explored through meta-regression using study characteristics as covariates. The Hedges et al. (2010) (26) and the Tipton (2015) small-sample corrected RVE method (27) will be applied to perform the meta-regression, this approach handles non-independent effect sizes without knowledge of the within-study covariance structure. Unlike the traditional meta-regression approaches, the RVE method has some unique benefits such as: a) the coefficients are consistent estimates of the underlying population parameters under a broad set of conditions including non-normality; b) the results do not need the predictor variables to be fixed; c) RVE yields valid

standard errors, point estimates, confidence intervals, and significance tests when effect sizes are non-independent, without requiring to model the exact nature of this dependence (27, 28). Hedges et al. (2010) (26) show that the RVE approach performs well when the number of studies is large. However, Tipton (2015) (27) made small-sample adjustments to both the RVE estimator and degrees of freedom and it has been suggested that the RVE method can also perform well when the number of studies is small, as few as ten. An inverse variance weighting will be used to provide asymptotically accurate estimates of standard errors and valid inferences. This approach is distribution-free, provides valid point estimates, standard errors and performs an appropriate hypothesis test even when the degree and structure of dependence between effect sizes are unknown, hence, the statistical inferences made will be unbiased and correct.

Patient and public involvement

No patient will be involved in the study.

Discussion and conclusion

This comprehensive systematic review will quantify the impacts of MDR-TB and second-line TB medication on adverse maternal and birth outcomes such as prematurity, low birth weight, and small for gestational age, and various other obstetrical and perinatal outcomes. The results will provide compressive information essential for healthcare providers and policymakers to better understand the impact of MDR-TB and its medication on adverse maternal and birth outcomes and to design appropriate treatment regimen and follow up for pregnant women with MDR-TB. This review also identifies research gaps in the literature regarding the subject and provides a basis for future studies. This review does not require a formal ethics approval as publicly available published studies will be used. The findings of this review will be disseminated through publication in a peer-reviewed journal and presentation at relevant national and international conferences and scientific meetings. The reviewer will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Contributors: KAA, AAA, and AJ conceived of the study**,** developed the search strategy, and drafted the protocol. All authors critically revised the manuscript for methodological and intellectual content and have read and approved the final manuscript.

Funding: This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: The authors declare that they have no competing interests.

Patient consent for publication: Not required.

Ethics approval: Not required.

Amendments of the protocol: If there is a need to amend this protocol, the date of each amendment and the reason for the change will be described.

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Supplementary information

Table S1: Search strategies

Number	Theme	Searching terms
1	population	"pregnancy" or "prenatal" or "antenatal"
2	exposures	"Tuberculosis, Multidrug-Resistant"[Mesh] or "mdr-tb" or "xdr-tb" or "second-line tuberculosis drugs" or "fluoroquinolones" or "aminoglycosides" or "levofloxacin" or "moxifloxacin" or "bedaquiline" or "linezolid" or "clofazimine" or "cycloserine" or "terizidone" or "delamanid" or "imipenem-cilastatin" or "meropenem" or "amikacin" or "ethionamide" or "prothionamide" or "p-aminosalicylic acid"
3	outcomes	"adverse birth outcomes" OR abortion OR miscarriage OR termination OR stillbirth OR premature OR preterm OR birthweight OR "birth weight" OR "gestational age" OR death OR morbidity OR "pregnancy complications" OR "birth complications"
4	Search	#1 AND #2 AND #3

Table S2: Data extraction tool for the characteristics of the studies.

