Extensively drug-resistant tuberculosis in Africa: prevalence and factors associated: A Systematic Review and Meta-analysis

February 2019

Petrus Ndiiluka Kosmas

Student No. KSMPET001

Study programme**: Master of Public Health**

Supervisors:

Dr. Jabulani Ncayiyana

Associate Professor. Mark E. Engel

A dissertation submitted to the Health Sciences Faculty, University of Cape Town, in partial fulfilment of the requirements for the degree of Master of Public Health.

PLAGIARISM DECLARATION

1. I know that plagiarism is wrong. Plagiarism is using the work of another person pretending that it is your own work.

2. I have used the Vancouver style as the convention for citation and referencing. Each significant contribution to, and quotation, in this dissertation from the work, or works, of other people has been attributed, cited and referenced.

3. I have not allowed, and will not allow, anyone to copy my work with the intention of passing it off as his or her own work.

4. I acknowledge that copying someone else's assignment or essay, or part of it, is wrong.

5. I declare that this is my own work.

SIGNATURE: Signed by candidate

DATE: 11 February 2019

Acknowledgements

I would like to sincerely thank:

Dr. Jabulani Ncayiyana and Prof Mark Engel for their supervision during the course of this research project.

Ms Elize Pietersen my co-reviewer for her constant assistance and encouragement throughout.

Ms Hlengiwe Moloi for her assistance with drafting the protocol.

Ms Mary Shelton and Ms Nhanhla Madini for assisting me with building the search strategy and searching the electronic databases for relevant records.

Finally, I would like to thank my parents, sisters, friends and colleagues for their support during this review.

SUMMARY OF CONTENT

In this MPH dissertation, comprising three parts, a systematic review on prevalence of XDR-TB, and factors associated with the prevalence of XDR-TB in Africa was performed.

Part A outlines the research protocol and provides a brief background to the research topic and the process of this systematic review.

Part B provides extensive literature that is relevant to the prevalence of and factors associated with XDR-TB in Africa.

Part C details the results and discussion of this systematic review. The part is written in a format of journal manuscript ready to publish in the PLOS journal.

Table of Contents

PART A: PROTOCOL

List of abbreviations

DST - Drug Susceptibility Test

DS-TB – Drug Susceptible Tuberculosis

DR-TB – Drug-resistant Tuberculosis

HIV – Human Immunodeficiency Virus

MDR-TB – Multi Drug-resistant Tuberculosis

MESH – Medical Subject Headings

TB - Tuberculosis

WHO - World Health Organization

XDR-TB – Extensively Drug-resistant Tuberculosis

Operational definitions

Children- refers to individuals who are <15 years of age (based on WHO criteria).

Factors associated with the prevalence of XDR-TB - any variable that is associated with the likelihood of a diagnosis with XDR-TB.

MDR-TB - disease caused by *Mycobacterium tuberculosis* with resistance to isoniazid and rifampicin, with or without resistance to other first-line drugs (FLD).

Prevalence – for this review, prevalence will refer to the proportion of XDR-TB cases reported in studies from January 2006 to May 2018.

Pre-XDR-TB – disease caused by *Mycobacterium tuberculosis* with resistance to isoniazid and rifampicin, and either a fluoroquinolone or second-line injectable drug, but not both.

Pulmonary tuberculosis - refers to any bacteriologically confirmed case of TB involving the lung parenchyma or the tracheobronchial tree.

XDR-TB – defined as a disease caused by *Mycobacterium tuberculosis* with resistance to at least isoniazid and rifampicin, any fluoroquinolone, and at least one of three injectable anti-TB treatment drugs (amikacin, capreomycin, or kanamycin).

1. BACKGROUND

Drug-resistant tuberculosis (DR-TB) continues to be a global public health burden. In 2016 the World Health Organization (WHO) estimated a global incidence of 600 000 drug-resistant TB cases, and extensively drug-resistant TB (XDR-TB) constituted 9.6% of the reported DR-TB cases (1). XDR-TB is defined as a disease caused by *Mycobacterium tuberculosis* with resistance to at least isoniazid and rifampicin, any fluoroquinolone, and at least one of three injectable anti- tuberculosis drugs (amikacin, capreomycin, or kanamycin) (2). To date, 123 countries have reported at least one case of XDR-TB compared to 92 in 2012, and 55 in 2008 respectively (3–5). Africa accounts for 13.6% of the global XDR-TB cases, with South Africa reporting the highest number (967 out of 1092) of those XDR-TB cases (1).

Available data on the prevalence of XDR-TB in Africa is limited. Although several studies (6–14) have been conducted in multiple settings in Africa to determine the prevalence of DR-TB, none of these studies reference XDR-TB. The reason why some of these studies could not identify XDR-TB is because drug susceptibility testing (DST) focused on first-line anti-tuberculosis drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) (6–8,14). A few studies have reported prevalence of XDR-TB as 5.9% in Burkina Faso (15), 4.9% in South Africa (16), while Lesotho and Mali respectively only reported XDR-TB cases but not the prevalence of XDR-TB (17,18). The true prevalence of XDR-TB in Africa is thus unknown as data on the prevalence of XDR-TB has not been systematically reviewed to establish the true burden of XDR-TB in Africa.

Multiple factors have been reported to influence the prevalence of XDR-TB. The lack of laboratory capacity to conduct DST to diagnose XDR-TB result in subsequent under diagnosis of XDR-TB (1). The unavailability of a rapid molecular diagnostic test for XDR-TB further

contributes to delayed and underdiagnosis of XDR-TB (19). Poor infection control in healthcare facilities has also been suspected of contributing to the spread of XDR-TB (18,20,21).

XDR-TB can develop during TB treatment (acquired) or from infection by an XDR-TB strain (primary resistance) (22). The practice of discharging patients who failed XDR-TB treatment back into the community poses a threat of primary transmission of XDR-TB in the community (23). This could potentially increase the prevalence of XDR-TB, by means of the transmission of XDR-TB from programmatically incurable patients to their contacts (23).

Favourable outcomes are reported for those patients who used new generation anti-tuberculosis drugs, such as bedaquiline, in the management of XDR-TB (24). Treatment with new generation anti-tuberculosis drugs thus have great potential to prevent primary transmission of XDR-TB as a result of increased cure rate (24). The successful management of XDR-TB cases suggests that primary transmission of XDR-TB to contacts is preventable and consequently reducing the prevalence of DR-TB.

Several factors have been reported to be associated with the likelihood of XDR-TB in Africa. These factors include, but might not be limited to; age, sex, HIV status, history of previous TB treatment, hospitalization history, CD4 count, weight, smoking status and diabetes (20,23,25,26). These factors are typically reported as characteristics of patients diagnosed with XDR-TB and not as factors associated with the likelihood of a diagnosis with XDR-TB (25). According to the only study that explicitly focused on XDR-TB predictive factors HIV status, history of previous TB treatment (treatment failure), and history of hospitalization for more than 14 days are independent factors associated with the diagnosis of XDR-TB (25).

Conducting a systematic review and meta-analysis will enable us to establish the prevalence of XDR-TB, and factors associated with the XDR-TB prevalence, in Africa. Furthermore, such knowledge will assist in identifying populations at substantial risk of being diagnosed with XDR-TB and guide appropriate XDR-TB intervention strategies including healthcare policies.

1.1. Problem statement

To date, there have been no published systematic review and or meta-analysis conducted on the prevalence of XDR-TB in Africa. Systematic reviews and meta-analysis on the prevalence of multi drug-resistant tuberculosis (MDR-TB) rather than XDR-TB are however reported (27,28). Furthermore, the only meta-analysis reported regarding Africa focused on the factors associated with MDR-TB in Africa (29). In 2017, the WHO reported a decrease in the rate of drug-susceptible tuberculosis (DS-TB) cases yet the prevalence rate of XDR-TB continue to increase (1). Prevalence rates are central to healthcare policy planning and hence the need to ascertain the prevalence rate of XDR-TB in Africa. Likewise, a meta-analysis of factors associated with the prevalence of XDR-TB in Africa will allow us to ascertain and assess the strength of association between factors associated with XDR-TB prevalence in an African context. The knowledge gained will not only further existing academic and professional knowledge related to XDR-TB but will similarly enhance clinical management.

1.2.Justification and Implications of this review

The dearth of African focused systematic reviews and meta-analysis related to prevalence, and factors associated with the prevalence of XDR-TB, emphasizes such demand. An African focused systematic review, and meta-analysis, will enable the synthesis of evidence and contribute to professional and academic knowledge on the prevalence and factors associated

with the prevalence of XDR-TB in Africa, ultimately benefitting patients and communities in Africa. Furthermore, findings related to an African focused systematic review and meta-analyses have the potential to inform healthcare policy and subsequent healthcare service planning. Results could be used in mathematical disease models to estimate the lifetime prevalence of XDR-TB in Africa. Moreover, the results of this review have potential to provide valuable information related to factors associated with the prevalence XDR-TB in Africa with ultimate impact on TB healthcare service delivery.

1.3. Research question

What is the prevalence of, and factors associated with the prevalence of XDR-TB in Africa?

2. OBJECTIVES OF THE STUDY

2.1 Primary objective

- To assess the prevalence of XDR-TB amongst participants tested for second-line anti-tuberculosis drug resistance in Africa.

2.2. Secondary objectives

- To assess the prevalence of XDR-TB amongst participants with resistance to at least one anti-TB drug
- To assess the prevalence of XDR-TB amongst participants with MDR-TB
- To assess the prevalence of XDR-TB amongst patients with resistance to at least one second-line anti-TB drug
- To assess the factors associated with the prevalence of XDR-TB in Africa.

