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## Burden of drug-resistant tuberculosis among contacts of index cases: a protocol for a systematic review

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Manuscripts

# 1 **Burden of drug-resistant tuberculosis among contacts of index cases:** 2 **a protocol for a systematic review**

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## 23 Abstract

24 **Introduction:** People having close contact with drug-resistant tuberculosis (DR-TB) patients are  
25 at increased risk of contracting and developing the disease. However, no comprehensive review  
26 has been undertaken to estimate the burden of active and latent DR-TB among contacts of DR-TB  
27 patients. Therefore, the current systematic review will quantify the prevalence and incidence of  
28 active and latent DR-TB among contacts of DR-TB patients.

29 **Method and analysis:** Systematic searches will be conducted in Medline, Embase, Web of  
30 Science, Scopus, Cochrane Central Register of Controlled trials (CENTRAL), and Cumulative  
31 Index to Nursing and Allied Health Literature (CINHAL) databases. The search will be conducted  
32 without restrictions on time, language, and geography. A random-effects meta-analysis will be  
33 conducted for effect estimates. The pooled prevalence and incidence of DR-TB will be compared  
34 between people with and without contact with DR-TB patients. We will also estimate an odds ratio  
35 or relative risk associated with direct contact. The presence of heterogeneity between studies will  
36 be assessed by Higgins  $I^2$  statistics. Sub-group analysis and meta-regression will be conducted to  
37 determine the source of heterogeneity. The risk of bias will be assessed using a visual inspection  
38 of the funnel plot and Egger's regression test statistics. Trim and fill analysis will be done in the  
39 presence of publication bias. A sensitivity analysis will be conducted by trimming low-quality  
40 studies. The systematic review will be reported according to Preferred Reporting Items for  
41 Systematic Reviews and Meta-Analyses (PRISMA-20).

42 **Ethics and dissemination:** Ethical approval will not be required for this study as it will be a  
43 systematic review and meta-analysis based on previously published evidence. The findings of the  
44 systematic review will be presented at scientific conferences and published in scientific journals.

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2  
3 45 **Protocol registration:** The protocol is published in PROSPERO with registration number  
4  
5 46 CRD42023390339.

6  
7  
8 47 **Keywords:** Contacts, drug-resistant tuberculosis, systematic review, protocol

## 9 10 48 **Background**

11  
12  
13 49 Drug-resistant tuberculosis (DR-TB) is an important public health concern. It is defined as  
14  
15 50 resistance to any of the anti-TB drugs, and it can be classified into mono-resistant (resistant to only  
16  
17 51 one anti-TB drug), multi-drug-resistant tuberculosis (MDR-TB: resistant to both isoniazid and  
18  
19 52 rifampicin), poly-resistant (resistant to more than two first-line drugs except combined resistance  
20  
21 53 to both isoniazid and rifampin), pre-XDR-TB (MDR-TB with resistance to either a  
22  
23 54 fluoroquinolone, or at least 1 of 3 injectable second-line TB drugs, but not both ), and extensively  
24  
25 55 drug-resistant (XDR-TB: MDR-TB with resistance to any fluoroquinolone and at least one of the  
26  
27 56 second-line injectable drugs) (1). In 2021, approximately half a million people were diagnosed  
28  
29 57 with DR-TB and nearly 3.9% of new TB cases and 20% of previously treated cases were DR-TB.  
30  
31 58 Three countries alone carry 42% of the global DR-TB burden in 2021: India (26%), the Russian  
32  
33 59 Federation (8.5%), and Pakistan (7.9%) (2).

34  
35  
36 60 Contact investigation is an active case detection approach among contacts of drug-susceptible TB  
37  
38 61 (DS-TB) and DR-TB patients and its primary is to foster early diagnosis and treatment. This will  
39  
40 62 interrupting disease transmission, slowing down the progression of the disease, preventing long-  
41  
42 63 term irreversible physical and mental health complications, as well as social, quality of life and  
43  
44 64 financial harms, and reducing the overall mortality from DR-TB (3-5). The treatment of MDR-TB  
45  
46 65 is costly, toxic, and takes an average treatment duration of two years (6, 7). Active case finding is  
47  
48 66 recommended for people having a history of exposure to DR-TB cases as they are at a higher risk  
49  
50 67 of developing the disease than the general population (8). However, the probability of developing

1  
2  
3 68 DR-TB among contacts will vary and depends on the infectiousness of the index case (9), duration  
4  
5 69 of contact (9), proximity to the index case (10), and susceptibility of the contact (11). As a result,  
6  
7 70 the timing of the disease occurrence among contacts varies from as short as six weeks to several  
8  
9 71 years (12).

10  
11 72 High-income countries, where the incidence of DR-TB is low in the general population, have  
12  
13 73 standard practices regarding DR-TB contact investigation (13). Approaches including radiological  
14  
15 74 investigation, sputum culture, drug susceptibility tests (DST), and sophisticated genomic methods  
16  
17 75 (e.g., targeted next-generation sequencing (tNGS)) are used in identifying active DR-TB cases  
18  
19 76 among contacts of DR-TB (14, 15). Tuberculin skin test (TST) and interferon-gamma tests are  
20  
21 77 used in latent TB case detection (16, 17). However, DR-TB contact screening among contacts of  
22  
23 78 DR-TB patients is very limited in low-income countries due to scarce resources, where the  
24  
25 79 incidence of DS-TB and DR-TB is high (18). Recently, a growing interest in contact screening  
26  
27 80 practices among contacts of DR-TB patients in low-income countries has been reported (19).

