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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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Manuscripts

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 pregnant 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 complications 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

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2
3 conducted in PubMed, Scopus, and Web of Science databases to identify all potential studies that
4 reported adverse maternal and perinatal outcomes among pregnant women who had MDR-TB
5 diagnosis or exposure to MDR-TB medications during pregnancy. The search will be conducted
6 from inception of each database to November 2019, with an English language restriction. The
7 Medical Subject Headings (MeSH) term and combination of keywords related to pregnancy,
8 MDR-TB and MDR-TB medications, and pregnancy outcomes will be used for the search. A
9 complete searching strategy for the PubMed database is available in the supplementary file
10 (Table S1). The reference lists and citations of the retrieved articles will be checked manually for
11 additional studies. The authors of the papers will be contacted through email when there is a
12 need for additional information.
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23 Eligibility criteria

24 **Inclusion criteria:** Studies will be included in the systematic review if they evaluate any maternal
25 morbidity and mortality as well as perinatal adverse outcomes among pregnant women with MDR-
26 TB (with or without MDR-TB medications). The selection criteria to identify potential studies will
27 be study population (pregnant women), intervention (MDR-TB and/or its medication during
28 pregnancy), comparator (pregnancies with no MDR-TB, pregnancies with MDR-TB not receiving
29 treatment), and outcomes (adverse perinatal outcomes, and maternal morbidity and mortality).
30 MDR-TB medications will be defined, according to the recent WHO guideline on drug-resistant
31 tuberculosis treatment, as second-line TB agents that are recommended for the treatment of drug-
32 resistant TB (21).
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41 **Exclusion criteria:** we will exclude correspondence, reviews, editorials, and conference abstracts.
42 Studies conducted only on drug-susceptible TB or on animals will be also excluded. When multiple
43 studies used the same data, we will include the study with the most detailed clinical data, with the
44 largest sample size or with the longest follow-up period to avoid duplication.
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49 Outcomes of the study

50 The review includes both perinatal adverse outcomes, and the maternal morbidity and mortality.
51 Table 1 shows the definition of the perinatal adverse outcomes and the maternal morbidity and
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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 <10 th percentile for gestational age
Severe growth restriction (SGR)	Birthweight <3 rd 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

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

15 **Quality and bias assessment**

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

30 **Data analysis**

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32 A systematic narrative synthesis will be conducted to describe the outcomes of the study. When
33 two or more studies are available, a random-effects meta-analysis will be used to obtain a pooled
34 estimate value for each of the outcomes of interest. Heterogeneity between studies will be
35 examined using the Cochran's Q test and quantitatively measured by the index of heterogeneity
36 squared (I^2) statistics and its 95% confidence interval (CI) (25). Heterogeneity will be considered
37 low, moderate and high when I^2 values are below 25%, between 25% and 75%, and above 75%,
38 respectively (25). When there is evidence of significant heterogeneity, the sources of this will be
39 explored through meta-regression using study characteristics as covariates. The Hedges et al.
40 (2010) (26) and the Tipton (2015) small-sample corrected RVE method (27) will be applied to
41 perform the meta-regression, this approach handles non-independent effect sizes without
42 knowledge of the within-study covariance structure. Unlike the traditional meta-regression
43 approaches, the RVE method has some unique benefits such as: a) the coefficients are consistent
44 estimates of the underlying population parameters under a broad set of conditions including non-
45 normality; b) the results do not need the predictor variables to be fixed; c) RVE yields valid
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3 standard errors, point estimates, confidence intervals, and significance tests when effect sizes are
4 non-independent, without requiring to model the exact nature of this dependence (27, 28). Hedges
5 et al. (2010) (26) show that the RVE approach performs well when the number of studies is large.
6
7 However, Tipton (2015) (27) made small-sample adjustments to both the RVE estimator and
8 degrees of freedom and it has been suggested that the RVE method can also perform well when
9 the number of studies is small, as few as ten. An inverse variance weighting will be used to provide
10 asymptotically accurate estimates of standard errors and valid inferences. This approach is
11 distribution-free, provides valid point estimates, standard errors and performs an appropriate
12 hypothesis test even when the degree and structure of dependence between effect sizes are
13 unknown, hence, the statistical inferences made will be unbiased and correct.
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22 **Patient and public involvement**

23 No patient will be involved in the study.
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28 **Discussion and conclusion**