First author	Year of publication	Country	Study design	Years of data collection	Mean/ median age (year)	DR-TB (%)	HIV, %	DM, %	Mean duration of treatment in months	Gravida	Sample size	Type of adverse birth outcomes	Number of cases with adverse birth outcomes	Type of exposures (MDR-TB vs MDR-TB medication

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	9
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3 & 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5&6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	13-15
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6&7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6&7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and	13	List and define all outcomes for which data will be sought, including prioritization of	6

prioritization		main and additional outcomes, with rationale	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7 &8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

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Article Type:	Protocol
Date Submitted by the Author:	24-Oct-2019
Complete List of Authors:	Alene, Kefyalew; Curtin University Bentley Campus, Health Sciences Adane, Akilew; Telethon Kids Institute Jegnie, Alemken; University of Western Australia Faculty of Science, Agriculture and Environment
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MDR-TB is common among pregnant women and may result in a higher risk of pregnancy-related complications and perinatal death (1, 5). It has also been suggested that MDR-TB during pregnancy could potentially trigger an increased risk of adverse birth outcomes such as spontaneous abortion, small for gestational age, and low birth weight (6-8). The impact of MDR-TB in pregnant women can be aggravated by several factors such as the severity of the disease, the site of infection and the treatment regimen, and substantially varies from mild symptoms to severe compilations and sometimes death (5, 9). Pregnant women with untreated MDR-TB are at increased risks of maternal and infant mortality, suggesting treatment with second-line TB drugs

(10). However, as the treatment of MDR-TB takes longer duration and is more toxic than DS-TB, the risk of adverse birth outcomes such as miscarriage, stillbirth, preterm birth, low birth-weight (LBW) is suggested to be higher in patients with MDR-TB than in patients with DS-TB (11). These adverse birth outcomes often occur as a result of the disease process itself or due to side effects related to second-line TB medications such as fluoroquinolones, aminoglycosides, ethionamide, and prothionamide. Some of these drugs have been identified to have teratogenic effects. For example, aminoglycosides including streptomycin, kanamycin, and amikacin have been shown to impact fetal birthweight and hearing capacity (6, 12, 13). As a result, some studies have recommended termination of pregnancy (8, 14) and others have suggested reducing the dose of teratogenic drugs or suspending the treatment during pregnancy (15, 16). On the contrary, some studies did not find an association between MDR-TB medications and the perinatal outcomes (17). However, previous studies have provided such conflicting evidence based on individual studies with a small sample size (8, 18, 19), and adequate data regarding the impact of second-line MDR-TB drugs in pregnant women are lacking (14). In addition, to the best of our knowledge, no MDR trial currently conducted worldwide includes pregnant patients which presents a major obstacle to develop guidance of what MDR-TB drugs are safe and effective in pregnancy.

As most previous studies revealed inconsistent results, mainly because of limited statistical power, a comprehensive systematic review including meta-analysis is required to have clarity regarding the impact of MDR-TB and second-line TB drugs on perinatal outcomes. Quantification of the effects of MDR-TB and its medication on birth outcomes is essential to inform service providers and policymakers in allocating resources and in the prevention of adverse birth outcomes in countries where MDR-TB is prevalent.

The objective of the study

The aim of this systematic review and meta-analysis is to assess the impact of MDR-TB and MDR-TB medications during pregnancy on adverse maternal and birth outcomes.

Methods

Search strategy

This systematic review and meta-analysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (20). Systematic searching will be conducted in PubMed, Scopus, and Web of Science databases to identify all potential studies that reported adverse maternal and perinatal outcomes among pregnant women who had MDR-TB diagnosis or exposure to MDR-TB medications during pregnancy. The search will be conducted from inception of each database to November 14, 2019, without language restriction. The overall study will be conducted from 14 December 2019 to 21 March 2020. The Medical Subject Headings (MeSH) term and combination of keywords related to pregnancy, MDR-TB and MDR-TB medications, and pregnancy outcomes will be used for the search. A complete searching strategy for the PubMed database is available in the supplementary file (Table S1). The reference lists and citations of the retrieved articles will be checked manually for additional studies. The authors of the papers will be contacted through email when there is a need for additional information.