3. METHODS

3.1. Criteria for considering studies for this review

3.1.1. Types of studies

For the assessment of XDR-TB prevalence observational studies, population-based studies, cross-sectional studies and cross-sectional surveys will be considered. Baseline data of cohort studies, cases control studies and experimental studies that report on the prevalence of XDR-TB among the study population will also be considered. Prevalence data will not be extracted from studies with an exclusive XDR-TB study population. For the assessment of factors associated with the prevalence of XDR-TB in Africa observational studies, population-based studies, cross-sectional studies and cross-sectional surveys will be considered. Baseline data of cohort studies (both retrospective and prospective), case control studies and experimental studies that report on the prevalence of XDR-TB among the study population data will be considered.

3.1.2. Types of participants

This review will include studies reporting laboratory confirmed pulmonary XDR-TB in adults (15 years and older), irrespective of gender and socio-economic backgrounds. Studies reporting patients suspected to have TB will also be included. Studies will be eligible for inclusion if XDR-TB diagnosis was reported as based on any of the WHO recommended laboratory procedures for first-line and second-line anti-tuberculosis drug resistance testing (30,31).

3.1.3. Study setting

This review will include studies conducted in Africa. The following countries will be included: Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo (Brazzaville), Congo (Democratic Republic), Cote d'Ivoire, Djibouti, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea- Bissau, Kenya, Lesotho, Libya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Mozambique, Namibia, Niger, Nigeria, Reunion, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, South Sudan, Swaziland, Tanzania, Togo, Tunisia, Uganda, Western Sahara, Zambia, and Zimbabwe (Appendix 1).

3.1.4. Types of outcome measures

- XDR-TB - as determined by WHO recommended laboratory diagnostic tests (30,31)
- DR-TB - refers to *Mtb* that is resistance to at least one anti-TB drug
- MDR-TB – refers to *Mtb* that is resistant to both isoniazid and rifampicin.
- Second-line resistance - refers to *Mtb* that is resistant to at least one second-line anti-TB drug

3.1.5. Exclusion criteria

The following studies will be excluded:

- XDR-TB prevalence is not explicitly reported (e.g. where results are inextricable including other types of DR-TB cases).

- Studies exclusively including children. Studies reporting results related to adults and children will be included provided results clearly differentiate between the prevalence, and factors associated with prevalence regarding children.
- Generic definition for XDR-TB not applied.
- Duplicate publications. The most recent report will be included when duplicate publications are encountered.
- Review studies (narratives, expert opinions).
- Studies that only include people living with HIV.
- Studies that lacks clear research methodology.
- Studies conducted with no ethical approval or clearance.
- Studies that only analyse laboratory specimens/results without enrolling any patients.
- Publications in languages other than in English.
- Studies that report on the evaluation and comparison of TB diagnostic tests.

3.2. Search methods for identification of studies

Published and unpublished literature will be comprehensively searched to identify relevant articles. A search strategy will be developed in MEDLINE, including both the medical subject headings (MESH) and free text (Appendix 2). Assistance from a librarian will be sought to help design an appropriate search strategy for this review. The search strategy will be adapted to various electronic databases using applicable vocabulary. A reference software programme (EndNote) will be used to manage study articles.

3.3. Electronic searches

Relevant articles will be sought and identified from electronic databases such as PubMed/ Medline, CINAHL, Scopus, Web of Science, ScieELO, PyschInfo, Cochrane Central Register of Controlled Trials (Central), (Africa-wide) allied health, Health Source: Academic Edition and Google Scholar. A search for XDR-TB prevalence data, and factors associated with the prevalence of XDR-TB will be performed regarding state health surveys of countries included in this review and meta-analysis.

Reference lists of the articles obtained from electronic data bases will be interrogated to identify articles missed during the electronic databases searches. Additionally, grey literature such as conference papers will be explored.

3.4. Data collection

3.4.1. Selection of studies

Step 1: One reviewer will scan relevant articles for possible eligibility. Articles will be excluded based on their titles.

Step 2: Two reviewers will then read titles and abstracts of all initially include articles to determine eligibility for inclusion in the study.

Step 3: Full texts of articles deemed eligible will be obtained and reviewed independently by the two reviewers.

A third reviewer will be consulted in the event that reviewers have a disagreement on exclusion or inclusion of an article during initial review process. A summary table will be compiled detailing reason for exclusion of documented studies.

3.4.2. Data extraction and management

Data from full text of eligible articles will be independently extracted by two reviewers using a standardised data extraction form (Appendix 3). The data extraction form will be piloted on at least 5 of studies randomly selected from the included studies.

Study characteristics such as country of study, study design, sample size, outcome measures, study population, study findings, and diagnostic criteria will be recorded. Each study will only contribute one estimate of an outcome measure and/or variable of interest. In the event that an individual study has multiple estimates of a single outcome measure of a variable of interest, only one estimate of each outcome variable will be selected to contribute to this review's pooled estimate of each study outcome of interest. If the two reviewers disagree regarding data extracted a third reviewer will act as a mediator.

3.5. Data analysis and synthesis

The PRISMAS 2009 guidelines will be used to report the study findings (32) (Appendix 4). Data analysis will be done in two phases. The first phase of analysis will be to calculate the pooled prevalence rate estimates from the included studies. An application of random effect, and / or fixed effect method, will be applied depending on the heterogeneity of the included prevalence study estimates. The prevalence of XDR-TB will be pooled together by method of meta-analysis using REVMAN and or the statistical software STATA (33).

The second phase will entail the synthesis of evidence relating to the second objective of this study. Factors associated with the prevalence of XDR-TB will be synthesised descriptively to understand individual factors associated with the prevalence of XDR-TB. The STATA, and or

REVMAN, statistical software will be used to pool together measurement outcomes of factors associated with the prevalence of XDR-TB.

3.5.1. Assessment of risk of bias of included studies

The quality of included studies will be assessed using various assessment tools. Observational studies will be assessed using the quality assessment tool developed by Hoy et al. 2012, and modified by Werfali et al. 2014 (34,35). This prevalence study quality appraisal tool categorises studies into three groups; 0-5 points as high-risk studies, 6-8 points as moderate risk studies, and >8 as low risk studies (Table 1). The Newcastle-Ottawa appraisal tool will be used to appraise both cohort and case-control studies (36,37).

Two reviewers will independently assess the quality of all included studies followed by the comparison of their quality appraisal scripts. Disagreement on the quality scores will be resolved by unanimity between the two reviewers. Failure to reach a consensus will be mediated by a third reviewer. Moreover, a funnel plot, if more than 10 studies included in the review, will be plotted to assess reporting bias of included studies.

Table 1: Assessment criteria for prevalence studies

Items	Quality score
External validity	
1. Was the study's target population a close representation of the national population in relation to relevant variables?	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of non-response bias minimal?	(1 point)
	Total (4 points)
Internal validity	
1. Were data collected directly from the participants (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all participants?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
	Total (6 points)

*Quality assessment tool as developed Hoy et al. (34) and modified by Werfali et al. 2014 (35).

3.5.2. Assessment of heterogeneity

The results of studies to be included in this review and meta-analysis are expected to vary hence the need to determine the statistical heterogeneity. Statistical heterogeneity of the included studies will be evaluated using the Chi-squared test of homogeneity. Chi-squared results will be considered statistically significant at alpha level 0.10 (38). Statistical heterogeneity will further be assessed using the I^2statistic to assess the degree of variation among the included studies. The I^2 squared statistic results will be reported as a percentage (38).

3.5.3. Dealing with missing data

Missing, and unreported data from study articles will be sought from the corresponding author of published articles. XDR-TB prevalence, and factors associated with the prevalence of XDR-TB, will be calculated from study articles that report unweighted data but have reported numerator and denominator relating to XDR-TB.

3.5.4. Subgroup and sensitivity analysis

Subgroup analysis will be conducted were plausible. Potential sources of heterogeneity will be examined by conducting sensitivity analysis. Sensitivity analysis will also be carried out to determine whether the pooled measures of effect change when only high-quality studies are considered. Sensitivity analysis will also be conducted to determine the effect on the pooled measures of effect when the studies that contribute the largest weight to the pooled effected are temporarily excluded. The chi-squared test for subgroup differences will be used to evaluate subgroup interactions.

3.5.5. Grading the quality of evidence

The quality of evidence will be assessed using the GRADE approach (39).

4. ETHICS

The researcher plans to use only data and or study articles that are available in the public domain hence participants consent, and ethical clearance will not be required (40). However, exemption for ethical clearance of this protocol will be sought from the Faculty of Health Sciences Human Research Ethics Committee, University of Cape Town, South Africa.

5. FUNDING

No funding is expected for this review.

6. DISSEMINATION

The findings of this study will be distributed through peer reviewed publications and conference presentations.

