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

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

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

Method and analysis: Systematic searches will be conducted in Medline, Embase, Web of Science, Scopus, Cochrane Central Register of Controlled trials (CENTRAL), and Cumulative Index to Nursing and Allied Health Literature (CINHAL) databases. The search will be conducted without restrictions on time, language, and geography. A random-effects meta-analysis will be conducted for effect estimates. The pooled prevalence and incidence of DR-TB will be compared between people with and without contact with DR-TB patients. We will also estimate an odds ratio or relative risk associated with direct contact. The presence of heterogeneity between studies will be assessed by Higgins I² statistics. Sub-group analysis and meta-regression will be conducted to determine the source of heterogeneity. The risk of bias will be assessed using a visual inspection of the funnel plot and Egger's regression test statistics. Trim and fill analysis will be done in the presence of publication bias. A sensitivity analysis will be conducted by trimming low-quality studies. The systematic review will be reported according to Preferred Reporting Items for 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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Protocol registration: The protocol is published in PROSPERO with registration number CRD42023390339.

47 Keywords: Contacts, drug-resistant tuberculosis, systematic review, protocol

48 Background

Drug-resistant tuberculosis (DR-TB) is an important public health concern. It is defined as resistance to any of the anti-TB drugs, and it can be classified into mono-resistant (resistant to only one anti-TB drug), multi-drug-resistant tuberculosis (MDR-TB: resistant to both isoniazid and rifampicin), poly-resistant (resistant to more than two first-line drugs except combined resistance to both isoniazid and rifampin), pre-XDR-TB (MDR-TB with resistance to either a fluoroquinolone, or at least 1 of 3 injectable second-line TB drugs, but not both), and extensively drug-resistant (XDR-TB: MDR-TB with resistance to any fluoroquinolone and at least one of the second-line injectable drugs) (1). In 2021, approximately half a million people were diagnosed with DR-TB and nearly 3.9% of new TB cases and 20% of previously treated cases were DR-TB. Three countries alone carry 42% of the global DR-TB burden in 2021: India (26%), the Russian Federation (8.5%), and Pakistan (7.9%) (2).

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Contact investigation is an active case detection approach among contacts of drug-susceptible TB (DS-TB) and DR-TB patients and its primary is to foster early diagnosis and treatment. This will interrupting disease transmission, slowing down the progression of the disease, preventing long-term irreversible physical and mental health complications, as well as social, quality of life and financial harms, and reducing the overall mortality from DR-TB (3-5). The treatment of MDR-TB is costly, toxic, and takes an average treatment duration of two years (6, 7). Active case finding is recommended for people having a history of exposure to DR-TB cases as they are at a higher risk of developing the disease than the general population (8). However, the probability of developing

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DR-TB among contacts will vary and depends on the infectiousness of the index case (9), duration
of contact (9), proximity to the index case (10), and susceptibility of the contact (11). As a result,
the timing of the disease occurrence among contacts varies from as short as six weeks to several
years (12).

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

Several systematic reviews have estimated the burden of DS-TB among people who were close contacts of DS-TB cases. Those studies showed that people having close contact with DR-TB patients are at increased risk of contracting and developing the disease. For example, a previous systematic review conducted in high-income countries in 2005 by Morrison et al. showed that the overall burden of TB (both DS-TB and DR-TB) among contacts was 4.5%. However, the study lacked a stratified analysis of high-risk groups such as DR-TB close contacts and addressed only the prevalence of TB overall (20). Another systematic review conducted in low-income countries in 2013 by Fox et al. among contacts of TB patients (DS-TB and DR-TB combined) showed that the overall prevalence of active TB was 3.1% (4). The findings from previous studies have provided inconclusive evidence and are now outdated (21). Therefore, the current systematic