28  
29 81 Several systematic reviews have estimated the burden of DS-TB among people who were close  
30  
31 82 contacts of DS-TB cases. Those studies showed that people having close contact with DR-TB  
32  
33 83 patients are at increased risk of contracting and developing the disease. For example, a previous  
34  
35 84 systematic review conducted in high-income countries in 2005 by Morrison et al. showed that the  
36  
37 85 overall burden of TB (both DS-TB and DR-TB) among contacts was 4.5%. However, the study  
38  
39 86 lacked a stratified analysis of high-risk groups such as DR-TB close contacts and addressed only  
40  
41 87 the prevalence of TB overall (20). Another systematic review conducted in low-income countries  
42  
43 88 in 2013 by Fox et al. among contacts of TB patients (DS-TB and DR-TB combined) showed that  
44  
45 89 the overall prevalence of active TB was 3.1% (4). The findings from previous studies have  
46  
47 90 provided inconclusive evidence and are now outdated (21). Therefore, the current systematic  
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3 91 review will quantify the burden of DR-TB among people in contact with DR-TB patients including  
4  
5 92 household, close, and casual contacts of DR-TB patients. The primary objective is to quantify the  
6  
7 93 pooled proportion of active and latent DR-TB among people in close contact with DR-TB patients.  
8  
9  
10 94 Our secondary objective is to assess study-level characteristics that may be associated with a high  
11  
12 95 proportion of DR-TB.  
13

## 14 96 **Review questions**

15  
16  
17 97 What is the burden of latent DR-TB cases among contacts of index cases?  
18

19  
20 98 What is the burden of active DR-TB cases among contacts of index cases?  
21

22 99 What is the risk of developing DR-TB among close contacts?  
23

24 100 What are the levels of adherence, treatment outcomes, and adverse drug reactions among contacts  
25  
26 101 of DR-TB cases?  
27  
28

29 102

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31 103

## 32 33 104 **Methods**

### 34 35 105 **Protocol registration**

36  
37  
38  
39 106 The protocol for this systematic review is registered in PROSPERO with a protocol registration  
40  
41 107 number CRD42023390339 and reported according to the Preferred Reporting Items for Systematic  
42  
43 108 Reviews and Meta-Analyses Protocols (PRISMA-P) statement 2015 (22). The article screening  
44  
45 109 and selection processes will be reported using the PRISMA-20 flow chart (**Supplementary file**  
46  
47  
48 110 **1**).  
49

### 50 51 111 **Search strategy**

52  
53 112 Systematic searches will be conducted in Medline (Via OVID), Embase, Web of Science, Scopus,  
54  
55 113 and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. We will use  
56  
57

114 the Cochrane Central Register of Controlled Trials (CENTRAL) database to search for  
 115 experimental and quasi-experimental studies. Other search engines such as Google and Google  
 116 Scholar will be searched for grey literature. The search will be conducted from the inception of  
 117 each database without restrictions on time, language, and geography. We will also perform hand-  
 118 searching of the reference lists of included studies. When additional information is required, we  
 119 will contact the corresponding authors. The search strategy for Medline is summarized in **Table**  
 120 **1**.

<b>Search</b>	<b>Query</b>
#1	("multidrug-resistant* tuberculosis" or "multidrug-resistant* TB" or "extensively drug-resistant*" or "drug-resistant* tuberculosis" or "MDR-TB" or "XDR-TB" or "DR-TB").mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
#2	("tracing" or "contact*" or "investigation" or "household" or "screening" or "infectious disease contact screening" or "household contact" or "close contact*" or "partner notification*" or "index case*").mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
#3	1 AND 2



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2  
3 121 **Eligibility criteria:** All studies reporting the burden (i.e., proportion, prevalence, or incidence)  
4  
5  
6 122 of DR-TB among people with contacts (i.e., households, close, and casual contacts) of DR-TB will  
7  
8 123 be included in this systematic review and meta-analysis. We will exclude reviews, commentaries,  
9  
10 124 editorials, case reports and case series, and animal studies. Moreover, studies that lack information  
11  
12 125 on the outcome variable and are conducted only on DS-TB patients will be excluded. Studies will  
13  
14  
15 126 be included based on the PICO (Population, Intervention, Comparator, and Outcome) framework.

## 17 127 **Outcome measures**

### 20 128 **Primary outcome measures**

21  
22 129 The study's primary outcomes are the prevalence and incidence of latent and active DR-TB among  
23  
24 130 people having contact with DR-TB patients. The incidence of DR-TB among people having  
25  
26 131 contact with DR-TB patients will be calculated by year of enrolment. The prevalence or incidence  
27  
28 132 of active DR-TB among people having contact with DR-TB will be determined. Contact will be  
29  
30 133 defined as a person living in the same household as the index case or exposure with DR-TB patients  
31  
32 134 in transportation, workplace, and recreational sites. Latent DR-TB will be taken in our study as  
33  
34 135 defined by the original papers.

### 38 136 **Secondary outcomes**

39  
40 137 Secondary outcomes will include levels of adherence, treatment side effects, and treatment  
41  
42 138 outcomes among DR-TB patients identified through contact screening.

### 45 139 **Study selection and data extraction**

46  
47  
48 140 After a comprehensive search, data will be imported to Endnote version X7.8 (THOMSON  
49  
50 141 REUTERS), and duplicates will be removed. Studies will be exported to Rayyan for screening by  
51  
52 142 title and abstract. Two independent reviewers (TYA and HFW) will screen the title, abstract, and  
53  
54 143 full texts to identify eligible studies. Any inconsistencies will be resolved through independent  
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3 144 screening by a third reviewer (FWS). TYA will prepare the data extraction checklist, and data will  
4  
5 145 be extracted in a Microsoft Excel (version 365) spreadsheet. The following data will be extracted  
6  
7  
8 146 from the included studies: 1) Bibliographic details: name of the first author, year of publication,  
9  
10 147 year of data collection, country, and World Health Organization (WHO) regions, 2) demographic  
11  
12 148 characteristics of participants: mean/median age, the proportion of males, residence (urban vs  
13  
14 149 rural), and the country's wealth status, 3) study characteristics: study design, sample size, type of  
15  
16 150 drug-resistant tuberculosis, comorbidities like HIV and diabetes mellitus, the total number of  
17  
18 151 people examined for DR-TB by gene Xpert, Line Prob Assay (LPA), and/or culture, the timing of  
19  
20 152 developing DR-TB, frequency of contact, and location of contact (household, work place, child-  
21  
22 153 care, and homeless), type of contacts (households, close, and casual), proportions of latent MDR-  
23  
24 154 and XDR-TB, active MDR- and XDR-TB, overall proportions of latent MDR- and XDR-TB, and  
25  
26 155 overall active MDR- and XDR-TB). Moreover, the index case characteristics (number, sex,  
27  
28 156 median/mean age, comorbidities, and treatment categories) will be extracted. For a study done in  
29  
30 157 multiple countries, the data from each country will be reported independently if available. The  
31  
32 158 study screening and selection process is summarized in **Fig 1**.