Eligibility criteria

Inclusion criteria: Studies will be included in the systematic review if they evaluate any maternal morbidity and mortality as well as perinatal adverse outcomes among pregnant women with MDR-TB (with or without MDR-TB medications). The selection criteria to identify potential studies will be study population (pregnant women), intervention (MDR-TB and/or its medication during pregnancy), comparator (pregnancies with no MDR-TB, pregnancies with MDR-TB not receiving treatment), and outcomes (adverse perinatal outcomes, and maternal morbidity and mortality). MDR-TB medications will be defined, according to the recent WHO guideline on drug-resistant tuberculosis treatment, as second-line TB agents that are recommended for the treatment of drug-resistant TB (21). These agents include levofloxacin, moxifloxacin, bedaquiline, linezolid, clofazimine, cycloserine, terizidone, delamanid, imipenem–cilastatin, meropenem, amikacin, ethionamide, prothionamide, p-aminosalicylic acid.

Exclusion criteria: we will exclude correspondence, reviews, editorials, and conference abstracts. Studies conducted only on drug-susceptible TB or on animals will be also excluded. When multiple studies used the same data, we will include the study with the most detailed clinical data, with the largest sample size or with the longest follow-up period to avoid duplication.

Outcomes of the study

The review includes both perinatal adverse outcomes, and the maternal morbidity and mortality. We will include studies that reported outcomes of pregnancies complicated by MDR-TB and non-drug resistant TB to construct risk ratios for each study and look for a pooled risk ratio. Table 1 shows the definition of the perinatal adverse outcomes and the maternal morbidity and mortality outcomes of the study. The outcomes of the study will be recorded as prevalence, incidence, and relative risks or odds ratios, as reported in the individual papers.

Table 1: definitions of adverse maternal and perinatal outcomes of the systematic review

Outcomes	Definitions of outcomes
Preterm	Birth before 37 completed weeks' gestation
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Severe growth restriction (SGR)	Birthweight <3rd percentile for gestational age
Stillbirth	An infant born with no signs of life at 20 or more weeks' gestation
Abortion	Termination of a pregnancy before 20 weeks' gestation
Congenital anomalies	Any major birth defect or as defined by individual studies
Neonatal mortality	Death of a liveborn infant in the first 28 days of life
Maternal morbidity	Any pregnancy and birth complications reported in the original studies
Maternal mortality	Death while pregnant or within 42 days of the end of the pregnancy

Data extraction

All identified articles from the systematic searching will be uploaded into Rayyan (https://rayyan.qcri.org). Two researchers (KAA and AJ) will independently screen the titles and abstracts of the studies and will then review the full text based on the eligibility criteria. The two researchers will compare the results and disagreements will be resolved through discussion. If consensus is not reached between these two researchers, disagreements will be resolved by discussion with a third investigator (AAA).

Data from the included studies will be extracted and compiled using a standardised excel spreadsheet. We will extract information from each study on the last name of the first author, year

of data collection and publication, report type (grey literature v published studies), study country, study design, and data source. Information will be also collected on maternal age, sample size, effect size as reported by a study, multiple pregnancies, type of pregnancy outcomes, and number of cases with adverse birth outcomes. When available, the following additional information will be also extracted from the primary studies: percentage of resistance to particular TB medicines, duration of MDR-TB treatment in months, percentage of pregnant women with HIV infection, and percentage of pregnant women with diabetes mellitus. Moreover, we will make an effort to include relevant information unavailable to the original study such as socio-economic setting (e.g., poor or rich country, the income level for each country, WB member or not), geographical dimension (the state/province where the study is conducted). A data extraction sheet is available in the supplementary information (Table S2).

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The methodological quality of the included studies will be assessed independently by the same two investigators (KAA and AJ), using a modified version of the Newcastle-Ottawa Quality Assessment Scales (22). This tool has scores ranging from zero to nine; scores between one and four will be defined as low quality, scores between five and seven will be defined as medium quality, and scores between eight and nine will be defined as high quality. Publication bias will be assessed graphically by a funnel plot and statistically using a recently developed Robust Variance Estimation (RVE) technique (23, 24).