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review will quantify the burden of DR-TB among people in contact with DR-TB patients including 91 household, close, and casual contacts of DR-TB patients. The primary objective is to quantify the 92 pooled proportion of active and latent DR-TB among people in close contact with DR-TB patients. 93 Our secondary objective is to assess study-level characteristics that may be associated with a high 94 proportion of DR-TB. 95 **Review questions** 96 What is the burden of latent DR-TB cases among contacts of index cases? 97 What is the burden of active DR-TB cases among contacts of index cases? 98 What is the risk of developing DR-TB among close contacts? 99 What are the levels of adherence, treatment outcomes, and adverse drug reactions among contacts 100 101 of DR-TB cases? reliev 102 103 **Methods** 104 **Protocol registration** 105 The protocol for this systematic review is registered in PROSPERO with a protocol registration 106 number CRD42023390339 and reported according to the Preferred Reporting Items for Systematic 107 108 Reviews and Meta-Analyses Protocols (PRISMA-P) statement 2015 (22). The article screening and selection processes will be reported using the PRISMA-20 flow chart (Supplementary file 109 1). 110 Search strategy 111 Systematic searches will be conducted in Medline (Via OVID), Embase, Web of Science, Scopus, 112

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and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. We will use

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> the Cochrane Central Register of Controlled Trials (CENTRAL) database to search for experimental and quasi-experimental studies. Other search engines such as Google and Google Scholar will be searched for grey literature. The search will be conducted from the inception of each database without restrictions on time, language, and geography. We will also perform handsearching of the reference lists of included studies. When additional information is required, we will contact 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		

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

Outcome measures

Primary outcome measures

The study's primary outcomes are the prevalence and incidence of latent and active DR-TB among people having contact with DR-TB patients. The incidence of DR-TB among people having contact with DR-TB patients will be calculated by year of enrolment. The prevalence or incidence of active DR-TB among people having contact with DR-TB will be determined. Contact will be defined as a person living in the same household as the index case or exposure with DR-TB patients in transportation, workplace, and recreational sites. Latent DR-TB will be taken in our study as defined by the original papers.

Secondary outcomes

137 Secondary outcomes will include levels of adherence, treatment side effects, and treatment138 outcomes among DR-TB patients identified through contact screening.

39 Study selection and data extraction

After a comprehensive search, data will be imported to Endnote version X7.8 (THOMSON REUTERS), and duplicates will be removed. Studies will be exported to Rayyan for screening by title and abstract. Two independent reviewers (TYA and HFW) will screen the title, abstract, and full texts to identify eligible studies. Any inconsistencies will be resolved through independent

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screening by a third reviewer (FWS). TYA will prepare the data extraction checklist, and data will be extracted in a Microsoft Excel (version 365) spreadsheet. The following data will be extracted from the included studies: 1) Bibliographic details: name of the first author, year of publication, year of data collection, country, and World Health Organization (WHO) regions, 2) demographic characteristics of participants: mean/median age, the proportion of males, residence (urban vs rural), and the country's wealth status, 3) study characteristics: study design, sample size, type of drug-resistant tuberculosis, comorbidities like HIV and diabetes mellitus, the total number of people examined for DR-TB by gene Xpert, Line Prob Assay (LPA), and/or culture, the timing of developing DR-TB, frequency of contact, and location of contact (household, work place, child-care, and homeless), type of contacts (households, close, and casual), proportions of latent MDR-and XDR-TB, active MDR- and XDR-TB, overall proportions of latent MDR- and XDR-TB, and overall active MDR- and XDR-TB). Moreover, the index case characteristics (number, sex, median/mean age, comorbidities, and treatment categories) will be extracted. For a study done in multiple countries, the data from each country will be reported independently if available. The study screening and selection process is summarized in Fig 1. Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)-2020

160 flow diagram for the summary of the systematic review study selection process

- - 163 Quality Assessment

The Newcastle-Ottawa quality assessment scale will be used to assess the quality of cohort and
case-control studies (23). The quality of cross-sectional studies will be assessed using the modified
version of the Newcastle-Ottawa Quality Assessment Scale (24). The score will classify studies

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into low-quality (a score between 1 and 4), moderate quality (a score between 5 and 7), and highquality studies (a score between 8 and 9). To assess the quality of interventional studies, the
Cochrane Handbook for Systematic Reviews of Interventions (Version 6.3, 2022) will be used
(25). The quality of the included studies will be done by the two reviewers (TYA and FWS). A
third reviewer (HFW) will be involved to resolve any disagreements between the two primary
reviewers. Moreover, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)
statement will be used for reporting the results of the systematic review and meta-analysis (26).