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38 159 **Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)-2020  
39  
40 160 flow diagram for the summary of the systematic review study selection process  
41  
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## 163 **Quality Assessment**

50 164 The Newcastle-Ottawa quality assessment scale will be used to assess the quality of cohort and  
51  
52 165 case-control studies (23). The quality of cross-sectional studies will be assessed using the modified  
53  
54 166 version of the Newcastle-Ottawa Quality Assessment Scale (24). The score will classify studies  
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3 167 into low-quality (a score between 1 and 4), moderate quality (a score between 5 and 7), and high-  
4  
5 168 quality studies (a score between 8 and 9). To assess the quality of interventional studies, the  
6  
7  
8 169 Cochrane Handbook for Systematic Reviews of Interventions (Version 6.3, 2022) will be used  
9  
10 170 (25). The quality of the included studies will be done by the two reviewers (TYA and FWS). A  
11  
12 171 third reviewer (HFW) will be involved to resolve any disagreements between the two primary  
13  
14 172 reviewers. Moreover, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)  
15  
16 173 statement will be used for reporting the results of the systematic review and meta-analysis (26).  
17  
18

### 19 174 **Data synthesis and analysis**

20  
21  
22 175 We are interested in estimating the burden of latent and active DR-TB reported as incidence or  
23  
24 176 prevalence at the global level. Stata version 17 software will be used to conduct the analysis. For  
25  
26 177 incidence studies, the incidence rate will be calculated as the number of incident cases per year  
27  
28 178 divided by the population at risk. Similarly, for the prevalence study, the prevalence will be  
29  
30 179 calculated as the number of prevalent cases divided by the total population and expressed as a  
31  
32 180 proportion. A forest plot will be generated to show individual and pooled prevalence of latent  
33  
34 181 and/or active DR-TB cases among DR-TB contacts, 95% confidence interval (CI), name of the  
35  
36 182 first author, publication years, and study weights. A random-effects meta-analysis will be used to  
37  
38 183 report the pooled estimates. The presence of heterogeneity among the included studies will be  
39  
40 184 evaluated using the  $I^2$  statistics and a 95% CI. An  $I^2$  value close to zero indicates no observed  
41  
42 185 heterogeneity and a larger value of  $I^2$  shows an increased level of heterogeneity. Heterogeneity  
43  
44 186 will be considered low, moderate, and high when the values are below 25%, between 25% and  
45  
46 187 75%, and above 75%, respectively (27). To identify the source of heterogeneity, sub-group  
47  
48 188 analysis will be carried out by study characteristics. Moreover, meta-regression will be conducted  
49  
50 189 to assure the existing source of heterogeneity. Publication bias will be assessed visually using  
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3 190 funnel plots and statistically using Egger's regression test. A trim and fill analysis will be  
4  
5 191 conducted as an adjustment if there is any publication bias (28). A sensitivity analysis will be done  
6  
7  
8 192 by trimming low-quality studies.  
9

## 10 193 **Implication of the review**

11  
12  
13 194 DR-TB contact investigation is a top priority in DR-TB infection control, being critical for locating  
14  
15 195 the source of infections as patients with smear-positive DR-TB are highly contagious.  
16  
17 196 Identification of cases through contact investigation can lead to timely treatment and preventative  
18  
19 197 measures to be undertaken, thereby minimizing the risk of disease transmission, and further  
20  
21 198 reducing the burden of DR-TB in the general population. Early diagnosis and detecting of DR-TB  
22  
23 199 will improve treatment outcomes and reduce adverse drug reactions and complications. It will also  
24  
25 200 reduce cost of the patients and households. Overall, the study will help to achieve the three END-  
26  
27 201 TB targets of 2035 (no catastrophic cost, 90% reduction in mortality, and 95% reduction in patients  
28  
29 202 suffering from TB) through early diagnosis and treatment.  
30  
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32  
33

## 34 203 **Article summary**

### 35 204 **Strength and limitation**

- 36  
37  
38  
39  
40 205 • To the best of our knowledge, there is limited and outdated evidence on the burden of DR-  
41  
42 206 TB among their contacts.  
43  
44 207 • This study will determine the burden of XDR-TB among contacts of DR-TB patients which  
45  
46 208 is not in previous systematic reviews.  
47  
48 209 • The study will not be representative of the 30 high-burden TB countries due to the scarcity  
49  
50 210 of published articles in some high-burden countries.  
51  
52 211 • Heterogeneity among included studies may be the other limitation of the study.  
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## 6 213 **Declaration**

## 8 214 **Acknowledgments**

11  
12 215 We would like to acknowledge Curtin University for financial funding.

## 15 216 **Author contributions**

18 217 TYA designed the study and wrote the initial draft of the manuscript. ACAC, EAG, HFW, FWS,  
19  
20 218 and KAA critically reviewed the final manuscript. All authors approved the final manuscript for  
21  
22 219 submission.

## 25 220 **Patient and public involvement**

28 221 Patients were not involved in the development of the research question, study design, and outcome  
29  
30 222 measures.

## 33 223 **Ethics and dissemination**

36 224 Ethical approval will not be required for this study as it will be a systematic review and meta-  
37  
38 225 analysis based on previously published studies. In addition to scientific publication, the results will  
39  
40 226 be disseminated on social media platforms including Twitter and LinkedIn to inform policymakers,  
41  
42 227 funders, and other researchers.