7. REFERENCES

1. World Health Organisation. Global Tuberculosis Report 2017. World Health Organization. 2017.
2. WHO. Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. Wkly Epidemiol Rec. 2006;81(45):430–2.
3. World Health Organisation. MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB). 2017.
4. Peter R. Donald PD van H. The Global Burden of Tuberculosis — Combating Drug Resistance in Difficult Times. N Engl J Med. 2009;360(23):2393–5.
5. World Health Organisation. Global Tuberculosis Report 2013. World Health Organization. 2013.
6. Minime-Lingoupou F, Manirakiza A, Yango F, Zandanga G, Faou A Le, Rigouts L. Relatively low primary resistance to anti-tuberculosis drugs in Bangui and Bimbo, Central African Republic. Int J Tuberc Lung Dis. 2011;15(5):657–61.
7. Hamusse SD, Teshome D, Suaudi Hussen M, Demissie M, Lindtjørn B. Primary and secondary anti-tuberculosis drug resistance in Hitossa District of Arsi Zone, Oromia Regional State, Central Ethiopia. BMC Public Health. 2016;16:593.
8. Ndung W, Kariuki S, Ng ’ang ’ Z, Revathi G, Ndung ’u W, Ng ’ang ’a Z. Resistance patterns of Mycobacterium tuberculosis isolates from pulmonary tuberculosis patients in Nairobi. J Infect Dev Ctries. 2012;6(1):33–9.
9. Lukoye D, Adatu F, Musisi K, Kasule GW, Were W, Odeke R, et al. Anti-Tuberculosis Drug Resistance among New and Previously Treated Sputum Smear-Positive Tuberculosis Patients in Uganda: Results of the First National Survey. PLoS One. 2013;8(8):e70763.
10. Tessema B, Beer J, Emmrich F, Sack U, Rodloff AC. First-and second-line anti-tuberculosis drug resistance in Northwest Ethiopia. Int J Tuberc Lung Dis. 2012;16(6):805–11.
11. Abubakar S. Hoza SGMM, Konig B. Anti-TB drug resistance in Tanga, Tanzania: A cross sectional facility-base prevalence among pulmonary TB patients. Asian Pac J Trop Med. 2015;8(11):907–13.
12. Gehre F, Otu J, Kendall L, Forson A, Kwara A, Kudzawu S, et al. The emerging threat of pre-extensively drug-resistant tuberculosis in West Africa: preparing for large-scale tuberculosis research and drug resistance surveillance. BMC Med. 2016;14(160).
13. Gudo PS, Cuna Z, Coelho E, Maungate S, Borroni E, Miotto P, Ahmadova S, Brouwer M, Migliori GB, Zignol M CD. Is MDR-TB on the rise in Mozambique? Results of a national drug resistance survey. Eur Respir J. 2011;38(1):222–4.
14. Lukoye D, Cobelens FGJ, Ezati N, Kirimunda S, Adatu FE, Lule JK, et al. Rates of Anti-Tuberculosis Drug Resistance in Kampala- Uganda Are Low and Not Associated with HIV Infection. PLoS One. 2011;6(1):e16130.
15. Saleri N, Badoum G, Ouedraogo M, Dembélé SM, Nacanabo R, Bonkoungou V, et al. Extensively Drug-Resistant Tuberculosis, Burkina Faso. Emerg Infect Dis. 2010;16(5):840–2.
16. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar S V, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779–87.

17. Hind Satti, Kwonjune Seung, Salmaan Keshavjee and JF. Extensively Drug-Resistant Tuberculosis, Lesotho. Emerg Infect Dis. 2008;14(6):992–3.

18. Diarra B, Toloba Y, Konate B, Sanogo M, Combo A, Togo G, et al. Extensively drug resistant tuberculosis in Mali: a case report. BMC Res Notes. 2017;10(1):561.

19. Kapwata T, Morris N, Campbell A, Mthiyane T, Mpangase P, Nelson KN, et al. Spatial distribution of extensively drug- resistant tuberculosis (XDR TB) patients in KwaZulu-Natal, South Africa. PLoS One. 2017;12(10):e0181797.

20. Gandhi NR, Moll A, Sturm W, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368:1575–80.

21. Andrews JR, Shah NS, Gandhi N, Moll T, Friedland G. Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: Implications for the HIV Epidemic and Antiretroviral Therapy Rollout in South Africa. J Infect Dis. 2007;196(3):482–90.

22. Shah NS, Auld SC, Brust JCM, Mathema B, Ismail N, Moodley P, et al. Transmission of Extensively Drug-Resistant Tuberculosis in South Africa. N Engl J Med. 2017;376(3):243–53.

23. Pietersen E, Ignatius E, Streicher EM, Mastrapa B, Padanilam X, Pooran A, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014;383(9924):1230–9.

24. Olayanju O, Limberis J, Esmail A, Oelofse S, Gina P, Pietersen E, et al. Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa. Eur Respir J. 2018;51:1800544.

25. Andrews JR, Shah NS, Weissman D, Moll AP, Friedland G, Gandhi NR. Predictors of Multidrug- and Extensively Drug-Resistant Tuberculosis in a High HIV Prevalence Community. PLoS One. 2010;5(12):e15735.

26. Shah NS, Auld SC, Brust JC, Mathema B, Ismail N, Moodley P, Mlisana K, Allana S, Campbell A, Mthiyane T MN. Transmission of Extensively Drug-Resistant Tuberculosis in South Africa. N Engl J Med. 2017;376(3):243–53.

27. Musa BM, Adamu AL, Galadanci NA, Zubayr B, Odoh CN, Aliyu MH. Trends in prevalence of multi drug resistant tuberculosis in sub-Saharan Africa: A systematic review and meta-analysis. PLoS One. 2017;12(9):e0185105.

28. Lukoye D, Ssengooba W, Musisi K, Kasule GW, Cobelens FGJ, Joloba M, et al. Variation and risk factors of drug resistant tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis. BMC Public Health. 2015;15(1):291.

29. Berhan A, Berhan Y, Yizengaw D. A meta-analysis of drug resistant tuberculosis in Sub-Saharan Africa: how strongly associated with previous treatment and HIV co-infection? Ethiop J Health Sci. 2013;23(3):271–82.

30. World Health Organisation. Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs. 2008.

31. World Health Organisation. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: Policy guidance. 2016.

32. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097.

33. Nyaga VN, Arbyn M, Aerts M, Nyaga V, Arbyn M, Aerts M. METAPROP_ONE: Stata module to perform fixed and random effects meta-analysis of proportions [Internet]. Boston College Department of Economics; 2017 [cited 2018 Mar 23]. Available from: https://econpapers.repec.org/software/bocbocode/S457861.htm

34. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65:934–9.

35. Werfalli M, Musekiwa A, Engel ME, Ross I, Kengne AP, Levitt NS, et al. The prevalence of type 2 diabetes mellitus among older people in Africa: a systematic review study protocol. BMJ Open. 2014;4(6):e004747.

36. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5.

37. Wells GA, Shea B, O'connell D, Peterson J, Welch V, Losos M TP. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. [cited 2017 Dec 6]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

38. Deeks JJ, Higgins JPT AD. Cochrane Handbook: General Methods For Cochrane Reviews: Ch 9: Analysing data and undertaking meta-analyses. In: Cochrane Handbook for Systematic Reviews of Interventions. 2011. p. 243–96.

39. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. GRADE: Going from Evidence to Recommendations. Br Med J. 2009;336(7652):1049–51.

40. Emanuel EJ, Wendler D, Killen J GC. What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical. J Infect Dis. 2004;189(5):930–7.

PART B: LITERATURE REVIEW

List of abbreviations

DR-TB – Drug-resistant Tuberculosis

DST – Drug Susceptible Test

HBC – High Burden Country

HIV - Human Immunodeficiency Virus

MDR-TB – Multi Drug-resistant Tuberculosis

Pre-XDR-TB – Pre-Extensively Drug-resistant Tuberculosis

RR-TB – Rifampicin Resistant Tuberculosis

TB - Tuberculosis

WHO – World Health Organization

XDR-TB – Extensively Drug-resistant Tuberculosis

1. Introduction

PubMed and Google Scholar searches were conducted regarding articles to include in the literature review. Key words such as prevalence, epidemiology, risk factors, extensively drug-resistant tuberculosis, drug-resistant tuberculosis, Africa, sub-Saharan Africa were used during the search. The search was not restricted to Humans and was done without any language restrictions. The aim of this literature review was to further an understanding of the prevalence of, and factors associate with, extensively drug-resistant tuberculosis (XDR-TB) in Africa.

2. Epidemiology of DR-TB

Drug-resistant tuberculosis (DR-TB), irrespective of the variety of different types of resistant profiles, is a global public health problem particularly in Africa (1). Extensively drug-resistant tuberculosis (XDR-TB) in particular is defined "*Mycobacterium tuberculosis* with resistance to at least isoniazid, rifampicin, any fluoroquinolone and any of the anti-tuberculosis injectable drugs (amikacin, capreomycin, and kanamycin)" (2).

DR-TB infection can either occur via primary or acquired transmission. Primary transmission occurs when the patients develops DR-TB by being infected with a drug-resistant strain. Acquired DR-TB occurs when a patient develops DR-TB during TB treatment (3,4). A particular mode of DR-TB mode of transmission (primary or acquired) can be confirmed through whole genome sequencing (5).

DR-TB can be transmitted through various transmission routes including community transmission, nosocomial transmission, inadequate treatment and contact with an infectious DR-TB patient (6). Previously inadequate XDR-TB treatment has been thought to be the major

risk factor to develop XDR-TB because most of the patients diagnosed with XDR-TB had a history of previous TB treatment (7). However, emerging evidence suggests that most XDR-TB infection could possibly be a result of primary transmission rather than infection from inadequate treatment (3). This implies that there is evidence to support the notion that XDR-TB could be a result of primary transmission.

DR-TB can be diagnosed through rapid testing. The GeneXpert MTB/ RIF diagnostic test is recommended by WHO as the diagnostic test for DR-TB (1). Resistance to rifampicin is used as indicator for multi drug-resistant tuberculosis (MDR-TB) (8). However, it is worth noting that there is no gold standard for evaluating drug resistance against anti-tuberculosis drugs (6). Patients thus testing as resistant to rifampicin should be subjected to further drug resistance testing to determine resistance to additional anti-tuberculosis drugs. Evaluation for extra drug resistance, against additional first and second-line anti-tuberculosis drugs in an attempt to diagnose DR-TB, can be done using tests such as a genotypic test called MTBDR*plus* (9).

Rapid diagnosis of DR-TB is significant in the control and prevention of TB (10). This is important because early diagnosis means that patients can be initiated on treatment, potentially preventing the spread of DR-TB (11). Adequate XDR-TB management entailing early diagnosis and treatment with the correct regimen is essential to preventing the transmission of XDR-TB (12)

Additional measures to prevent DR-TB include infection control, and adequate treatment for DR-TB cases. Currently there is no vaccine for the prevention of TB infection in adults. The existing TB vaccine (Bacille Calmette-Guerin) prevents severe forms of TB in children (1).