174 Data synthesis and analysis

We are interested in estimating the burden of latent and active DR-TB reported as incidence or prevalence at the global level. Stata version 17 software will be used to conduct the analysis. For incidence studies, the incidence rate will be calculated as the number of incident cases per year divided by the population at risk. Similarly, for the prevalence study, the prevalence will be calculated as the number of prevalent cases divided by the total population and expressed as a proportion. A forest plot will be generated to show individual and pooled prevalence of latent and/or active DR-TB cases among DR-TB contacts, 95% confidence interval (CI), name of the first author, publication years, and study weights. A random-effects meta-analysis will be used to report the pooled estimates. The presence of heterogeneity among the included studies will be evaluated using the I² statistics and a 95% CI. An I² value close to zero indicates no observed heterogeneity and a larger value of I² shows an increased level of heterogeneity. Heterogeneity will be considered low, moderate, and high when the values are below 25%, between 25% and 75%, and above 75%, respectively (27). To identify the source of heterogeneity, sub-group analysis will be carried out by study characteristics. Moreover, meta-regression will be conducted to assure the existing source of heterogeneity. Publication bias will be assessed visually using

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funnel plots and statistically using Egger's regression test. A trim and fill analysis will be
conducted as an adjustment if there is any publication bias (28). A sensitivity analysis will be done
by trimming low-quality studies.

Implication of the review

DR-TB contact investigation is a top priority in DR-TB infection control, being critical for locating the source of infections as patients with smear-positive DR-TB are highly contagious. Identification of cases through contact investigation can lead to timely treatment and preventative measures to be undertaken, thereby minimizing the risk of disease transmission, and further reducing the burden of DR-TB in the general population. Early diagnosis and detecting of DR-TB will improve treatment outcomes and reduce adverse drug reactions and complications. It will also reduce cost of the patients and households. Overall, the study will help to achieve the three END-TB targets 0f 2035 (no catastrophic cost, 90% reduction in mortality, and 95% reduction in patients suffering from TB) through early diagnosis and treatment.

203 Article summary

- 204 Strength and limitation
 - To the best of our knowledge, there is limited and outdated evidence on the burden of DR-TB among their contacts.
- This study will determine the burden of XDR-TB among contacts of DR-TB patients which
 is not in previous systematic reviews.
 - The study will not be representative of the 30 high-burden TB countries due to the scarcity of published articles in some high-burden countries.
 - Heterogeneity among included studies may be the other limitation of the study.

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5 6 7	213	Declaration
8 9 10	214	Acknowledgments
11 12 13	215	We would like to acknowledge Curtin University for financial funding.
14 15 16	216	Author contributions
17 18 19	217	TYA designed the study and wrote the initial draft of the manuscript. ACAC, EAG, HFW, FWS,
20 21 22	218	and KAA critically reviewed the final manuscript. All authors approved the final manuscript for
23 24	219	submission.
25 26 27	220	Patient and public involvement
28 29	221	Patients were not involved in the development of the research question, study design, and outcome
30 31 32	222	measures.
33 34 25	223	Ethics and dissemination
36 37	224	Ethical approval will not be required for this study as it will be a systematic review and meta-
38 39 40	225	analysis based on previously published studies. In addition to scientific publication, the results will
41 42	226	be disseminated on social media platforms including Twitter and LinkedIn to inform policymakers,
43 44	227	funders, and other researchers.
45 46 47	228	Funding
48 49	229	This work is supported by the Australian National Health and Medical Research Council
50 51 52	230	(NHMRC) through an Emerging Leadership Investigator Grant APP1196549. KAA is a senior
52 53 54 55 56	231	researcher at Curtin University who received the fund. TYA is also supported by Curtin University
57 58		11
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

232	Higher Degree Research (HDR) Scholarship and acknowledges Curtin University for providing
233	support. However, the funders had no role in design, analysis, and interpretations of findings.
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
220	Data will be evailable when a measurable request from the corresponding outbor
239	Data will be available upon a reasonable request from the corresponding author.
240	
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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.