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51  
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### 234 **Competing interest**

235 The authors declare that they have no conflicts of interest.

### 236 **Patient consent for publication**

237 Not required

### 238 **Data sharing statement**

239 Data will be available upon a reasonable request from the corresponding author.

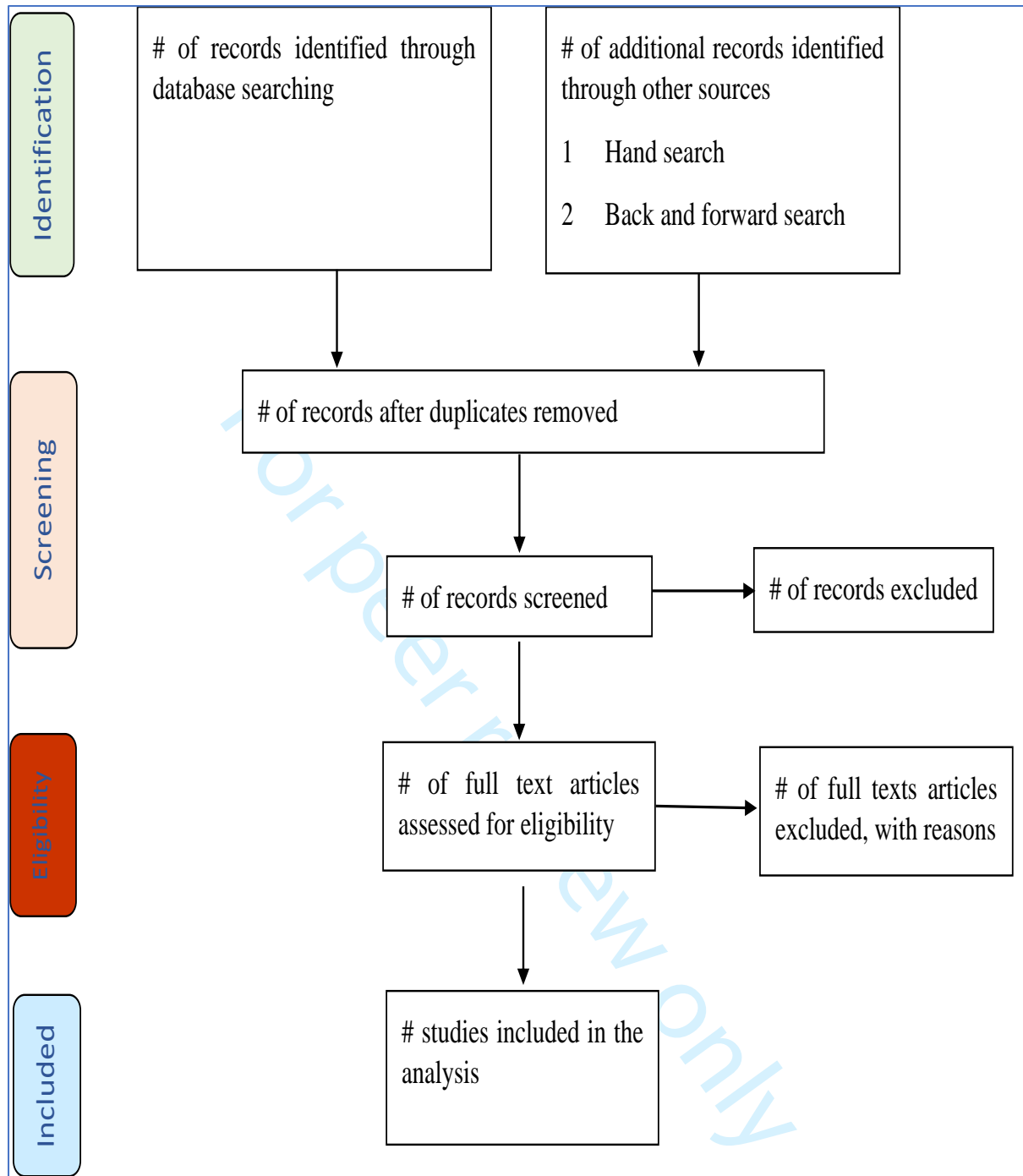
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309



**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)-2020 flow diagram for the summary of the systematic review study selection process



# Reporting checklist for protocol of a systematic review and meta-analysis.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	NA

## 1 Registration

2  
3  
4 [#2](#) If registered, provide the name of the registry (such as 2  
5  
6 PROSPERO) and registration number  
7  
8

## 9 Authors

10  
11  
12  
13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all 1  
14  
15 protocol authors; provide physical mailing address of  
16  
17 corresponding author  
18

19  
20 Contribution [#3b](#) Describe contributions of protocol authors and identify the 3  
21  
22 guarantor of the review  
23  
24

## 25 Amendments

26  
27  
28  
29 [#4](#) If the protocol represents an amendment of a previously  
30  
31 completed or published protocol, identify as such and list  
32  
33 changes; otherwise, state plan for documenting important  
34  
35 protocol amendments  
36  
37

## 38 Support

39  
40  
41  
42 Sources [#5a](#) Indicate sources of financial or other support for the review 12  
43

44  
45 Sponsor [#5b](#) Provide name for the review funder and / or sponsor 12  
46

47  
48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), 12  
49  
50 funder if any, in developing the protocol  
51  
52

## 53 Introduction

54  
55  
56 Rationale [#6](#) Describe the rationale for the review in the context of what is 3-4  
57  
58