29 This comprehensive systematic review will quantify the impacts of MDR-TB and second-line TB
30 medication on adverse maternal and birth outcomes such as prematurity, low birth weight, and
31 small for gestational age, and various other obstetrical and perinatal outcomes. The results will
32 provide compressive information essential for healthcare providers and policymakers to better
33 understand the impact of MDR-TB and its medication on adverse maternal and birth outcomes and
34 to design appropriate treatment regimen and follow up for pregnant women with MDR-TB. This
35 review also identifies research gaps in the literature regarding the subject and provides a basis for
36 future studies. This review does not require a formal ethics approval as publicly available
37 published studies will be used. The findings of this review will be disseminated through
38 publication in a peer-reviewed journal and presentation at relevant national and international
39 conferences and scientific meetings. The reviewer will adhere to the Preferred Reporting Items
40 for Systematic Reviews and Meta-Analyses guidelines.
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52 **Contributors:** KAA, AAA, and AJ conceived of the study, developed the search strategy, and
53 drafted the protocol. All authors critically revised the manuscript for methodological and
54 intellectual content and have read and approved the final manuscript.
55
56
57

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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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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.

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25 Abstract

26 **Introduction:** Multidrug-resistant tuberculosis (MDR-TB) is a common public health problem,
27 affecting pregnant women. However, the impacts of MDR-TB and its medication on pregnancy
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29 the available literature, we aim to determine whether MDR-TB and MDR-TB medications during
30 pregnancy impact maternal and perinatal outcomes.

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35 birth outcomes include miscarriage or abortion, stillbirth, preterm birth, low birth-weight, small
36 and large for gestational age, and neonatal death. Two independent reviewers will screen search
37 records, extract data and assess the quality of the studies. The Newcastle-Ottawa quality
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40 data are available. I^2 statistics will be used to assess the heterogeneity between studies.

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45 **Strengths and limitations of this study**

- 46 • As to our knowledge, this systematic review will be the first to synthesise and quantify
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53 of interest.
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55 **Introduction**

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

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

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3 73 (10). However, as the treatment of MDR-TB takes longer duration and is more toxic than DS-TB,
4 74 the risk of adverse birth outcomes such as miscarriage, stillbirth, preterm birth, low birth-weight
5 75 (LBW) is suggested to be higher in patients with MDR-TB than in patients with DS-TB (11). These
6 76 adverse birth outcomes often occur as a result of the disease process itself or due to side effects
7 77 related to second-line TB medications such as fluoroquinolones, aminoglycosides, ethionamide,
8 78 and prothionamide. Some of these drugs have been identified to have teratogenic effects. For
9 79 example, aminoglycosides including streptomycin, kanamycin, and amikacin have been shown to
10 80 impact fetal birthweight and hearing capacity (6, 12, 13). As a result, some studies have
11 81 recommended termination of pregnancy (8, 14) and others have suggested reducing the dose of
12 82 teratogenic drugs or suspending the treatment during pregnancy (15, 16). On the contrary, some
13 83 studies did not find an association between MDR-TB medications and the perinatal outcomes (17).
14 84 However, previous studies have provided such conflicting evidence based on individual studies
15 85 with a small sample size (8, 18, 19), and adequate data regarding the impact of second-line MDR-
16 86 TB drugs in pregnant women are lacking (14). In addition, to the best of our knowledge, no MDR
17 87 trial currently conducted worldwide includes pregnant patients which presents a major obstacle to
18 88 develop guidance of what MDR-TB drugs are safe and effective in pregnancy.

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32 89 As most previous studies revealed inconsistent results, mainly because of limited statistical power,
33 90 a comprehensive systematic review including meta-analysis is required to have clarity regarding
34 91 the impact of MDR-TB and second-line TB drugs on perinatal outcomes. Quantification of the
35 92 effects of MDR-TB and its medication on birth outcomes is essential to inform service providers
36 93 and policymakers in allocating resources and in the prevention of adverse birth outcomes in
37 94 countries where MDR-TB is prevalent.

38 39 40 41 42 43 95 **The objective of the study**

44 96 The aim of this systematic review and meta-analysis is to assess the impact of MDR-TB and
45 97 MDR-TB medications during pregnancy on adverse maternal and birth outcomes.