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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 Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Syst Rev. 2015;4(1):1.			statement.
			Page
		Reporting Item	Number
Title			(
Identification	<u>#1a</u>	Identify the report as a protocol of a systematic review	1
Update	<u>#1b</u>	If the protocol is for an update of a previous systematic	NA
		review, identify as such	
	For po	er review only - http://bmionen.hmi.com/site/about/guidelines.yhtml	

1 2 3	Registration			
4 5		<u>#2</u>	If registered, provide the name of the registry (such as	2
6 7 8			PROSPERO) and registration number	
9 10 11 12	Authors			
12 13 14	Contact	<u>#3a</u>	Provide name, institutional affiliation, e-mail address of all	1
15 16			protocol authors; provide physical mailing address of	
17 18 19			corresponding author	
20 21 22	Contribution	<u>#3b</u>	Describe contributions of protocol authors and identify the	3
22 23 24			guarantor of the review	
25 26 27	Amendments			
28 29		<u>#4</u>	If the protocol represents an amendment of a previously	
30 31 32			completed or published protocol, identify as such and list	
33 34			changes; otherwise, state plan for documenting important	
35 36			protocol amendments	
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39 40	Support			
41 42 43 44	Sources	<u>#5a</u>	Indicate sources of financial or other support for the review	12
45 46 47	Sponsor	<u>#5b</u>	Provide name for the review funder and / or sponsor	12
48 49	Role of sponsor or	<u>#5c</u>	Describe roles of funder(s), sponsor(s), and / or institution(s),	12
50 51 52	funder		if any, in developing the protocol	
53 54 55	Introduction			
50 57 58 59	Rationale	<u>#6</u>	Describe the rationale for the review in the context of what is	3-4
60		For pee	r review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2			already known	
3 4	Objectives	<u>#7</u>	Provide an explicit statement of the question(s) the review will	4
5 6 7			address with reference to participants, interventions,	
7 8 9			comparators, and outcomes (PICO)	
10 11 12	Methods			
13 14 15	Eligibility criteria	<u>#8</u>	Specify the study characteristics (such as PICO, study design,	7
16 17			setting, time frame) and report characteristics (such as years	
18 19 20			considered, language, publication status) to be used as	
20 21 22 23			criteria for eligibility for the review	
23 24 25	Information	<u>#9</u>	Describe all intended information sources (such as electronic	6
26 27	sources		databases, contact with study authors, trial registers or other	
28 29 30			grey literature sources) with planned dates of coverage	
31 32 33	Search strategy	<u>#10</u>	Present draft of search strategy to be used for at least one	6-7
33 34 35			electronic database, including planned limits, such that it	
36 37 38			could be repeated	
39 40	Study records -	<u>#11a</u>	Describe the mechanism(s) that will be used to manage	9
41 42 43	data management		records and data throughout the review	
44 45 46	Study records -	<u>#11b</u>	State the process that will be used for selecting studies (such	8
40 47 48	selection process		as two independent reviewers) through each phase of the	
49 50			review (that is, screening, eligibility and inclusion in meta-	
51 52 53			analysis)	
54 55 56	Study records -	<u>#11c</u>	Describe planned method of extracting data from reports	8
50 57 58	data collection		(such as piloting forms, done independently, in duplicate), any	
59 60		For pee	r review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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process		processes for obtaining and confirming data from investigators	
Data items	<u>#12</u>	List and define all variables for which data will be sought	7
		(such as PICO items, funding sources), any pre-planned data	
		assumptions and simplifications	
Outcomes and	<u>#13</u>	List and define all outcomes for which data will be sought,	7
prioritization		including prioritization of main and additional outcomes, with	
		rationale	
Risk of bias in	<u>#14</u>	Describe anticipated methods for assessing risk of bias of	10
individual studies		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	
Data synthesis	#15a	Describe criteria under which study data will be quantitatively	9
		synthesised	
Data synthesis	<u>#15b</u>	If data are appropriate for quantitative synthesis, describe	9
		planned summary measures, methods of handling data and	
		methods of combining data from studies, including any	
		planned exploration of consistency (such as I2, Kendall's τ)	
Data synthesis	<u>#15c</u>	Describe any proposed additional analyses (such as	10
		sensitivity or subgroup analyses, meta-regression)	
Data synthesis	<u>#15d</u>	If quantitative synthesis is not appropriate, describe the type	NA
		of summary planned	
Meta-bias(es)	<u>#16</u>	Specify any planned assessment of meta-bias(es) (such as	10
		publication bias across studies, selective reporting within	