Thus a vaccine with a high efficacy rate is needed in order to help prevent the infection of TB in adults (13).

3. The burden of DR-TB

3.1. The global burden of DR-TB

The burden of tuberculosis remains high (1). In 2016, 123 countries reported at least one case of XDR-TB (1). Amongst the countries that recorded DR-TB cases, 91 countries stated the proportion of MDR-TB cases infected with XDR-TB (1).

Globally, at the end of 2016, the proportion of XDR-TB cases among MDR-TB cases was 6.2 % (95%CI 3.6-9.5%). In 2016 the proportion of XDR-TB was lower compared to previous years reported as 9.5%, 9.7% and 9.0% in 2015, 2014 and 2013 respectively (1). This indicates a slight decrease in the global burden of XDR-TB which could be attributed to early detection of MDR through increased diagnostic testing.

Globally, 600 000 new cases of rifampicin resistant tuberculosis (RR-TB) were detected in 2016, while 82% (490 000) of these cases had MDR-TB (1). The global incidence of MDR-TB/RR-TB is estimated to be 4.1% while this burden varies across WHO regions (1). The WHO Europe region has the highest MDR-TB/RR-TB burden at 19% compared to other regions; Africa 2.7%, South East-Asia 2.8%, the Americas 2.9%, Eastern Mediterranean 4.2% and Western pacific 5.3% (1). It is worth noting that WHO regions with a high incidence burden of MDR-TB/RR-TB also have a high incidence of MDR-TB/RR-TB among patients with a history of previous TB treatment (1). This suggests that most of the patients with DR-TB develop DR-TB while on treatment or they represent DR-TB cases that relapsed.

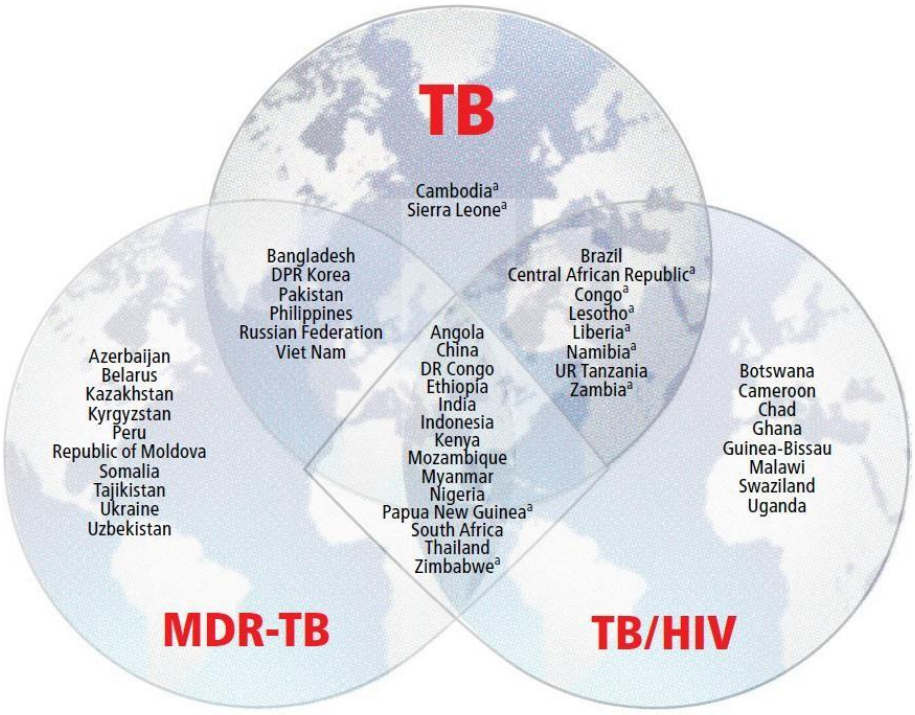
3.2. The burden of DR-TB in Africa

WHO defined three new TB High Burden Countries (HBC) categories, applicable globally to the period 2016 to 2020, namely: 1) TB HBC, 2) TB/HIV HBC and 3) MDR-TB HBC (1). Countries overlapping in all three categories could be considered as having a triple burden of TB disease. The MDR-TB category includes XDR-TB given that XDR-TB cases are mostly reported as part of the MDR-TB data (1). Globally 48 countries are categorised as HBC of which more than 50% (25/48) are in Africa (Figure 1).

Nine countries in Africa are categorised as MDR-TB HBC (Figure 1) of which 8, Angola, DR Congo, Ethiopia, Kenya, Mozambique, Nigeria and South Africa fall into the triple burden category (1). Somalia however, although considered a MDR-TB high burden country does not fall into the TB HBC category (Figure 1).

Globally 14 countries fall into the triple burden HBC category. In Africa, Angola, Democratic Republic of Congo, Ethiopia, Kenya, Mozambique, Nigeria, South Africa and Zimbabwe are listed in this category,

A total of 1092 XDR-TB cases were notified from the African region amongst the 8014 XDR-TB cases reported globally in 2016(1). WHO estimates the MDR-TB/RR-TB incidence among the 30 MDR-TB HBC in Sub-Sahara as; Mozambique 3.7%, Nigeria 4.3%, Somalia 8.7% and South Africa 3.4%. Furthermore, there is a high incidence of MDR-TB/RR-TB among patients with a history of previous tuberculosis treatment in African countries like Somalia 47%, Nigeria 25% (1).



DPR Korea, Democratic People's Republic of Korea; DR Congo, Democratic Republic of the Congo; HIV, human immunodeficiency virus; MDR, multidrug-resistant; TB, tuberculosis; UR Tanzania, United Republic of Tanzania; WHO, World Health Organization.

[a] Indicates countries that are included in the list of 30 high TB burden countries on the basis of the severity of their TB burden (i.e. TB incidence per 100 000 population), as opposed to the top 20, which are included on the basis of their absolute number of incident cases per year.

Figure 1: Countries as categorised into the three HBC categories being used by during the period 2016-2020 (1).

3.3. Prevalence of DR-TB in Africa

Available data regarding the prevalence of XDR-TB in Africa is limited. Albeit several studies (14–22) have been conducted in multiple settings in Africa to determine the prevalence of DR-TB, none of these studies reference XDR-TB. The reason why some of these studies could not identify XDR-TB is because drug susceptibility testing (DST) focused on first-line anti-tuberculosis drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) (14–16,22). A few studies have reported prevalence of XDR-TB as 5.9% in Burkina Faso (23), 4.9% in South Africa (24), while Lesotho and Mali respectively only reported XDR-TB cases but not the prevalence of XDR-TB (25,26). The true prevalence of XDR-TB in Africa is thus unknown as data on the prevalence of XDR-TB has not been systematically reviewed to establish the true burden of XDR-TB in Africa.

From 2006 to 2016, only 12 out of 54 countries in Sub-Saharan African have completed national TB prevalence surveys (1). These countries include Ethiopia, Nigeria, Gambia, Rwanda, United Republic of Tanzania, Malawi, Ghana, Sudan, Zambia, Zimbabwe, Kenya, and Uganda (1). This illustrates why there is limited data on the prevalence of XDR-TB in Africa. It is thus crucial for more countries in Africa to conduct prevalence surveys as this would provide data on the level of drug-resistance in Africa. Moreover, some research publications only report on MDR-TB and do no further stratify the XDR-TB cohort or state whether the MDR-TB cohort includes any XDR-TB case. This further hampers XDR-TB prevalence data in Africa.

Anti-tuberculosis drug-resistance susceptibility testing surveys provide data to ascertain the level of drug-resistance in each country (1). This is important especially in countries where not all TB patients receive routine DST for anti-TB drugs(1). The level of out-dated TB drug-resistance prevalence data in certain African countries is evident when considering that countries like Angola, Congo and Liberia have never carried out an anti-tuberculosis drug-resistant survey. Furthermore, Botswana, Zambia, and Mozambique last conducted anti-tuberculosis drug-resistant surveys in the 2005-2009 (1). Therefore, it would be beneficial if African countries regularly conduct drug-resistance surveys to ensure current anti-tuberculosis drug-resistance data.

In recent years, however, the number of countries which conducted anti-tuberculosis drug-resistance surveys has slightly increased. During 2015-2016, Burkina Faso, Ghana, and Zimbabwe completed anti-tuberculosis drug-resistance surveys for the first time (1). This increases available data regarding drug-resistance in Africa and inform healthcare drug-

resistant policies in Africa. The increase in number of countries conducting drug-resistance testing could be due to increased availability of TB/diagnostic equipment such as the Xpert MTB/RIF test. However, the reported prevalence of XDR-TB in Africa could still be an underestimation due to lack of laboratory capacity to conduct DST for second-line anti-tuberculosis drugs in countries in Africa (27). In cases where second-line DST was performed on MDR-TB cases DST only included testing for kanamycin and ofloxacin (17). This could potentially lead to the underdiagnosis of XDR-TB cases resulting in the underestimation of XDR-TB prevalence in Africa.

A study conducted in 8 countries in West Africa found that none of the isolates met the criteria for XDR-TB diagnosis. However, pre-extensively drug-resistant tuberculosis (Pre-XDR-TB) was detected among 21% of the MDR-TB population (20). Data from a genotyping surveillance study in Mozambique showed that XDR-TB was not detected in any of the isolates, however 7 out of 16 isolates were resistance to fluoroquinolones, indicating the presence of Pre-XDR-TB (27). The presence of Pre-XDR-TB in these studies highlights that there is a growing burden of Pre-XDR-TB that has potential to result in an increased burden of XDR-TB in Africa.