46 47 48 49 98 **Methods**

50 51 52 99 **Search strategy**

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3 100 This systematic review and meta-analysis will adhere to the Preferred Reporting Items for
4 101 Systematic Reviews and Meta-analyses (PRISMA) guidelines (20). Systematic searching will be
5 102 conducted in PubMed, Scopus, and Web of Science databases to identify all potential studies that
6 103 reported adverse maternal and perinatal outcomes among pregnant women who had MDR-TB
7 104 diagnosis or exposure to MDR-TB medications during pregnancy. The search will be conducted
8 105 from inception of each database to November 14, 2019, without language restriction. The overall
9 106 study will be conducted from 14 December 2019 to 21 March 2020. The Medical Subject
10 107 Headings (MeSH) term and combination of keywords related to pregnancy, MDR-TB and MDR-
11 108 TB medications, and pregnancy outcomes will be used for the search. A complete searching
12 109 strategy for the PubMed database is available in the supplementary file (Table S1). The reference
13 110 lists and citations of the retrieved articles will be checked manually for additional studies. The
14 111 authors of the papers will be contacted through email when there is a need for additional
15 112 information.

113 **Eligibility criteria**

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

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

129 **Outcomes of the study**

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3 130 The review includes both perinatal adverse outcomes, and the maternal morbidity and mortality.
4
5 131 We will include studies that reported outcomes of pregnancies complicated by MDR-TB and
6
7 132 non-drug resistant TB to construct risk ratios for each study and look for a pooled risk ratio.
8
9 133 Table 1 shows the definition of the perinatal adverse outcomes and the maternal morbidity and
10
11 134 mortality outcomes of the study. The outcomes of the study will be recorded as prevalence,
12
13 135 incidence, and relative risks or odds ratios, as reported in the individual papers.

14
15 136 **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 <10 th percentile for gestational age
Severe growth restriction (SGR)	Birthweight <3 rd 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

39
40 137 **Data extraction**

41
42 138 All identified articles from the systematic searching will be uploaded into Rayyan
43
44 139 (<https://rayyan.qcri.org>). Two researchers (KAA and AJ) will independently screen the titles and
45
46 140 abstracts of the studies and will then review the full text based on the eligibility criteria. The two
47
48 141 researchers will compare the results and disagreements will be resolved through discussion. If
49
50 142 consensus is not reached between these two researchers, disagreements will be resolved by
51
52 143 discussion with a third investigator (AAA).
53
54 144 Data from the included studies will be extracted and compiled using a standardised excel
55
56 145 spreadsheet. We will extract information from each study on the last name of the first author, year

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3 146 of data collection and publication, report type (grey literature v published studies), study country,
4 147 study design, and data source. Information will be also collected on maternal age, sample size,
5 148 effect size as reported by a study, multiple pregnancies, type of pregnancy outcomes, and number
6 149 of cases with adverse birth outcomes. When available, the following additional information will
7 150 be also extracted from the primary studies: percentage of resistance to particular TB medicines,
8 151 duration of MDR-TB treatment in months, percentage of pregnant women with HIV infection, and
9 152 percentage of pregnant women with diabetes mellitus. Moreover, we will make an effort to include
10 153 relevant information unavailable to the original study such as socio-economic setting (e.g., poor
11 154 or rich country, the income level for each country, WB member or not), geographical dimension
12 155 (the state/province where the study is conducted). A data extraction sheet is available in the
13 156 supplementary information (Table S2).

157 **Quality and bias assessment**

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

165 **Data analysis**

166 A systematic narrative synthesis will be conducted to describe the outcomes of the study. When
167 two or more studies are available, a random-effects meta-analysis will be used to obtain a pooled
168 estimate value for each of the outcomes of interest. Heterogeneity between studies will be
169 examined using the Cochran's Q test and quantitatively measured by the index of heterogeneity
170 squared (I^2) statistics and its 95% confidence interval (CI) (25). Heterogeneity will be considered
171 low, moderate and high when I^2 values are below 25%, between 25% and 75%, and above 75%,
172 respectively (25). When there is evidence of significant heterogeneity, the sources of this will be
173 explored through meta-regression using study characteristics as covariates. The Hedges et al.
174 (2010) (26) and the Tipton (2015) small-sample corrected RVE method (27) will be applied to
175 perform the meta-regression, this approach handles non-independent effect sizes without

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

190 **Patient and public involvement**

191 No patient will be involved in the study.

192 **Discussion and conclusion**

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

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3 205 **Contributors:** KAA, AAA, and AJ conceived of the study, developed the search strategy, and
4 206 drafted the protocol. All authors critically revised the manuscript for methodological and
5 207 intellectual content and have read and approved the final manuscript.