Data analysis

A systematic narrative synthesis will be conducted to describe the outcomes of the study. When two or more studies are available, a random-effects meta-analysis will be used to obtain a pooled estimate value for each of the outcomes of interest. Heterogeneity between studies will be examined using the Cochran's Q test and quantitatively measured by the index of heterogeneity squared (I^2) statistics and its 95% confidence interval (CI) (25). Heterogeneity will be considered low, moderate and high when I^2 values are below 25%, between 25% and 75%, and above 75%, respectively (25). When there is evidence of significant heterogeneity, the sources of this will be explored through meta-regression using study characteristics as covariates. The Hedges et al. (2010) (26) and the Tipton (2015) small-sample corrected RVE method (27) will be applied to perform the meta-regression, this approach handles non-independent effect sizes without

knowledge of the within-study covariance structure. Unlike the traditional meta-regression approaches, the RVE method has some unique benefits such as: a) the coefficients are consistent estimates of the underlying population parameters under a broad set of conditions including non-normality; b) the results do not need the predictor variables to be fixed; c) RVE yields valid standard errors, point estimates, confidence intervals, and significance tests when effect sizes are non-independent, without requiring to model the exact nature of this dependence (27, 28). Hedges et al. (2010) (26) show that the RVE approach performs well when the number of studies is large. However, Tipton (2015) (27) made small-sample adjustments to both the RVE estimator and degrees of freedom and it has been suggested that the RVE method can also perform well when the number of studies is small, as few as ten. An inverse variance weighting will be used to provide asymptotically accurate estimates of standard errors and valid inferences. This approach is distribution-free, provides valid point estimates, standard errors and performs an appropriate hypothesis test even when the degree and structure of dependence between effect sizes are unknown, hence, the statistical inferences made will be unbiased and correct.

Patient and public involvement

No patient will be involved in the study.

Discussion and conclusion

This comprehensive systematic review will quantify the impacts of MDR-TB and second-line TB medication on adverse maternal and birth outcomes such as prematurity, low birth weight, and small for gestational age, and various other obstetrical and perinatal outcomes. The results will provide compressive information essential for healthcare providers and policymakers to better understand the impact of MDR-TB and its medication on adverse maternal and birth outcomes and to design appropriate treatment regimen and follow up for pregnant women with MDR-TB. This review also identifies research gaps in the literature regarding the subject and provides a basis for future studies. This review does not require a formal ethics approval as publicly available published studies will be used. The findings of this review will be disseminated through publication in a peer-reviewed journal and presentation at relevant national and international conferences and scientific meetings. The reviewer will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Contributors: KAA, AAA, and AJ conceived of the study**,** developed the search strategy, and drafted the protocol. All authors critically revised the manuscript for methodological and intellectual content and have read and approved the final manuscript.

Funding: This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: The authors declare that they have no competing interests.

Patient consent for publication: Not required.

Ethics approval: Not required.

Amendments of the protocol: If there is a need to amend this protocol, the date of each amendment and the reason for the change will be described.

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Supplementary information

Table S1: Search strategies

Number	Theme	Searching terms
1	population	"pregnancy" or "prenatal" or "antenatal"
2	exposures	"Tuberculosis, Multidrug-Resistant"[Mesh] or "mdr-tb" or "xdr-tb" or "second-line tuberculosis drugs" or "fluoroquinolones" or "aminoglycosides" or "levofloxacin" or "moxifloxacin" or "bedaquiline" or "linezolid" or "clofazimine" or "cycloserine" or "terizidone" or "delamanid" or "imipenem-cilastatin" or "meropenem" or "amikacin" or "ethionamide" or "prothionamide" or "p-aminosalicylic acid"
3	outcomes	"adverse birth outcomes" OR abortion OR miscarriage OR termination OR stillbirth OR premature OR preterm OR birthweight OR "birth weight" OR "gestational age" OR death OR morbidity OR "pregnancy complications" OR "birth complications"
4	Search	#1 AND #2 AND #3

Table S2: Data extraction tool for the characteristics of the studies.