4. Factors associated with the prevalence of DR-TB

Several factors have been reported to be associated with the likelihood of XDR-TB in Africa. These factors include, but might not be to limited to; age, sex, sex, HIV status, history of previous TB treatment, hospitalization history, CD4 count, weight, smoking status and diabetes (3,28–30). These factors are typically reported as characteristics of patients diagnosed with XDR-TB and not as factors associated with the likelihood of a diagnosis with XDR-TB

(29). One study explicitly investigated the predictive factors related to XDR-TB (29). According to this study HIV status, history of previous TB treatment (treatment failure), and history of hospitalization for more than 14 days are independent factors associated with the diagnosis of XDR-TB (29).

4.1. Laboratory capacity

The lack of laboratory capacity in Africa to conduct DST for anti-tuberculosis second-line drugs result in samples sent abroad for DST analysis with subsequent delayed diagnosis of XDR-TB (26). Currently the WHO recommended Xpert MTB/RIF diagnostic test is the most used DR-TB diagnostic test worldwide including Africa (1). However this test can only detect resistance against Rifampicin, a first-line anti-tuberculosis drug (1). There is no rapid diagnostic test to detect TB resistance against second-line drugs within the same time frame as the Xpert MTB/RIF test. There is a need to improve access to accurate and rapid TB second-line anti-tuberculosis testing and thus diagnosis is important. This is emphasised in the End TB strategy as one of the objectives for strengthening laboratories (1).

Non-rapid laboratory tests, to detect resistance to second-line anti-tuberculosis drugs, like the BACTEC MGIT 960 SL DST kit and the GenoType MTBDRsl are currently used (31). The BACTEC MGIT 960 SL DST kit has a higher sensitivity, specificity and accuracy compared to the GenoType MTBDRsl (31) as evident from a systematic review (32). The GenoType MTBDRsl sensitivity in detecting kanamycin resistance is the lowest among second-line injectable drugs and one in three cases of XDR-TB could be missed (32). This suggests that used of the GenoType MTBDRsl test could potentially lead to underdiagnosis of XDR-TB which has a bearing on prevalence. A true and accurate diagnosis of XDR-TB is important as it enables us to know the true burden of XDR-TB in Africa.

The BACTEC MGIT 960 SL being the most accurate DST implies that it is a suitable test for detecting XDR-TB. Unfortunately, the GenoType MTBDRsl is not accessible via routine TB management in public health facilities (27). This leads us to the conclusion that the most accurate diagnostic tool is not accessible to public health facility users thus potentially contributing to the underdiagnosis of XDR-TB in Africa.

4.2. Nosocomial transmission

It is difficult to prove nosocomial transmission in low resource settings, as genome sequencings need to be carried out to confirm nosocomial transmission. Furthermore, it needs to be established that patients were not infected before they were admitted to the health facility and / or had no prior contact with a suspected index case. However, nosocomial transmission has been associated an XDR-TB outbreak in Kwa-Zulu Natal (33). Furthermore, nosocomial transmission of XDR-TB has been suspected as the route of infection of two cases XDR-TB, who shared a hospital room with an XDR-TB infected patient, in Mali (26).

Patients infected with XDR-TB are infectious for a longer period of time even after treatment has been initiated (12). This means that XDR-TB patients can spread the disease for longer period of time and thus putting their contacts at risk of contracting XDR-TB. It is crucial that people infected with XDR-TB are separated from the public for a lengthy period and if possible, until cured. The separation is important as it prevents the spread of XDR-TB from infected patients to their healthy contacts.

Various TB infection control measures can be applied to prevent the transmission of XDR-TB in health facilities (34,35). These measures can include; adequate ventilation in TB wards,

wearing of protective clothing and the involuntary detention and isolation of patients who refuse treatment (36).

4.3. Discharge into community

In certain instances patients who programmatically fail XDR-TB treatment are discharged back into the community due to limited bed capacity in designated tuberculosis treatment facilities (37). The discharged patients have potential to spread XDR-TB to their contacts in the community (37). The prevalence of XDR-TB is thus likely to increase within the communities in which XDR-TB patients reside (37).

The practice of discharging patients, who pragmatically failed treatment, into the society goes against the principle of preventing XDR-TB transmission by separating infectious patients from the TB healthy population. Recent evidence suggests that primary transmission of XDR-TB is high among XDR-TB infected patients. The majority, 69% (280 out of 404), of XDR-TB patients in KwaZulu-Natal, South Africa had no history of receiving MDR-TB treatment prior to diagnosis (3). This forewarns of XDR-TB primary transmission in the communities, of which some could have been caused by uncured patients who are discharged back into the community. Furthermore, household contacts of people infected with TB are at risk of developing TB and this risk can be as high as 10 times compared to those who were not contacts of TB patients (38). TB infection control needs to be implemented at household and community level to prevent the spread of XDR-TB from infectious patients to the healthy contacts.

4.4. Treatment failure

Inadequate treatment of MDR-TB is associated with the development of XDR-TB (3). An MDR patient from Mali, who developed additional resistance to fluoroquinolones, is suspected to have received inadequate treatment for a 6 months period which unsurprisingly resulted in the patient developing XDR-TB (26). Ensuring that there are sufficient drugs, including appropriate treatment, to treat XDR-TB cases with is very important because even when patients are diagnosed with XDR-TB but there the correct medication to treat them is not available, a timely diagnosis will have no significant impact on controlling XDR-TB (26).

4.5. HIV status

Patients, from South Africa, involved in the outbreak that brought XDR-TB to the global attention had a high rate of HIV/TB co-infection (39). However, this is expected since South Africa is burdened with HIV/TB co-infection (1). Twenty-three countries in Africa are categorised as TB/HIV HBC of which eight have a triple burden namely TB/HIV, MDR-TB and TB (Figure 1). However, Ethiopia although categorised as a triple burden country, has low HIV burden of 77.4% HIV seronegative TB/HIV co-infection among the DR-TB study cohort (40). Thereby correlation between HIV prevalence and HIV/TB co-infection within a population needs to be investigated.

4.6. Previous TB treatment

A history of previous TB treatment is associated with the likelihood of developing DR-TB (29,41). This is further supported by evidence from a study done in South Africa, where 95% of the patients infected with XDR-TB had a history of a previous diagnosis with MDR-TB (37). An Ethiopian case descriptive study found that 82.6% of drug-resistance cases were

previously treated for tuberculosis infection (40). This evidence suggests that a history of previous TB treatment is a factor associated with development of DR-TB.

4.7.Age

Current evidence suggest that XDR-TB infection is common among the age group range of 27 to 43, with a mean age of 34 (3,29,37).

5. The END TB strategy

The End TB strategy is grounded on three pillars: 1) integrated, patient care and prevention 2) bold policies and supportive systems and 3) intensified research and innovation (42). The strategy will provide TB management guideline programmes until December 2035 (43). Furthermore, the strategy envisions a world free of TB and free of mortality and morbidity related to TB (44). However this does not mean a notification of zero TB cases, but rather reduction of TB notification to less than 10/100 000 in the population and reducing TB related deaths by 95% (42).

The End TB strategy demands from all member countries to provide universal access to rifampicin DST for all TB cases; access to DST for injectable drugs and fluoroquinolone treatment for all TB cases with rifampicin resistance (1). Solving the TB burden in countries that account for the majority of the global TB burden is fundamental in achieving the global End TB strategy. This systematic review is a contribution to achieving the End TB Strategy goals through conducting research to determine prevalence, and factors associated with prevalence, regarding XDR-TB in Africa.

6. Conclusion

The lack of national anti-tuberculosis drug-resistance data contributes to the scarcity of DR-TB prevalence results in Africa. The ultimate difficulty is to ascertain the true drug-resistance prevalence in Africa, subsequently leading to misinformed healthcare policies due of unavailable and outdated data. A recent systematic review on the prevalence of drug-resistance in Sub-Saharan Africa highlighted the importance of having a review that includes XDR-TB prevalence in Africa (41). Systematic reviews and meta-analysis have been done on the association between DR-TB and various risk factors (41,45,46). However, none of these reviews provided results on the association between XDR-TB and known risk factors associated with DR-TB. This systematic review and meta-analysis anticipate filling the gap in research.

7. REFERNCES

1. World Health Organisation. Global Tuberculosis Report 2017. World Health Organization. 2017.
2. World Health Organisation. Definitions and reporting framework for tuberculosis – 2013 revision. 2014;
3. Shah NS, Auld SC, Brust JC, Mathema B, Ismail N, Moodley P, Mlisana K, Allana S, Campbell A, Mthiyane T MN. Transmission of Extensively Drug-Resistant Tuberculosis in South Africa. N Engl J Med. 2017;376(3):243–53.
4. Dheda K, McNerney R, Esmail A, Gumbo T, Pasipanodya JG, Maartens MMed G, et al. The Lancet Respiratory Medicine Commission The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir. 2017;5:291–360.
5. Cohen KA, Abeel T, Mcguire AM, Desjardins CA, Munsamy V, Shea TP, et al. Evolution of Extensively Drug-Resistant Tuberculosis over Four Decades: Whole Genome Sequencing and Dating Analysis of Mycobacterium tuberculosis Isolates from KwaZulu-Natal. PLoS Med. 2015;12(9).
6. Seung KJ, Keshavjee S, Rich ML. Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis. 2015;
7. Dheda K, Shean K, Badri M, Willcox FCP P, Padanilam MCFP X, Dziwiecki A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet. 2010;375:1798–807.
8. Dagnra AY, Mlaga KD, Adjoh K, Kadanga E, Disse K, Adekambi T. Prevalence of multidrug-resistant tuberculosis cases among HIV-positive and HIV-negative patients eligible for retreatment regimen in Togo using GeneXpert MTB/RIF. New Microbes New Infect. 2015;8:24–7.
9. Namburete EI, Tivane I, Lisboa M, Passeri M, Pocente R, Ferro JJ, et al. Drug-resistant tuberculosis in Central Mozambique: the role of a rapid genotypic susceptibility testing. BMC Infect Dis. 2016;16(423).
10. Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M DN. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Review). cochrane Libr. 2013;(1).
11. Rabna P, Ramos J, Ponce G, Sanca L, Mané M, Armada A, et al. Direct Detection by the Xpert MTB/RIF Assay and Characterization of Multi and Poly Drug-Resistant Tuberculosis in Guinea-Bissau, West Africa. PLoS One. 2015;10(5):e0127536.
12. Matteelli A, Roggi A, Cc Carvalho A. Extensively drug-resistant tuberculosis: epidemiology and management. Clin Epidemiol. 2014;6:11–118.
13. Manjelievskaia J, Erck D, Piracha S, Schrager L. Drug-resistant TB: deadly, costly and in need of a vaccine. Trans R Soc Trop Med Hyg. 2016;110:186–91.
14. Minime-Lingoupou F, Manirakiza A, Yango F, Zandanga G, Faou A Le, Rigouts L. Relatively low primary resistance to anti-tuberculosis drugs in Bangui and Bimbo, Central African Republic. Int J Tuberc Lung Dis. 2011;15(5):657–61.