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1 2			studies)	
3 4	Confidence in	<u>#17</u>	Describe how the strength of the body of evidence will be	10-11
5 6 7	cumulative		assessed (such as GRADE)	
, 8 9	evidence			
10 11 12	None The PRISMA	∖-P elab	oration and explanation paper is distributed under the terms of th	e Creative
13 14	Commons Attributi	ion Licer	nse CC-BY. This checklist can be completed online using	
15 16	https://www.goodro	eports.o	rg/, a tool made by the EQUATOR Network in collaboration with	
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BMJ Open

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

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



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1	Burden of drug-resistant tuberculosis among contacts of index cases:
2	a protocol for a systematic review
3	Temesgen Yihunie Akalu ^{1,2,3*} , Archie C. A. Clements ^{3,4} , Eyob Alemayehu Gebreyohannes ^{3,5} ,
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23 Abstract

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

Method and analysis: Systematic searches will be conducted in Medline, Embase, Web of Science, Scopus, Cochrane Central Register of Controlled trials (CENTRAL), and Cumulative Index to Nursing and Allied Health Literature (CINHAL) databases. The search will be conducted without restrictions on time, language, and geography. A random-effects meta-analysis will be conducted for effect estimates. The pooled prevalence and incidence of DR-TB will be compared between people with and without contact with DR-TB patients. The presence of heterogeneity between studies will be assessed by Higgins I² statistics. Sub-group analysis will be conducted to determine the source of heterogeneity. The risk of bias will be assessed using a visual inspection of the funnel plot and Egger's regression test statistics. Trim and fill analysis will be done in the presence of publication bias. A sensitivity analysis will be conducted by trimming low-quality studies. The systematic review will be reported according to Preferred Reporting Items for 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.

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2 3	46	Keywords: Contacts drug-resistant tuberculosis systematic review protocol				
4 5	10					
6 7	47	Article summary				
8 9 10	48	Strength and limitation				
11 12 12	49	• The review will use a comprehensive search strategy to obtain unbiased summary.				
13 14 15	50	• Sub-group analysis will be performed to compare the prevalence and incidence of DR-TB				
16 17	51	by study characteristics.				
18 19	52	• Findings will be reported according to Preferred Reporting Items for Systematic Reviews				
20 21 22	53	and Meta-Analyses protocol.				
23 24	54	• The search will be conducted without time and geographical restriction.				
25 26	55	• Substantial heterogeneity among included studies may be the possible limitation of the				
27 28	56	study.				
29 30 31	57	Background				
32 33 34	58	Drug-resistant tuberculosis (DR-TB) is an important public health concern. It is defined as				
35 36	59	resistance to any of the anti-TB drugs, and it can be classified into mono-resistant (resistant to only				
37 38	60	one anti-TB drug), multi-drug-resistant tuberculosis (MDR-TB: resistant to both isoniazid and				
39 40 41	61	rifampicin), poly-resistant (resistant to more than two first-line drugs except combined resistance				
42 43	62	to both isoniazid and rifampin), pre-XDR-TB (MDR-TB with resistance to either a				
44 45	63	fluoroquinolone, or at least 1 of 3 injectable second-line TB drugs, but not both), and extensively				
46 47 48	64	drug-resistant (XDR-TB: MDR-TB with resistance to any fluoroquinolone and at least one of the				
49 50	65	second-line injectable drugs) (1). In 2021, approximately half a million people were diagnosed				
51 52 53 54 55	66	with DR-TB and nearly 3.9% of new TB cases and 20% of previously treated cases were DR-TB.				

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Three countries alone carry 42% of the global DR-TB burden in 2021: India (26%), the Russian
Federation (8.5%), and Pakistan (7.9%) (2).