First author	Year of publication	Country	Study design	Years of data collection	Mean/ median age (year)	DR-TB (%)	HIV, %	DM, %	Mean duration of treatment in months	Gravida	Sample size	Type of adverse birth outcomes	Number of cases with adverse birth outcomes	Type of exposures (MDR-TB vs MDR-TB medication

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	9
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3 & 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5&6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	13-15
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6&7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6&7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and	13	List and define all outcomes for which data will be sought, including prioritization of	6

prioritization		main and additional outcomes, with rationale	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7 &8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034821.R2
Article Type:	Protocol
Date Submitted by the Author:	25-Nov-2019
Complete List of Authors:	Alene, Kefyalew; Curtin University Bentley Campus, Health Sciences Adane, Akilew; Telethon Kids Institute Jegnie, Alemken; University of Western Australia Faculty of Science, Agriculture and Environment
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	PUBLIC HEALTH, EPIDEMIOLOGY, Tuberculosis < INFECTIOUS DISEASES

Impact of multidrug-resistant tuberculosis and its medications on adverse maternal and perinatal outcomes: Protocol for a systematic review and meta-analysis

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Keywords: Multidrug-resistant tuberculosis, MDR-TB medications, adverse maternal outcomes, adverse perinatal outcomes, protocol, systematic review

Abstract

Introduction: Multidrug-resistant tuberculosis (MDR-TB) is a common public health problem, affecting pregnant women. However, the impacts of MDR-TB and its medication on pregnancy and perinatal outcomes has been poorly understood and inconsistently reported. Therefore, using the available literature, we aim to determine whether MDR-TB and MDR-TB medications during pregnancy impact maternal and perinatal outcomes.

Methods and analysis: This systematic review and meta-analysis will adhere to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Systematic searches will be conducted in PubMed, Scopus and Web of Science on 10 February 2020 for studies that reported adverse maternal and perinatal outcomes due to MDR-TB and/or its medication. The search will be performed without language and time restrictions. Adverse birth outcomes include miscarriage or abortion, stillbirth, preterm birth, low birth-weight, small and large for gestational age, and neonatal death. Two independent reviewers will screen search records, extract data and assess the quality of the studies. The Newcastle-Ottawa quality assessment scales will be used to assess the methodological quality of the included studies. In addition to a narrative synthesis, a random-effects meta-analysis will be conducted when sufficient data are available. I^2 statistics will be used to assess the heterogeneity between studies.

Ethics and dissemination: As it will be a systematic review and meta-analysis based on previously published evidence, there will be no requirement for ethical approval. Findings will be published in the peer-reviewed journal and will be presented at various conferences.

Strengths and limitations of this study

- As to our knowledge, this systematic review will be the first to synthesise and quantify the impact of MDR-TB and its medication on adverse birth and maternal outcomes.
- Databases will be searched without time restrictions and independent evaluation will be employed.
- A recently developed robust variance meta-analysis technique will be applied to detect and correct for publication bias.
- The potential limitation of this review could be the heterogeneity of studies in outcomes of interest.

Introduction

Tuberculosis (TB) is a common non-obstetric cause of death among pregnant women and one of the risk factors for adverse birth outcomes (1). It has been estimated that more than 200 000 pregnant women are affected by TB globally; with 41% and 31% of the cases occurred in African and South-East Asian countries, respectively (2). The emergence of multidrug-resistant tuberculosis (MDR-TB) with resistance to rifampicin and isoniazid (the two most important first-line therapeutic agents) and extensively resistant TB (XDR-TB), with additional resistance to a fluoroquinolone and a second-line injectable drug, has become a major global concern that poses additional challenges for the treatment of TB among pregant women (3). In 2017, globally, there were an estimated 490 000 incident MDR-TB cases, of which 9% were XDR-TB cases (4).