15. Hamusse SD, Teshome D, Suaudi Hussen M, Demissie M, Lindtjørn B. Primary and secondary anti-tuberculosis drug resistance in Hitossa District of Arsi Zone, Oromia Regional State, Central Ethiopia. BMC Public Health. 2016;16:593.

16. Ndung W, Kariuki S, Ng 'ang ' Z, Revathi G, Ndung 'u W, Ng 'ang 'a Z. Resistance patterns of Mycobacterium tuberculosis isolates from pulmonary tuberculosis patients in Nairobi. J Infect Dev Ctries. 2012;6(1):33–9.

17. Lukoye D, Adatu F, Musisi K, Kasule GW, Were W, Odeke R, et al. Anti-Tuberculosis Drug Resistance among New and Previously Treated Sputum Smear-Positive Tuberculosis Patients in Uganda: Results of the First National Survey. PLoS One. 2013;8(8):e70763.

18. Tessema B, Beer J, Emmrich F, Sack U, Rodloff AC. First-and second-line anti-tuberculosis drug resistance in Northwest Ethiopia. Int J Tuberc Lung Dis. 2012;16(6):805–11.

19. Abubakar S. Hoza SGMM, Konig B. Anti-TB drug resistance in Tanga, Tanzania: A cross sectional facility-base prevalence among pulmonary TB patients. Asian Pac J Trop Med. 2015;8(11):907–13.

20. Gehre F, Otu J, Kendall L, Forson A, Kwara A, Kudzawu S, et al. The emerging threat of pre-extensively drug-resistant tuberculosis in West Africa: preparing for large-scale tuberculosis research and drug resistance surveillance. BMC Med. 2016;14(160).

21. Gudo PS, Cuna Z, Coelho E, Maungate S, Borroni E, Miotto P, Ahmadova S, Brouwer M, Migliori GB, Zignol M CD. Is MDR-TB on the rise in Mozambique? Results of a national drug resistance survey. Eur Respir J. 2011;38(1):222–4.

22. Lukoye D, Cobelens FGJ, Ezati N, Kirimunda S, Adatu FE, Lule JK, et al. Rates of Anti-Tuberculosis Drug Resistance in Kampala- Uganda Are Low and Not Associated with HIV Infection. PLoS One. 2011;6(1):e16130.

23. Saleri N, Badoum G, Ouedraogo M, Dembélé SM, Nacanabo R, Bonkoungou V, et al. Extensively Drug-Resistant Tuberculosis, Burkina Faso. Emerg Infect Dis. 2010;16(5):840–2.

24. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar S V, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779–87.

25. Hind Satti, Kwonjune Seung, Salmaan Keshavjee and JF. Extensively Drug-Resistant Tuberculosis, Lesotho. Emerg Infect Dis. 2008;14(6):992–3.

26. Diarra B, Toloba Y, Konate B, Sanogo M, Combo A, Togo G, et al. Extensively drug resistant tuberculosis in Mali: a case report. BMC Res Notes. 2017;10(1):561.

27. Namburete EI, Tivane I, Lisboa M, Passeri M, Pocente R, Ferro JJ, et al. Drug-resistant tuberculosis in Central Mozambique: the role of a rapid genotypic susceptibility testing. BMC Infect Dis. 2016;16(423).

28. Pietersen E, Ignatius E, Streicher EM, Mastrapa B, Padanilam X, Pooran A, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014;383(9924):1230–9.

29. Andrews JR, Shah NS, Weissman D, Moll AP, Friedland G, Gandhi NR. Predictors of

Multidrug-and Extensively Drug-Resistant Tuberculosis in a High HIV Prevalence Community. PLoS One. 2010;5(12):e15735.

30. Gandhi NR, Moll A, Sturm W, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368:1575–80.

31. Tekin K, Albay A, Simsek H, Sig AK, Guney M. Evaluation of the BACTEC MGIT 960 SL DST Kit and the GenoType MTBDRsl Test for Detecting Extensively Drugresistant Tuberculosis Cases. Eurasian J Med. 2017;49:183–7.

32. Theron G, Richardson PJ, Donegan BM, Warren R, Kr S, Dheda K. The diagnostic accuracy of the GenoType ® MTBDRsl assay for the detection of resistance to second-line anti-tuberculosis drugs (Review). Cochrane Database Syst Rev. 2014;(10).

33. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368(9547):1575–80.

34. Engelbrecht M, Janse Van Rensburg A, Kigozi G, Dingie H(, Van Rensburg). Factors associated with good TB infection control practices among primary healthcare workers in the Free State Province, South Africa. BMC Infect Dis. 2016;16(633).

35. Nathavitharana RR, Bond P, Dramowski A, Kotze K, Lederer P, Oxley I, et al. Agents of Change: The Role of Healthcare Workers in the Prevention of Nosocomial and Occupational Tuberculosis. Presse Med. 2017;46(2):53–62.

36. Basu S, Andrews J, Poolman EM, Gandhi NR, Shah NS, Moll A, et al. The Epidemic-level Impact of Preventing Nosocomial Transmission of Extensively Drug-Resistant (XDR) Tuberculosis in Rural South African District Hospitals. Lancet. 2007;370(9597):1500–7.

37. Pietersen E, Ignatius E, Streicher EM, Mastrapa B, Padanilam X, Pooran A, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014;383:1230–9.

38. Otero L, Shah L, Verdonck K, Battaglioli T, Brewer T, Gotuzzo E, et al. A prospective longitudinal study of tuberculosis among household contacts of smear-positive tuberculosis cases in Lima, Peru. BMC Infect Dis. 2016;16(259).

39. Gandhi NR, Moll A, Sturm W, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368(9547):1575–80.

40. Worku Y, Getinet T, Mohammed S, Yang Z. Drug-Resistant tuberculosis in Ethiopia: Characteristics of cases in a referral hospital and the implications. Int J Mycobacteriology. 2018;7(2):167–72.

41. Lukoye D, Ssengooba W, Musisi K, Kasule GW, Cobelens FGJ, Joloba M, et al. Variation and risk factors of drug resistant tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis. BMC Public Health. 2015;15(1):291.

42. World Health Organisation. The End TB Strategy. 2016.

43. Lö K, Raviglione M. The WHO's new End TB Strategy in the post-2015 era of the Sustainable Development Goals. Trans R Soc Trop Med Hyg. 2016;110:148–50.

44. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new End TB Strategy for WHO's Global TB Programme. Lancet. 2015;385:1799–801.

45. Berhan A, Berhan Y, Yizengaw D. A meta-analysis of drug resistant tuberculosis in Sub-Saharan Africa: how strongly associated with previous treatment and HIV co-infection? Ethiop J Health Sci. 2013;23(3):271–82.

46. Asgedom SW, Teweldemedhin M, Gebreyesus H. Prevalence of Multidrug-Resistant Tuberculosis and Associated Factors in Ethiopia : A Systematic Review. J Pathog. 2018;

PART C: JOURNAL MANUSCRIPT

List of abbreviations

DR-TB – Drug-resistant tuberculosis

DST – Drug Susceptibility Testing

MDR-TB – Multi drug-resistant Tuberculosis

MESH – Medical Subject Headings

PRISMA - preferred reporting items for systematic reviews and meta-analyses

TB – Tuberculosis

WHO – World Health Organization

XDR-TB – Extensively Drug-resistant Tuberculosis

Prevalence of, and factors associated with extensively drug-resistant tuberculosis in Africa: A systematic review and meta-analysis

Petrus Ndiiluka Kosmas[1], Elize Pietersen[2], Jabulani Ncayiyana[1], Mark Engel[2]

1. Department of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. Cape Town. South Africa

2. Department of Medicine, Faculty of Health Sciences, University of Cape Town. Cape Town. South Africa

Corresponding author

Petrus Kosmas

Email: ksmpet001@myuct.ac.za

ABSTRACT

Background: There is a dearth of information regarding prevalence of extensively drug-resistant tuberculosis (XDR-TB) in Africa. Although countries in Africa conduct national tuberculosis surveys on a regular basis, this information has not been systematically reviewed to ascertain the overall prevalence of XDR-TB in Africa.

Methods: The study aimed to perform a systematic review and meta-analysis of the prevalence and factors associated with prevalence of pulmonary XDR-TB among adults in Africa. Eligible studies, published between 2006 and 2018, were sourced from various electronic databases including PubMed, Scopus, and Web of Science. Meta-analysis was performed using STATA (version 14.2) statistical software. The protocol of this review was registered with PROSPERO, reg No CRD42018117037.