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

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

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Several systematic reviews have estimated the burden of DS-TB among people who were close contacts of DS-TB cases. Those studies showed that people having close contact with DR-TB patients are at increased risk of contracting and developing the disease. For example, a previous systematic review conducted in high-income countries in 2005 by Morrison et al. showed that the overall burden of TB (both DS-TB and DR-TB) among contacts was 4.5%. However, the study lacked a stratified analysis of high-risk groups such as DR-TB close contacts and addressed only the prevalence of TB overall (20). Another systematic review conducted in low-income countries in 2013 by Fox et al. among contacts of TB patients (DS-TB and DR-TB combined) showed that the overall prevalence of TB was 3.1% (4). The findings from previous studies have provided inconclusive evidence and are now outdated (21). Therefore, the current systematic review will quantify the burden of DR-TB among people in contact with DR-TB patients including household, close, and casual contacts of DR-TB patients. The primary objective is to quantify the pooled proportion of DR-TB among people in close contact with DR-TB patients. Our secondary objective is to assess study-level characteristics that may be associated with a high proportion of DR-TB.

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- **Review questions**
- What is the prevalence of DR-TB among contacts of DR-TB patients?
- What is the incidence of DR-TB among contacts of DR-TB patients?
- What are the study level characteristics associated with high prevalence and incidences of DR-TB
- among contacts of DR-TB patients?

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112 Methods

Protocol registration

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

1).

119 Search strategy

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

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				

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	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					
Eligibi	lity criteria: All studies reporting the burden (i.e., proportion, prevalence, or incidence					
of DR-T	B among people with contacts (i.e., households, close, and casual contacts) of DR-TB with					
be inclue	led in this systematic review and meta-analysis. We will exclude reviews, commentaries					
editorials, case reports and case series, and animal studies. Moreover, studies that lack information						
on the outcome variable and are conducted only on DS-TB patients will be excluded. Studies will						
be included based on the PICO (Population, Intervention, Comparator, and Outcome) framework.						
Outcor	Outcome measures					
Primary outcome measures						
The primary outcomes of the study are the prevalence and incidence of DR-TB among people						
having contact with DR-TB patients. The incidence of DR-TB among people having contact with						
DR-TB	DR-TB patients will be calculated by year of enrolment. The prevalence or incidence of DR-TB					
among p	eople having contact with DR-TB will be determined. Contact will be defined as a perso					

living in the same household as the index case or exposure to DR-TB patients in transportation, workplace, and recreational sites.

Study selection and data extraction

After a comprehensive search, data will be imported to Endnote version X7.8 (THOMSON REUTERS), and duplicates will be removed. Studies will be exported to Ravyan for screening by title and abstract. Two independent reviewers (TYA and EAG) will screen the title, abstract, and full texts to identify eligible studies. Any inconsistencies will be resolved through consensus between the two reviewers. TYA will prepare the data extraction checklist, and data will be extracted in a Microsoft Excel (version 365) spreadsheet. The following data will be extracted from the included studies: 1) Bibliographic details: name of the first author, year of publication, year of data collection, country, and World Health Organization (WHO) regions, 2) demographic characteristics of participants: mean/median age, the proportion of males, and the country's wealth status, 3) study characteristics: study design, sample size, type of drug-resistant tuberculosis, comorbidities like HIV and diabetes mellitus, the total number of people examined for DR-TB by gene Xpert, Line Prob Assay (LPA), and/or culture, the timing of developing DR-TB, frequency of contact, and location of contact (household, work place, child-care, and homeless), type of contacts (households, close, and casual), proportions of MDR- and XDR-TB,). For a study done in multiple countries, the data from each country will be reported independently if available. The study screening and selection process is summarized in Fig 1.