1		already known	
2			
3			
4	Objectives	<a href="#">#7</a> Provide an explicit statement of the question(s) the review will	4
5		address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
7			
8			
9			
10			
11	<b>Methods</b>		
12			
13			
14	Eligibility criteria	<a href="#">#8</a> Specify the study characteristics (such as PICO, study design,	7
15		setting, time frame) and report characteristics (such as years	
16		considered, language, publication status) to be used as	
17		criteria for eligibility for the review	
18			
19			
20			
21			
22			
23			
24	Information	<a href="#">#9</a> Describe all intended information sources (such as electronic	6
25		databases, contact with study authors, trial registers or other	
26	sources	grey literature sources) with planned dates of coverage	
27			
28			
29			
30			
31			
32	Search strategy	<a href="#">#10</a> Present draft of search strategy to be used for at least one	6-7
33		electronic database, including planned limits, such that it	
34		could be repeated	
35			
36			
37			
38			
39	Study records -	<a href="#">#11a</a> Describe the mechanism(s) that will be used to manage	9
40		records and data throughout the review	
41	data management		
42			
43			
44			
45	Study records -	<a href="#">#11b</a> State the process that will be used for selecting studies (such	8
46		as two independent reviewers) through each phase of the	
47	selection process	review (that is, screening, eligibility and inclusion in meta-	
48		analysis)	
49			
50			
51			
52			
53			
54	Study records -	<a href="#">#11c</a> Describe planned method of extracting data from reports	8
55		(such as piloting forms, done independently, in duplicate), any	
56	data collection		
57			
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1	process		processes for obtaining and confirming data from investigators	
2				
3				
4	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	7
5			(such as PICO items, funding sources), any pre-planned data	
6			assumptions and simplifications	
7				
8				
9				
10				
11	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	7
12				
13	prioritization		including prioritization of main and additional outcomes, with	
14			rationale	
15				
16				
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18				
19	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	10
20				
21	individual studies		individual studies, including whether this will be done at the	
22			outcome or study level, or both; state how this information will	
23			be used in data synthesis	
24				
25				
26				
27				
28				
29	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be quantitatively	9
30			synthesised	
31				
32				
33				
34	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	9
35			planned summary measures, methods of handling data and	
36			methods of combining data from studies, including any	
37			planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
38				
39				
40				
41				
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43				
44	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	10
45			sensitivity or subgroup analyses, meta-regression)	
46				
47				
48				
49	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the type	NA
50			of summary planned	
51				
52				
53				
54	Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as	10
55			publication bias across studies, selective reporting within	
56				
57				
58				
59				
60				

studies)

Confidence in [#17](#) Describe how the strength of the body of evidence will be assessed (such as GRADE) 10-11  
cumulative  
evidence

None The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

# BMJ Open

## Burden of drug-resistant tuberculosis among contacts of index cases: a protocol for a systematic review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-074364.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Oct-2023
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<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health, Research methods
Keywords:	Systematic Review, Epidemiology < TROPICAL MEDICINE, TROPICAL MEDICINE

SCHOLARONE™  
Manuscripts

# 1 **Burden of drug-resistant tuberculosis among contacts of index cases:** 2 **a protocol for a systematic review**

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## 23 Abstract

24 **Introduction:** People having close contact with drug-resistant tuberculosis (DR-TB) patients are  
25 at increased risk of contracting and developing the disease. However, no comprehensive review  
26 has been undertaken to estimate the burden of DR-TB among contacts of DR-TB patients.  
27 Therefore, the current systematic review will quantify the prevalence and incidence of DR-TB  
28 among contacts of DR-TB patients.

29 **Method and analysis:** Systematic searches will be conducted in Medline, Embase, Web of  
30 Science, Scopus, Cochrane Central Register of Controlled trials (CENTRAL), and Cumulative  
31 Index to Nursing and Allied Health Literature (CINHAL) databases. The search will be conducted  
32 without restrictions on time, language, and geography. A random-effects meta-analysis will be  
33 conducted for effect estimates. The pooled prevalence and incidence of DR-TB will be compared  
34 between people with and without contact with DR-TB patients. The presence of heterogeneity  
35 between studies will be assessed by Higgins  $I^2$  statistics. Sub-group analysis will be conducted to  
36 determine the source of heterogeneity. The risk of bias will be assessed using a visual inspection  
37 of the funnel plot and Egger's regression test statistics. Trim and fill analysis will be done in the  
38 presence of publication bias. A sensitivity analysis will be conducted by trimming low-quality  
39 studies. The systematic review will be reported according to Preferred Reporting Items for  
40 Systematic Reviews and Meta-Analyses (PRISMA-P) guideline.

41 **Ethics and dissemination:** Ethical approval will not be required for this study as it will be a  
42 systematic review and meta-analysis based on previously published evidence. The findings of the  
43 systematic review will be presented at scientific conferences and published in scientific journals.

44 **Protocol registration:** The protocol is published in PROSPERO with registration number  
45 CRD42023390339.



1  
2  
3 46 **Keywords:** Contacts, drug-resistant tuberculosis, systematic review, protocol  
4  
5

## 6 47 **Article summary**

7

### 8 48 **Strength and limitation**

- 9  
10  
11 49 • The review will use a comprehensive search strategy to obtain unbiased summary.  
12  
13 50 • Sub-group analysis will be performed to compare the prevalence and incidence of DR-TB  
14  
15 by study characteristics.  
16 51  
17  
18 52 • Findings will be reported according to Preferred Reporting Items for Systematic Reviews  
19  
20 and Meta-Analyses protocol.  
21 53  
22  
23 54 • The search will be conducted without time and geographical restriction.  
24  
25 55 • Substantial heterogeneity among included studies may be the possible limitation of the  
26  
27 study.  
28 56  
29

### 30 57 **Background**

31  
32  
33 58 Drug-resistant tuberculosis (DR-TB) is an important public health concern. It is defined as  
34  
35 59 resistance to any of the anti-TB drugs, and it can be classified into mono-resistant (resistant to only  
36  
37 one anti-TB drug), multi-drug-resistant tuberculosis (MDR-TB: resistant to both isoniazid and  
38 60 rifampicin), poly-resistant (resistant to more than two first-line drugs except combined resistance  
39  
40 61 to both isoniazid and rifampin), pre-XDR-TB (MDR-TB with resistance to either a  
41  
42 62 fluoroquinolone, or at least 1 of 3 injectable second-line TB drugs, but not both ), and extensively  
43  
44 63 drug-resistant (XDR-TB: MDR-TB with resistance to any fluoroquinolone and at least one of the  
45  
46 64 second-line injectable drugs) (1). In 2021, approximately half a million people were diagnosed  
47  
48 65 with DR-TB and nearly 3.9% of new TB cases and 20% of previously treated cases were DR-TB.  
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67 Three countries alone carry 42% of the global DR-TB burden in 2021: India (26%), the Russian  
68 Federation (8.5%), and Pakistan (7.9%) (2).