Result: A total of 6242 records were retrieved. Forty-eight studies were screened for eligibility and seven, which varied in terms of country setting and study design, were included. The prevalence of XDR-TB is 4% (95%CI 2-7) among participants tested for second-line anti-TB drug resistance, and 3% (95%1-6) among participants with drug resistant TB. The prevalence of XDR-TB was 7% (95%CI 1-18) among participants with MDR-TB. A few studies reported on the factors associated with the prevalence of XDR-TB.

Discussion: The reported prevalence of XDR-TB among participants tested for second-line anti-TB drug resistance is low compared to WHO estimates. The systematic review underscores a dearth of studies depicting the reality regarding the prevalence of XDR-TB in Africa. Policymakers and stakeholders interested in drug-resistant TB should apply prudence when considering XDR-TB prevalence reported for Africa.

Keywords: prevalence, tuberculosis, extensively drug-resistant tuberculosis, drug resistance, drug susceptibility testing

1. INTRODUCTION

Drug-resistant tuberculosis (DR-TB) continues to be a global public health burden. In 2016, the World Health Organization (WHO) estimated a global incidence of 600 000 drug-resistant TB cases, and extensively drug-resistant TB (XDR-TB) constituted 9.6% of the reported DR-TB cases (1). XDR-TB is defined as a disease caused by *Mycobacterium tuberculosis* with resistance to at least isoniazid and rifampicin, any fluoroquinolone, and at least one of three injectable anti-tuberculosis drugs (amikacin, capreomycin, or kanamycin) (2). To date, 123 countries have reported at least one case of XDR-TB compared to 92 in 2012, and 55 in 2008 respectively (3–5). Africa accounts for 13.6% of the global XDR-TB cases, with South Africa reporting the highest number (967 out of 1092) of those XDR-TB cases (1).

Available data on the prevalence of XDR-TB in Africa is limited. Although several studies (6–14) have been conducted in multiple settings in Africa to determine the prevalence of DR-TB, none of these studies reference XDR-TB. The reason why some of these studies could not identify XDR-TB is because DST focused on first-line anti-tuberculosis drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) (6–8,14). A few studies have reported prevalence of XDR-TB as 5.9% in Burkina Faso (15), 4.9% in South Africa (16), while Lesotho and Mali respectively only reported XDR-TB cases but not the prevalence of XDR-TB (17,18). The true prevalence of XDR-TB in Africa is thus unknown as data on the prevalence of XDR-TB has not been systematically reviewed to establish the true burden of XDR-TB in Africa.

Several factors have been reported to be associated with the likelihood of XDR-TB in Africa. These factors include, but might not be limited to; age, sex, sex, HIV status, history of previous TB treatment, hospitalization history, CD4 count, weight, smoking status and diabetes (19–22). These factors are typically reported as characteristics of patients diagnosed with XDR-TB

and not as factors associated with the likelihood of a diagnosis with XDR-TB (20). One study, that explicitly investigated predictive factors related to XDR-TB, reported HIV status, history of previous TB treatment (treatment failure), and history of hospitalization for more than 14 days as independent factors associated with the diagnosis of XDR-TB (20).

To date, there have been no published systematic review and or meta-analysis of the prevalence of XDR-TB in Africa. Systematic reviews and meta-analysis on the prevalence of MDR-TB rather than XDR-TB are reported (23,24). Prevalence rates are central to healthcare policy planning and hence the need to ascertain an exact prevalence rate of XDR-TB in Africa. Likewise, a meta-analysis of factors associated with the prevalence of XDR-TB in Africa will allow us to ascertain and assess the strength of association between associated factors of XDR-TB prevalence in an African context. The knowledge gained will not only further existing academic and clinical understanding of XDR-TB but will similarly enhance clinical management.

1.3. Objectives

1.3.1. Primary objective

- To assess the prevalence of XDR-TB amongst participants tested for second-line anti-tuberculosis drug resistance in Africa.

1.3.2. Secondary objectives

- To assess the prevalence of XDR-TB amongst participants with resistance to at least one anti-TB drug
- To assess the prevalence of XDR-TB amongst participants with MDR-TB
- To assess the prevalence of XDR-TB amongst participants with resistance to at least one second-line anti-TB drug
- To assess the factors associated with the prevalence of XDR-TB in Africa.

2. METHODS

The protocol of this systematic review and meta-analysis has been registered with the PROSPERO International Prospective Register of systematic reviews. Registration number CRD42018117037.

2.1. Inclusion criteria

2.1.1. Types of studies

Observational studies, cross-sectional studies, cross-sectional surveys, population-based studies and cohort studies were included in this review.

2.1.2. Types of participants

This review included studies reporting laboratory confirmed pulmonary XDR-TB in adults (15 years and older), irrespective of gender and socio-economic backgrounds. Studies were eligible for inclusion if XDR-TB diagnosis was reported based on ay WHO recommended laboratory procedures for first line and second line drug resistance testing(25,26). Studies reported patients suspected to have TB were also included. There was no comparison group.

2.1.3. Study setting

This review included studies conducted in Africa. The following countries were included ; Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo (Brazzaville), Congo (Democratic Republic), Cote d'Ivoire, Djibouti, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea- Bissau, Kenya, Lesotho, Libya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Mozambique, Namibia, Niger, Nigeria, Reunion, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan,

South Sudan, Swaziland, Tanzania, Togo, Tunisia, Uganda, Western Sahara, Zambia, and Zimbabwe (Appendix 1).

2.2. Exclusion criteria

- XDR-TB prevalence is not explicitly reported (results are inextricable including other types of DR-TB cases)
- Studies including children, and the results do not differentiate between adults and children
- Studies using study designs other than those mentioned in inclusion criteria study design
- Studies that did not identify/ diagnose/ report on XDR-TB
- Studies not conducted in Africa
- Studies not reporting the age range of included participants
- Studies including participants with extra pulmonary TB
- Studies whose full-text was not accessible
- Studies conducted in multi-country and the results are not stratified per country setting of study
- Studies published outside the review period
- Studies reporting the prevalence without stating the actual proportion of XDR-TB cases diagnose

2.3. Outcome measurements and definition of terms.

- XDR-TB - as determined by WHO recommended laboratory diagnostic tests (25,26)
- DR-TB - refers to *Mtb* that is resistant to at least one anti-TB drug
- MDR-TB – refers to *Mtb* that is resistant to both isoniazid and rifampicin.

- Second-line resistance - refers to *Mtb* that is resistant to at least one second-line anti-TB drug

2.4. Search strategy

We conducted an extensive search of the literature to identify studies relevant to this systematic review. The search has an English language limit and time limit for the period 1 January 2006 up to 31 July 2018. Moreover, we examined the list of references of included study articles to identify additional study articles.

The following keywords were used during the search of articles; tuberculosis, drug resistant tuberculosis, multi drug resistant tuberculosis, extensively drug resistant tuberculosis, XDR tuberculosis, MDR tuberculosis, XDR TB, MDR TB, mycobacterium tuberculosis, prevalence, proportion, rate, statistic, epidemiology, epidemiological, frequency, Africa, risk, associated, association, associations, predict, predictor, prediction, predictors, probability, correlation, determinant.

Our search strategy was developed in PubMed using both medical subject headings (MESH) and free text (Appendix 2). The search strategy was subsequently then adapted to search for studies in other electronic databases.

2.5. Data sources

The electronic databases were searched from 18 September 2018 until 26 September 2018 and included; PubMed/ Medline, Scopus, Web of Science (excluding PubMed/ Medline and zoological records), PyscINFO, Africa-wide Allied Health, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Health Source: Nursing Academic, grey literature and google scholar. Africa-Wide Allied Health, CINHAL, and Health Source: Nursing

Academic databases were accessed through EBSCOhost electronic database. Grey literature was sourced from the Open UCT electronic database, WHO global tuberculosis reports from 2007 to 2018, Google Scholar and screening of reference lists.

A total of 7409 records were retrieved from different electronic databases. The 6242 eligibility records that remained, after duplicate records were removed, were accounted for by various databases; Africa- Wide Allied Health 2200, CINHAL 111, Cochrane Central 636, Health source; Nursing Academic 138, PubMed/ Medline 2307, PsycINFO 27, Scopus 414, Web of Science 409 (Table 1).

Table 1: Records retrieved from various electronic databases

Electronic databases searched	Number of records retrieved	Number of records remaining after duplicates records were removed
Africa- Wide Allied Health	2473	2200
CINHAL	207	111
Cochrane Central	714	636
Health source; Nursing Academic	219	138
PubMed/ Medline	3266	2307
PsycINFO	42	27
Scopus	448	414
Web of science	440	409
Total	**7409**	**6242**

2.6. Study selection

One author screened all the titles and abstracts of the identified study records. Two authors then read the headings and abstracts of the initially included articles with the purpose of

selecting potential eligible studies. Full text articles were independently reviewed by two authors (PK and EP). A third author (JN) was consulted regarding any disagreement or uncertainties regarding the inclusion or exclusion of articles into this review.

Data extraction and management

Two authors (PK and EP) independently extracted data from full text of eligible articles was using a standardized data extraction form (Appendix 3). The data extraction was piloted and modified to enhance the robustness of the data being extracted.

The following study characteristic were extracted; country of study, study design, condition of interest, study duration, diagnostic criteria, study population, age range of participants, data sources, sample size, and outcome measures. Each study contributed one outcome measure of interests. In case on missing data, corresponding or first authors of published articles were contacted to provide further details.

A third author (JN) was consulted whenever there was an uncertainty regarding the data extracted.

Assessment of risk of bias in included studies

The quality of included studies was assessed using the quality assessment tool developed by Hoy et al. 2012, and modified by Werfali et al. 2014 (27,28). The prevalence study quality appraisal tool categorises studies into three groups; 0-5 points as high-risk studies, 6-8 points as moderate risk studies, and >8 as low risk studies (Table 2). The Newcastle-Ottawa appraisal tool was be used to appraise cohort studies included in this review (29,30). The Newcastle-Ottawa appraisal tool was modified to suit use for this review.