8
9 208 **Funding:** This study received no specific grant from any funding agency in the public,
10 209 commercial or not-for-profit sectors.

11
12 210 **Competing interests:** The authors declare that they have no competing interests.

13
14 211 **Patient consent for publication:** Not required.

15
16 212 **Ethics approval:** Not required.

17
18 213 **Amendments of the protocol:** If there is a need to amend this protocol, the date of each
19 214 amendment and the reason for the change will be described.

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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.

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	PUBLIC HEALTH, EPIDEMIOLOGY, Tuberculosis < INFECTIOUS DISEASES

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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

25 Abstract

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

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

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

45

46 **Strengths and limitations of this study**

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

55 **Introduction**

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

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

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2
3 74 the risk of adverse birth outcomes such as miscarriage, stillbirth, preterm birth, low birth-weight
4 (LBW) is suggested to be higher in patients with MDR-TB than in patients with DS-TB (11). These
5 75
6 76 adverse birth outcomes often occur as a result of the disease process itself or due to side effects
7
8 77 related to second-line TB medications such as fluoroquinolones, aminoglycosides, ethionamide,
9
10 78 and prothionamide. Some of these drugs have been identified to have teratogenic effects. For
11
12 79 example, aminoglycosides including streptomycin, kanamycin, and amikacin have been shown to
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14 80 impact fetal birthweight and hearing capacity (6, 12, 13). As a result, some studies have
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16 81 recommended termination of pregnancy (8, 14) and others have suggested reducing the dose of
17
18 82 teratogenic drugs or suspending the treatment during pregnancy (15, 16). On the contrary, some
19
20 83 studies did not find an association between MDR-TB medications and the perinatal outcomes (17).
21
22 84 However, previous studies have provided such conflicting evidence based on individual studies
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24 85 with a small sample size (8, 18, 19), and adequate data regarding the impact of second-line MDR-
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26 86 TB drugs in pregnant women are lacking (14). In addition, to the best of our knowledge, no MDR
27
28 87 trial currently conducted worldwide includes pregnant patients which presents a major obstacle to
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30 88 develop guidance of what MDR-TB drugs are safe and effective in pregnancy.

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32 89 As most previous studies revealed inconsistent results, mainly because of limited statistical power,
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34 90 a comprehensive systematic review including meta-analysis is required to have clarity regarding
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36 91 the impact of MDR-TB and second-line TB drugs on perinatal outcomes. Quantification of the
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38 92 effects of MDR-TB and its medication on birth outcomes is essential to inform service providers
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40 93 and policymakers in allocating resources and in the prevention of adverse birth outcomes in
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42 94 countries where MDR-TB is prevalent.

43 44 45 95 **The objective of the study**

46
47 96 The aim of this systematic review and meta-analysis is to assess the impact of MDR-TB and
48
49 97 MDR-TB medications during pregnancy on adverse maternal and birth outcomes.

50 51 52 98 **Methods**

53 54 55 99 **Search strategy**

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3 100 This systematic review and meta-analysis will adhere to the Preferred Reporting Items for
4 101 Systematic Reviews and Meta-analyses (PRISMA) guidelines (20). Systematic searching will be
5 102 conducted in PubMed, Scopus, and Web of Science databases to identify all potential studies that
6 103 reported adverse maternal and perinatal outcomes among pregnant women who had MDR-TB
7 104 diagnosis or exposure to MDR-TB medications during pregnancy. The search will be conducted
8 105 from the inception of each database to February 10, 2020, without language and time restrictions.
9 106 The overall study will be conducted from 14 December 2019 to 21 March 2020. The Medical
10 107 Subject Headings (MeSH) term and combination of keywords related to pregnancy, MDR-TB
11 108 and MDR-TB medications, and pregnancy outcomes will be used for the search. A complete
12 109 searching strategy for the PubMed database is available in the supplementary file (Table S1).
13 110 The reference lists and citations of the retrieved articles will be checked manually for additional
14 111 studies. The authors of the papers will be contacted through email when there is a need for
15 112 additional information.