69 Contact investigation is an active case detection approach among contacts of drug-susceptible TB  
70 (DS-TB) and DR-TB patients, and its primary is to foster early diagnosis and treatment. This will  
71 interrupt disease transmission, slowing down the progression of the disease, preventing long-term  
72 irreversible physical and mental health complications, as well as social, quality of life, and  
73 financial harms, and reducing the overall mortality from DR-TB (3-5). The treatment of MDR-TB  
74 is costly, toxic, and takes an average treatment duration of two years (6, 7). Active case finding is  
75 recommended for people having a history of exposure to DR-TB cases as they are at a higher risk  
76 of developing the disease than the general population (8). However, the probability of developing  
77 DR-TB among contacts will vary and depends on the infectiousness of the index case (9), duration  
78 of contact (9), proximity to the index case (10), and susceptibility of the contact (11). As a result,  
79 the timing of the disease occurrence among contacts varies from as short as six weeks to several  
80 years (12).

81 High-income countries, where the incidence of DR-TB is low in the general population, have  
82 standard practices regarding DR-TB contact investigation (13). Approaches including radiological  
83 investigation, sputum culture, drug susceptibility tests (DST), and sophisticated genomic methods  
84 (e.g., targeted next-generation sequencing (tNGS)) are used in identifying DR-TB cases among  
85 contacts of DR-TB (14, 15). Tuberculin skin test (TST) and interferon-gamma tests are used in  
86 latent TB case detection (16, 17). However, DR-TB contact screening among contacts of DR-TB  
87 patients is very limited in low-income countries due to scarce resources, where the incidence of  
88 DS-TB and DR-TB is high (18). Recently, a growing interest in contact screening practices among  
89 contacts of DR-TB patients in low-income countries has been reported (19).

1  
2  
3 90 Several systematic reviews have estimated the burden of DS-TB among people who were close  
4  
5 91 contacts of DS-TB cases. Those studies showed that people having close contact with DR-TB  
6  
7  
8 92 patients are at increased risk of contracting and developing the disease. For example, a previous  
9  
10 93 systematic review conducted in high-income countries in 2005 by Morrison et al. showed that the  
11  
12 94 overall burden of TB (both DS-TB and DR-TB) among contacts was 4.5%. However, the study  
13  
14 95 lacked a stratified analysis of high-risk groups such as DR-TB close contacts and addressed only  
15  
16  
17 96 the prevalence of TB overall (20). Another systematic review conducted in low-income countries  
18  
19 97 in 2013 by Fox et al. among contacts of TB patients (DS-TB and DR-TB combined) showed that  
20  
21 98 the overall prevalence of TB was 3.1% (4). The findings from previous studies have provided  
22  
23 99 inconclusive evidence and are now outdated (21). Therefore, the current systematic review will  
24  
25  
26 100 quantify the burden of DR-TB among people in contact with DR-TB patients including household,  
27  
28 101 close, and casual contacts of DR-TB patients. The primary objective is to quantify the pooled  
29  
30 102 proportion of DR-TB among people in close contact with DR-TB patients. Our secondary  
31  
32 103 objective is to assess study-level characteristics that may be associated with a high proportion of  
33  
34  
35 104 DR-TB.

## 38 105 **Review questions**

40 106 What is the prevalence of DR-TB among contacts of DR-TB patients?

42 107 What is the incidence of DR-TB among contacts of DR-TB patients?

44 108 What are the study level characteristics associated with high prevalence and incidences of DR-TB  
46 109 among contacts of DR-TB patients?

50 110

53 111

## 112 **Methods**

### 113 **Protocol registration**

114 The protocol for this systematic review is registered in PROSPERO with a protocol registration  
 115 number CRD42023390339 and reported according to the Preferred Reporting Items for Systematic  
 116 Reviews and Meta-Analyses Protocols (PRISMA-P) statement 2015 (22). The article screening  
 117 and selection processes will be reported using the PRISMA-20 flow chart (**Supplementary file**  
 118 **1**).

### 119 **Search strategy**

120 Systematic searches will be conducted in Medline (Via OVID), Embase, Web of Science, Scopus,  
 121 and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. We will use  
 122 the Cochrane Central Register of Controlled Trials (CENTRAL) database to search for  
 123 experimental and quasi-experimental studies. Other search engines such as Google and Google  
 124 Scholar will be searched for grey literature. The search will be conducted from the inception of  
 125 each database without restrictions on time and geography. We will also perform hand-searching  
 126 of the reference lists of included studies. When additional information is required, we will contact  
 127 the corresponding authors. The search strategy for Medline is summarized in **Table 1**.

**Table 1: Proposed search strategy in Medline**

Search	Query
#1	(“multidrug-resistant* tuberculosis” or “multidrug-resistant* TB” or “extensively drug-resistant*” or “drug-resistant* tuberculosis” or “MDR-TB” or “XDR-TB” or “DR-TB”).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism

	supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
#2	("tracing" or "contact*" or "investigation" or "household" or "screening" or "infectious disease contact screening" or "household contact" or "close contact*" or "partner notification*" or "index case*").mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
#3	1 AND 2

128 **Eligibility criteria:** All studies reporting the burden (i.e., proportion, prevalence, or incidence)  
 129 of DR-TB among people with contacts (i.e., households, close, and casual contacts) of DR-TB will  
 130 be included in this systematic review and meta-analysis. We will exclude reviews, commentaries,  
 131 editorials, case reports and case series, and animal studies. Moreover, studies that lack information  
 132 on the outcome variable and are conducted only on DS-TB patients will be excluded. Studies will  
 133 be included based on the PICO (Population, Intervention, Comparator, and Outcome) framework.