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

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	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
2 3	167	classify studies into low-quality (a score between 1 and 4), moderate quality (a score between 5
+ 5 5	168	and 7), and high-quality studies (a score between 8 and 9). The quality of the included studies will
7 3	169	be done by the two reviewers (TYA and EAG). Disagreements will be resolved by the consensus
))	170	between the two reviewers.
 <u>2</u> 3	171	Data synthesis and analysis
1 5	172	We are interested in estimating the burden of DR-TB reported as incidence or prevalence at the
5 7 3	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
 2	175	population at risk. Similarly, for the prevalence study, the prevalence will be calculated as the
3 1 -	176	number of prevalent cases divided by the total population and expressed as a proportion. A forest
5	177	plot will be generated to show individual and pooled prevalence of DR-TB cases among DR-TB
3	170	contacts 95% confidence interval (CI) name of the first author publication years and study

weights. A random-effects meta-analysis will be used to report the pooled estimates. The presence

of heterogeneity among the included studies will be evaluated using the I² statistics and a 95% CI.

An I² value close to zero indicates no observed heterogeneity and a larger value of I² shows an

increased level of heterogeneity. Heterogeneity will be considered low, moderate, and high when

the values are below 25%, between 25% and 75%, and above 75%, respectively (25). To identify

the source of heterogeneity, sub-group analysis will be carried out by study characteristics.

Moreover, meta-regression will be conducted to assure the existing source of heterogeneity.

Publication bias will be assessed visually using funnel plots and statistically using Egger's

regression test. A trim and fill analysis will be conducted as an adjustment if there is any

publication bias (26). A sensitivity analysis will be done by trimming low-quality studies.

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Implication of the review

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

Declaration

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

203 Author contributions

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

207 Patient and public involvement

Patients were not involved in the development of the research question, study design, and outcomemeasures.

210 Ethics and dissemination

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

215 Funding

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Competing interest

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

223 Patient consent for publication

224 Not required

Data sharing statement

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

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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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to text Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Page
	Reporting Item	Number
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<u>#1a</u>	Identify the report as a protocol of a systematic review	1
<u>#1b</u>	If the protocol is for an update of a previous systematic review, identify as such	NA
<u>#2</u>	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
<u>#3a</u>	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
<u>#3b</u> For peer	Describe contributions of protocol authors and identify the review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	10
	#1a #1b #2 #3a For peer	Reporting Item #1a Identify the report as a protocol of a systematic review #1b If the protocol is for an update of a previous systematic review, identify as such #2 If registered, provide the name of the registry (such as PROSPERO) and registration number #3a Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author #3b Describe contributions of protocol authors and identify the For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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1 2			guarantor of the review	
3	Amendments			
4 5 6 7 8 9 10		<u>#4</u>	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	
11 12 13	Support			
14 15	Sources	<u>#5a</u>	Indicate sources of financial or other support for the review	11
16 17	Sponsor	<u>#5b</u>	Provide name for the review funder and / or sponsor	11
18 19 20 21	Role of sponsor or funder	<u>#5c</u>	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	11
22	Introduction			
24 25 26 27 28 29 30 31 32	Rationale	<u>#6</u>	Describe the rationale for the review in the context of what is already known	3-4
	Objectives	<u>#7</u>	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
33 34 35	Methods			
36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52	Eligibility criteria	<u>#8</u>	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	<u>#9</u>	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	<u>#10</u>	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
53 54 55 56	Study records - data management	<u>#11a</u>	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
57 58	Study records -	<u>#11b</u>	State the process that will be used for selecting studies (such	8
59 60		For peer	review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2 3 4	selection process		as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta- analysis)	
5 6 7 8 9 10	Study records - data collection process	<u>#11c</u>	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	8
12 13 14 15 16	Data items	<u>#12</u>	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
17 18 19 20 21	Outcomes and prioritization	<u>#13</u>	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
22 23 24 25 26 27 28	Risk of bias in individual studies	<u>#14</u>	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	10
29 30 31 32	Data synthesis	<u>#15a</u>	Describe criteria under which study data will be quantitatively synthesised	9
33 34 35 36 37 38 39	Data synthesis	<u>#15b</u>	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 I2, Kendall's τ)	9
40 41 42 43	Data synthesis	<u>#15c</u>	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
44 45 46	Data synthesis	<u>#15d</u>	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
47 48 49 50 51 52	Meta-bias(es)	<u>#16</u>	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
53 54 55 56 57 58	Confidence in cumulative evidence	<u>#17</u>	Describe how the strength of the body of evidence will be assessed (such as GRADE)	3
59 60		For peer	review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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