113 **Eligibility criteria**

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

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

129 **Outcomes of the study**

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2
3 130 The review includes both perinatal adverse outcomes, and the maternal morbidity and mortality.
4
5 131 We will include studies that reported outcomes of pregnancies complicated by MDR-TB and
6
7 132 non-drug resistant TB to construct risk ratios for each study and look for a pooled risk ratio.
8
9 133 Table 1 shows the definition of the perinatal adverse outcomes and the maternal morbidity and
10
11 134 mortality outcomes of the study. The outcomes of the study will be recorded as prevalence,
12
13 135 incidence, relative risks or odds ratios, as reported in the individual papers.

14
15 136 **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 <10 th percentile for gestational age
Severe growth restriction (SGR)	Birthweight <3 rd 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

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40 137 **Data extraction**

41
42 138 All identified articles from the systematic searching will be uploaded into Rayyan
43
44 139 (<https://rayyan.qcri.org>). Two researchers (KAA and AJ) will independently screen the titles and
45
46 140 abstracts of the studies and will then review the full text based on the eligibility criteria. The two
47
48 141 researchers will compare the results and disagreements will be resolved through discussion. If
49
50 142 consensus is not reached between these two researchers, disagreements will be resolved by
51
52 143 discussion with a third investigator (AAA).
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54 144 Data from the included studies will be extracted and compiled using a standardised excel
55
56 145 spreadsheet. We will extract information from each study on the last name of the first author, year

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3 146 of data collection and publication, report type (grey literature v published studies), study country,
4 147 study design, and data source. Information will be also collected on maternal age, sample size,
5 148 effect size as reported by a study, multiple pregnancies, type of pregnancy outcomes, and the
6 149 number of cases with adverse birth outcomes. When available, the following additional
7 150 information will be also extracted from the primary studies: percentage of resistance to particular
8 151 TB medicines, duration of MDR-TB treatment in months, percentage of pregnant women with
9 152 HIV infection, and percentage of pregnant women with diabetes mellitus. Moreover, we will make
10 153 an effort to include relevant information unavailable to the original study such as socio-economic
11 154 setting (e.g., poor or rich country, the income level for each country, WB member or not),
12 155 geographical dimension (the state/province where the study is conducted). A data extraction sheet
13 156 is available in the supplementary information (Table S2).

157 **Quality and bias assessment**

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

165 **Data analysis**

166 A systematic narrative synthesis will be conducted to describe the outcomes of the study. When
167 two or more studies are available, a random-effects meta-analysis will be used to obtain a pooled
168 estimate value for each of the outcomes of interest. Heterogeneity between studies will be
169 examined using the Cochran's Q test and quantitatively measured by the index of heterogeneity
170 squared (I^2) statistics and its 95% confidence interval (CI) (25). Heterogeneity will be considered
171 low, moderate and high when I^2 values are below 25%, between 25% and 75%, and above 75%,
172 respectively (25). When there is evidence of significant heterogeneity, the sources of this will be
173 explored through meta-regression using study characteristics as covariates. The Hedges et al.
174 (2010) (26) and the Tipton (2015) small-sample corrected RVE method (27) will be applied to
175 perform the meta-regression, this approach handles non-independent effect sizes without

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

190

191 **Patient and public involvement**

192 No patient will be involved in the study.

193

194 **Discussion and conclusion**

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

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2
3 205 conferences and scientific meetings. The reviewer will adhere to the Preferred Reporting Items
4 206 for Systematic Reviews and Meta-Analyses guidelines.

5
6 207 **Ethics and dissemination:** As it will be a systematic review and meta-analysis based on
7 208 previously published evidence, there will be no requirement for ethical approval. Findings will be
8 209 published in the peer-reviewed journal and will be presented at various conferences.

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11
12 210 **Contributors:** KAA, AAA, and AJ conceived of the study, developed the search strategy, and
13 211 drafted the protocol. All authors critically revised the manuscript for methodological and
14 212 intellectual content and have read and approved the final manuscript.

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18 213 **Funding:** This study received no specific grant from any funding agency in the public,
19 214 commercial or not-for-profit sectors.

20
21
22 215 **Competing interests:** The authors declare that they have no competing interests.

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25 216 **Patient consent for publication:** Not required.

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28 217 **Ethics approval:** Not required.

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31 218 **Amendments of the protocol:** If there is a need to amend this protocol, the date of each
32 219 amendment and the reason for the change will be described.

33 34 35 220 **References**

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For peer review only

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.