MDR-TB is common among pregnant women and may result in a higher risk of pregnancy-related complications and perinatal death (1, 5). It has also been suggested that MDR-TB during pregnancy could potentially trigger an increased risk of adverse birth outcomes such as spontaneous abortion, small for gestational age, and low birth weight (6-8). The impact of MDR-TB in pregnant women can be aggravated by several factors such as the severity of the disease, the site of infection and the treatment regimen, and substantially varies from mild symptoms to severe compilations and sometimes death (5, 9). Pregnant women with untreated MDR-TB are at increased risks of maternal and infant mortality, suggesting treatment with second-line TB drugs (10). However, as the treatment of MDR-TB takes longer duration and is more toxic than DS-TB,

the risk of adverse birth outcomes such as miscarriage, stillbirth, preterm birth, low birth-weight (LBW) is suggested to be higher in patients with MDR-TB than in patients with DS-TB (11). These adverse birth outcomes often occur as a result of the disease process itself or due to side effects related to second-line TB medications such as fluoroquinolones, aminoglycosides, ethionamide, and prothionamide. Some of these drugs have been identified to have teratogenic effects. For example, aminoglycosides including streptomycin, kanamycin, and amikacin have been shown to impact fetal birthweight and hearing capacity (6, 12, 13). As a result, some studies have recommended termination of pregnancy (8, 14) and others have suggested reducing the dose of teratogenic drugs or suspending the treatment during pregnancy (15, 16). On the contrary, some studies did not find an association between MDR-TB medications and the perinatal outcomes (17). However, previous studies have provided such conflicting evidence based on individual studies with a small sample size (8, 18, 19), and adequate data regarding the impact of second-line MDR-TB drugs in pregnant women are lacking (14). In addition, to the best of our knowledge, no MDR trial currently conducted worldwide includes pregnant patients which presents a major obstacle to develop guidance of what MDR-TB drugs are safe and effective in pregnancy.

As most previous studies revealed inconsistent results, mainly because of limited statistical power, a comprehensive systematic review including meta-analysis is required to have clarity regarding the impact of MDR-TB and second-line TB drugs on perinatal outcomes. Quantification of the effects of MDR-TB and its medication on birth outcomes is essential to inform service providers and policymakers in allocating resources and in the prevention of adverse birth outcomes in countries where MDR-TB is prevalent.

The objective of the study

The aim of this systematic review and meta-analysis is to assess the impact of MDR-TB and MDR-TB medications during pregnancy on adverse maternal and birth outcomes.

Methods

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This systematic review and meta-analysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (20). Systematic searching will be conducted in PubMed, Scopus, and Web of Science databases to identify all potential studies that reported adverse maternal and perinatal outcomes among pregnant women who had MDR-TB diagnosis or exposure to MDR-TB medications during pregnancy. The search will be conducted from the inception of each database to February 10, 2020, without language and time restrictions. The overall study will be conducted from 14 December 2019 to 21 March 2020. The Medical Subject Headings (MeSH) term and combination of keywords related to pregnancy, MDR-TB and MDR-TB medications, and pregnancy outcomes will be used for the search. A complete searching strategy for the PubMed database is available in the supplementary file (Table S1). The reference lists and citations of the retrieved articles will be checked manually for additional studies. The authors of the papers will be contacted through email when there is a need for additional information.

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Data analysis

A systematic narrative synthesis will be conducted to describe the outcomes of the study. When two or more studies are available, a random-effects meta-analysis will be used to obtain a pooled estimate value for each of the outcomes of interest. Heterogeneity between studies will be examined using the Cochran's Q test and quantitatively measured by the index of heterogeneity squared (I^2) statistics and its 95% confidence interval (CI) (25). Heterogeneity will be considered low, moderate and high when I^2 values are below 25%, between 25% and 75%, and above 75%, respectively (25). When there is evidence of significant heterogeneity, the sources of this will be explored through meta-regression using study characteristics as covariates. The Hedges et al. (2010) (26) and the Tipton (2015) small-sample corrected RVE method (27) will be applied to perform the meta-regression, this approach handles non-independent effect sizes without