## 134 **Outcome measures**

### 135 **Primary outcome measures**

136 The primary outcomes of the study are the prevalence and incidence of DR-TB among people  
 137 having contact with DR-TB patients. The incidence of DR-TB among people having contact with  
 138 DR-TB patients will be calculated by year of enrolment. The prevalence or incidence of DR-TB  
 139 among people having contact with DR-TB will be determined. Contact will be defined as a person

1  
2  
3 140 living in the same household as the index case or exposure to DR-TB patients in transportation,  
4  
5 141 workplace, and recreational sites.  
6  
7

## 8 142 **Study selection and data extraction**

9  
10 143 After a comprehensive search, data will be imported to Endnote version X7.8 (THOMSON  
11  
12 144 REUTERS), and duplicates will be removed. Studies will be exported to Rayyan for screening by  
13  
14 145 title and abstract. Two independent reviewers (TYA and EAG) will screen the title, abstract, and  
15  
16 146 full texts to identify eligible studies. Any inconsistencies will be resolved through consensus  
17  
18 147 between the two reviewers. TYA will prepare the data extraction checklist, and data will be  
19  
20 148 extracted in a Microsoft Excel (version 365) spreadsheet. The following data will be extracted  
21  
22 149 from the included studies: 1) Bibliographic details: name of the first author, year of publication,  
23  
24 150 year of data collection, country, and World Health Organization (WHO) regions, 2) demographic  
25  
26 151 characteristics of participants: mean/median age, the proportion of males, and the country's wealth  
27  
28 152 status, 3) study characteristics: study design, sample size, type of drug-resistant tuberculosis,  
29  
30 153 comorbidities like HIV and diabetes mellitus, the total number of people examined for DR-TB by  
31  
32 154 gene Xpert, Line Prob Assay (LPA), and/or culture, the timing of developing DR-TB, frequency  
33  
34 155 of contact, and location of contact (household, work place, child-care, and homeless), type of  
35  
36 156 contacts (households, close, and casual), proportions of MDR- and XDR-TB.). For a study done  
37  
38 157 in multiple countries, the data from each country will be reported independently if available. The  
39  
40 158 study screening and selection process is summarized in **Fig 1**.

41  
42 159 **Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)-2020  
43  
44 160 flow diagram for the summary of the systematic review study selection process  
45  
46

47 161

48 162

## 163 **Quality Assessment**

164 The Newcastle-Ottawa quality assessment scale will be used to assess the quality of retrospective  
165 and prospective cohort studies (23). The quality of cross-sectional studies will be assessed using  
166 the modified version of the Newcastle-Ottawa Quality Assessment Scale (24). The score will  
167 classify studies into low-quality (a score between 1 and 4), moderate quality (a score between 5  
168 and 7), and high-quality studies (a score between 8 and 9). The quality of the included studies will  
169 be done by the two reviewers (TYA and EAG). Disagreements will be resolved by the consensus  
170 between the two reviewers.

## 171 **Data synthesis and analysis**

172 We are interested in estimating the burden of DR-TB reported as incidence or prevalence at the  
173 global level. Stata version 17 software will be used to conduct the analysis. For incidence studies,  
174 the incidence rate will be calculated as the number of incident cases per year divided by the  
175 population at risk. Similarly, for the prevalence study, the prevalence will be calculated as the  
176 number of prevalent cases divided by the total population and expressed as a proportion. A forest  
177 plot will be generated to show individual and pooled prevalence of DR-TB cases among DR-TB  
178 contacts, 95% confidence interval (CI), name of the first author, publication years, and study  
179 weights. A random-effects meta-analysis will be used to report the pooled estimates. The presence  
180 of heterogeneity among the included studies will be evaluated using the  $I^2$  statistics and a 95% CI.  
181 An  $I^2$  value close to zero indicates no observed heterogeneity and a larger value of  $I^2$  shows an  
182 increased level of heterogeneity. Heterogeneity will be considered low, moderate, and high when  
183 the values are below 25%, between 25% and 75%, and above 75%, respectively (25). To identify  
184 the source of heterogeneity, sub-group analysis will be carried out by study characteristics.  
185 Moreover, meta-regression will be conducted to assure the existing source of heterogeneity.



186 Publication bias will be assessed visually using funnel plots and statistically using Egger's  
187 regression test. A trim and fill analysis will be conducted as an adjustment if there is any  
188 publication bias (26). A sensitivity analysis will be done by trimming low-quality studies.

## 189 **Implication of the review**

190 DR-TB contact investigation is a top priority in DR-TB infection control, being critical for locating  
191 the source of infections as patients with smear-positive DR-TB are highly contagious.  
192 Identification of cases through contact investigation can lead to timely treatment and preventative  
193 measures to be undertaken, thereby minimizing the risk of disease transmission, and further  
194 reducing the burden of DR-TB in the general population. Early diagnosis and detection of DR-TB  
195 will improve treatment outcomes and reduce adverse drug reactions and complications. It will also  
196 reduce the cost for the patients and households. Overall, the study will help to achieve the three  
197 END-TB targets of 2035 (no catastrophic cost, 90% reduction in mortality, and 95% reduction in  
198 patients suffering from TB) through early diagnosis and treatment.

## 200 **Declaration**

## 201 **Acknowledgments**

202 We would like to acknowledge Curtin University for financial funding.

## 203 **Author contributions**

204 TYA designed the study and wrote the initial draft of the manuscript. ACAC, EAG, HFW, FWS,  
205 and KAA critically reviewed the final manuscript. All authors approved the final manuscript for  
206 submission.



## 207 **Patient and public involvement**

208 Patients were not involved in the development of the research question, study design, and outcome  
209 measures.

## 210 **Ethics and dissemination**

211 Ethical approval will not be required for this study as it will be a systematic review and meta-  
212 analysis based on previously published studies. In addition to scientific publication, the results will  
213 be disseminated on social media platforms including Twitter and LinkedIn to inform policymakers,  
214 funders, and other researchers.