knowledge of the within-study covariance structure. Unlike the traditional meta-regression approaches, the RVE method has some unique benefits such as: a) the coefficients are consistent estimates of the underlying population parameters under a broad set of conditions including non-normality; b) the results do not need the predictor variables to be fixed; c) RVE yields valid standard errors, point estimates, confidence intervals, and significance tests when effect sizes are non-independent, without requiring to model the exact nature of this dependence (27, 28). Hedges et al. (2010) (26) show that the RVE approach performs well when the number of studies is large. However, Tipton (2015) (27) made small-sample adjustments to both the RVE estimator and degrees of freedom and it has been suggested that the RVE method can also perform well when the number of studies is small, as few as ten. An inverse variance weighting will be used to provide asymptotically accurate estimates of standard errors and valid inferences. This approach is distribution-free, provides valid point estimates, standard errors and performs an appropriate hypothesis test even when the degree and structure of dependence between effect sizes are unknown, hence, the statistical inferences made will be unbiased and correct.

Patient and public involvement

No patient will be involved in the study.

Discussion and conclusion

This comprehensive systematic review will quantify the impacts of MDR-TB and second-line TB medication on adverse maternal and birth outcomes such as prematurity, low birth weight, and small for gestational age, and various other obstetrical and perinatal outcomes. The results will provide compressive information essential for healthcare providers and policymakers to better understand the impact of MDR-TB and its medication on adverse maternal and birth outcomes and to design appropriate treatment regimen and follow up for pregnant women with MDR-TB. This review also identifies research gaps in the literature regarding the subject and provides a basis for future studies. This review does not require a formal ethics approval as publicly available published studies will be used. The findings of this review will be disseminated through publication in a peer-reviewed journal and presentation at relevant national and international

conferences and scientific meetings. The reviewer will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Ethics and dissemination: As it will be a systematic review and meta-analysis based on previously published evidence, there will be no requirement for ethical approval. Findings will be published in the peer-reviewed journal and will be presented at various conferences.

Contributors: KAA, AAA, and AJ conceived of the study**,** developed the search strategy, and drafted the protocol. All authors critically revised the manuscript for methodological and intellectual content and have read and approved the final manuscript.

Funding: This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: The authors declare that they have no competing interests.

Patient consent for publication: Not required.

Ethics approval: Not required.

Amendments of the protocol: If there is a need to amend this protocol, the date of each amendment and the reason for the change will be described.

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Supplementary information

Table S1: Search strategies

Number	Theme	Searching terms
1	population	"pregnancy" or "prenatal" or "antenatal"
2	exposures	"Tuberculosis, Multidrug-Resistant"[Mesh] or "mdr-tb" or "xdr-tb" or "second-line tuberculosis drugs" or "fluoroquinolones" or "aminoglycosides" or "levofloxacin" or "moxifloxacin" or "bedaquiline" or "linezolid" or "clofazimine" or "cycloserine" or "terizidone" or "delamanid" or "imipenem-cilastatin" or "meropenem" or "amikacin" or "ethionamide" or "prothionamide" or "p-aminosalicylic acid"
3	outcomes	"adverse birth outcomes" OR abortion OR miscarriage OR termination OR stillbirth OR premature OR preterm OR birthweight OR "birth weight" OR "gestational age" OR death OR morbidity OR "pregnancy complications" OR "birth complications"
4	Search	#1 AND #2 AND #3

Table S2: Data extraction tool for the characteristics of the studies.

First author	Year of publication	Country	Study design	Years of data collection	Mean/ median age (year)	DR-TB (%)	HIV, %	DM, %	Mean duration of treatment in months	Gravida	Sample size	Type of adverse birth outcomes	Number of cases with adverse birth outcomes	Type of exposures (MDR-TB vs MDR-TB medication

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	9
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3 & 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5&6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	13-15
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6&7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6&7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and	13	List and define all outcomes for which data will be sought, including prioritization of	6

prioritization		main and additional outcomes, with rationale	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7 &8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.