## 215 **Funding**

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## 221 **Competing interest**

222 The authors declare that they have no conflicts of interest.

## 223 **Patient consent for publication**

224 Not required

## 225 **Data sharing statement**

226 Data will be available upon a reasonable request from the corresponding author.

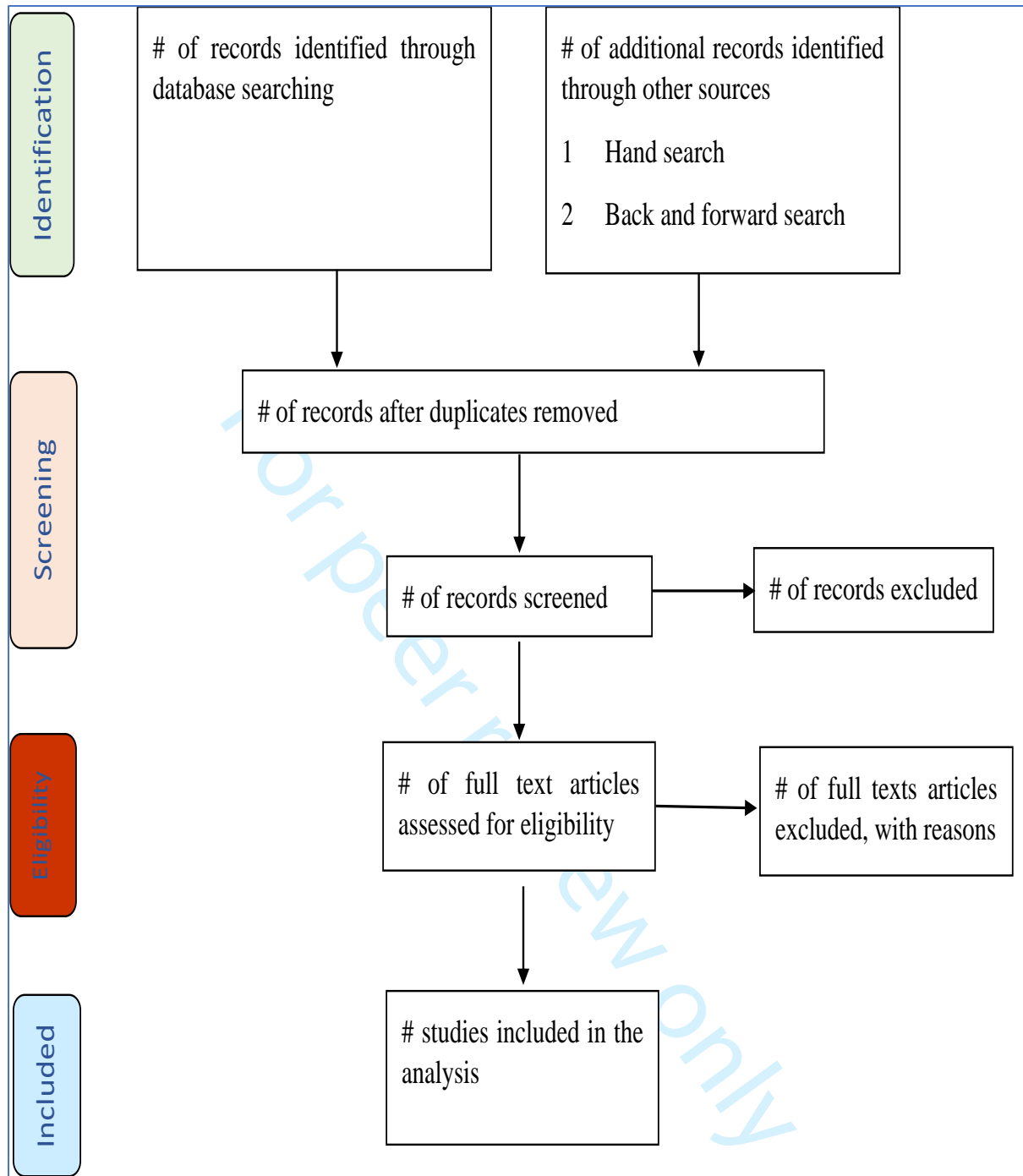
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**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)-2020 flow diagram for the summary of the systematic review study selection process

# Reporting checklist for protocol of a systematic review and meta-analysis.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preorting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	NA
<b>Registration</b>			
	<a href="#">#2</a>	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
<b>Authors</b>			
Contact	<a href="#">#3a</a>	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	<a href="#">#3b</a>	Describe contributions of protocol authors and identify the	10

guarantor of the review

## 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

## Support

Sources [#5a](#) Indicate sources of financial or other support for the review 11

Sponsor [#5b](#) Provide name for the review funder and / or sponsor 11

Role of sponsor or funder [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol 11

## 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 7

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 6

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 6-7

Study records - data management [#11a](#) Describe the mechanism(s) that will be used to manage records and data throughout the review 9

Study records - [#11b](#) State the process that will be used for selecting studies (such 8

1	selection process		as two independent reviewers) through each phase of the	
2			review (that is, screening, eligibility and inclusion in meta-	
3			analysis)	
4				
5	Study records -	<a href="#">#11c</a>	Describe planned method of extracting data from reports	8
6	data collection		(such as piloting forms, done independently, in duplicate),	
7	process		any processes for obtaining and confirming data from	
8			investigators	
9				
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11	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	7
12			(such as PICO items, funding sources), any pre-planned data	
13			assumptions and simplifications	
14				
15	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	7
16	prioritization		including prioritization of main and additional outcomes, with	
17			rationale	
18				
19	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	10
20	individual studies		individual studies, including whether this will be done at the	
21			outcome or study level, or both; state how this information will	
22			be used in data synthesis	
23				
24	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be quantitatively	9
25			synthesised	
26				
27	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	9
28			planned summary measures, methods of handling data and	
29			methods of combining data from studies, including any	
30			planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
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32	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	10
33			sensitivity or subgroup analyses, meta-regression)	
34				
35	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the type	NA
36			of summary planned	
37				
38	Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as	10
39			publication bias across studies, selective reporting within	
40			studies)	
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42	Confidence in	<a href="#">#17</a>	Describe how the strength of the body of evidence will be	3
43	cumulative		assessed (such as GRADE)	
44	evidence			
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2 Commons Attribution License CC-BY. This checklist can be completed online using  
3 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with  
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