The first author assessed the quality of all included studies. The second author validated the quality appraisal script of the included studies script. Disagreement on the quality scores was resolved by unanimity between the two authors.

Table 2. Assessment criteria for prevalence studies

Items	**Quality score**
External validity	
1. Was the study's target population a close representation of the national population in relation to relevant variables?	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of non-response bias minimal?	(1 point)
	Total (4 points)
Internal validity	
1. Were data collected directly from the participants (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all participants?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
	Total (6 points)
Summary item on the overall risk of study bias	
Overall score Quality	
>8 points Low Risk: Further research is unlikely to change our confidence in the estimate 6-8 points Moderate Risk: further research is likely to have an important impact on our confidence in the estimate and may change the estimate 0-5 points High Risk: Further research is very likely to have an important impact on or confidence in the estimate and is likely to change the estimate	

*Quality assessment tool as developed Hoy et al. (27) and modified by Werfali et al. 2014 (28).

2.7. Statistical methods, heterogeneity and analysis

The statistical software Stata version 14.2 was used to carry out the meta-analysis. The user-written *metaprop* command was used to calculate the prevalence of XDR-TB among participants groups of interest (31). An application of random effect (random) command was used to take into account the heterogeneity of the included studies. We used the Freeman-Tukey Double Arcsine Transformation (*ftt*) method to stabilize the variances (31). The 95% confidence interval was used to provide a range of the estimated prevalence.

Statistical heterogeneity of the included studies was assessed using the Chi-squared test of homogeneity. Chi-squared results were considered statistically significant at alpha level 0.10 (32). Statistical heterogeneity was further assessed using the I^2statistic. The I^2 squared statistic results are reported as a percentage value (32). During the meta-analysis process, studies were subgrouped according to their study setting. Studies were further grouped according to their MDR-TB HBC status when we assessed the prevalence of XDR-TB among countries categorised as MDR-TB HBC. Study authors were contacted via the provided email of the corresponding author to request for additional information and clarity on the reported study information.

3. RESULTS

3.1. Literature search

The screening of study records is reported using the Preferred reporting Items for Systematic Reviews and Meta-analysis (PRISMA) format (33) (Appendix 4).

A total of 7409 records were retrieved from all the identified databases. EndNote version X9 referencing software was used to remove 1167 duplicates. Tittle and abstracts of 6242 articles were screened for potential eligibility resulting in excluding 6194. Forty-eight (48) full-text articles were screened for eligibility and 7 studies met the inclusion criteria (Figure 1).

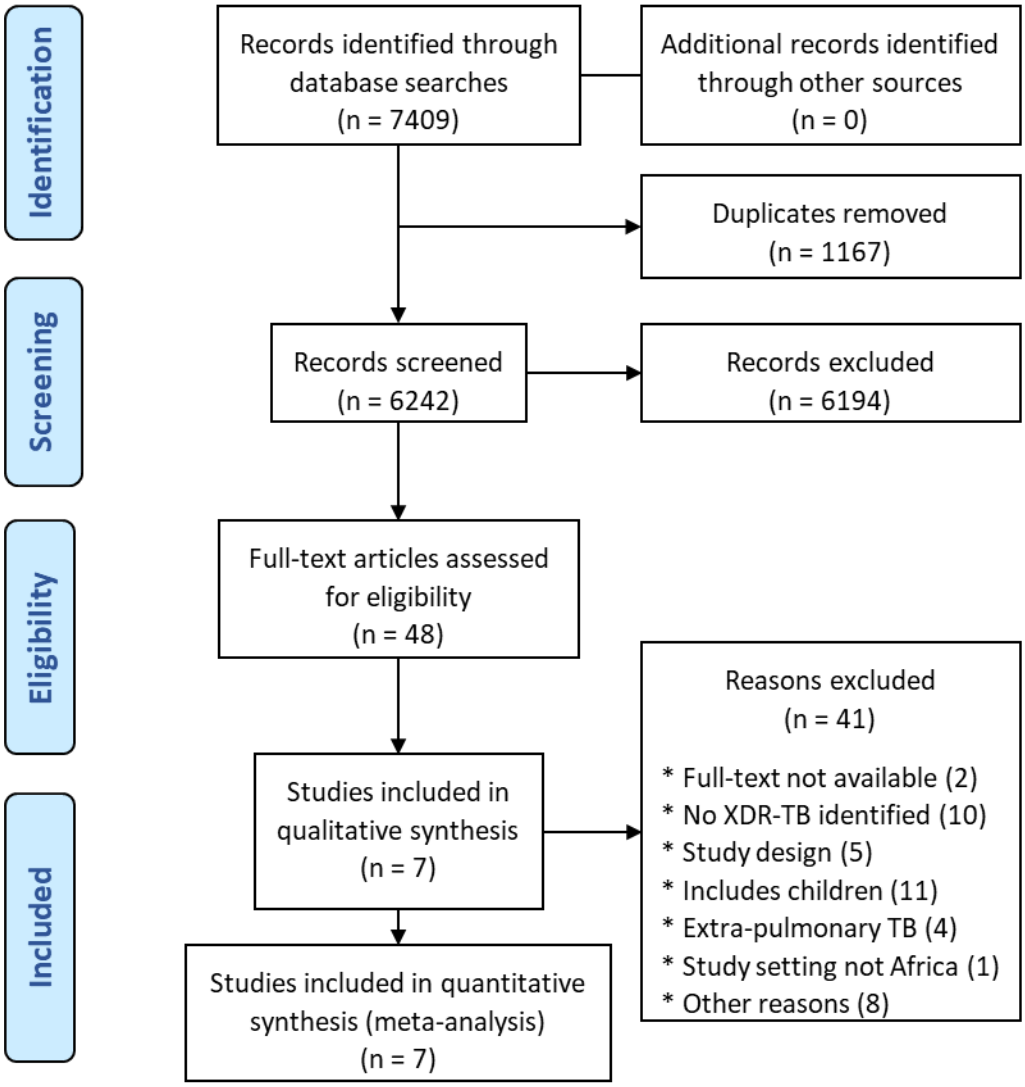


Figure 1: PRISMA flow diagram process followed to include articles eligible to review regarding XDR-TB prevalence in Africa

3.2. Characteristics of studies

This review includes 7 studies, published from 2008 to 2018 (Table 3). Three studies were conducted in South Africa (34–36), one in multiple countries including South Africa (37), and one each in Swaziland, Uganda, and Morocco (38–40). All studies included participants older than 14 years. Only two studies (38,39) were conducted on a national level. The characteristics of the excluded studies are summarised in Table 4.

Table 3: The characteristics of studies included in the systematic review of XDR-TB prevalence in Africa

Study ID	Study duration	Country of study	Study design	Study population	No of participants with TB	No of XDR-TB	DST method	Drugs tested for resistance
Bantubani 2014 (34)	Phase 1: August 2007-August 2009 Phase 2: August 2008 – November 2009	South Africa	Cross-sectional study Subnational study Conducted in Hospitals in Kwa-Zulu Natal	Adult inpatients reporting "coughing" >18 years Age median 37 (30-48)	543	16	Middlebrook 7H11 selective agar (Difco) and liquid medium (BACTEC MGIT 960, Becton Dickenson Diagnostics)	INH, RMP, SM, EMB,ETH, OFX, KAN, CPM
Cox 2010 (35)	May 2008 – November 2008	South Africa	Cross-sectional survey Subnational survey Conducted in two primary care clinics in Khayelitsha, Cape Town	Clinic attendees suspected for pulmonary tuberculosis Not currently on treatment > 18 years	535	2	BACTEC MGIT 960 system, Hain GenoType MTBDRplus, Ziehl-Neelsen staining and p- nitrobenzoic acid testing	INH, RMP, SM, EMB, PZA, ETH, OFX, KAN, CPM, AMK

Dalton 2012 (36)	January 2005 – December 2008	Multi-country including South Africa	Population based study Subnational study Conducted in four provinces of South Africa (Eastern Cape, KwaZulu Natal, Mpumalanga, and Northwest	Adults within the catchment areas with locally confirmed, pulmonary MDR-TB who started treatment with second-line drugs >18 years	293	31	Middlebrook 7H10 agar (BD)	INH, RMP, SM, EMB, ETH, OFX, KAN, CPM, AMK, CPX, amino salicylic acid
Ennassiri, 2017 (38)	2015	Morocco	Cohort study National	MDR-TB patients amongst suspected DR-TB patients whose strain were sent to NTRL in the National Institute of Hygiene (NIH) (Rabat, Morocco) Age range 15-72 years	155	4	Lowenstein– Jensen (LJ) medium	INH, RMP, EMB, SM, OFX, KAN, AMK
Jacobson 2017 (37)	November 2012 - December 2013	South Africa	Prospective observational study Conducted in 3 provinces	Adults diagnosed with RIF-resistant MTB by Expert ≥18 years)	497	6	MTB/RIF (Xpert; Cepheid, California), MTBDRplus LPA (version 2), BACTEC MGIT 960 system culture (BD Diagnostics Systems, Maryland)	INH, RMP, PZA, ETH, OFX, KAN, AMK

			(Eastern Cape, Gauteng, and Free State)					
Sanchez-Padilla 2012 (39)	May 2009 - February 2010	Swaziland (Now known as Eswatini)	Cross-sectional survey National survey	Consecutive smear-positive patients who were given a new diagnosis of TB >14 years of age Age median 33 (27-41)	658	1	BACTEC MGIT 960 system (Becton Dickinson) , Löwenstein-Jensen and Stonebrink, GenoType MTBC test (HAIN Lifescience GmbH, Nehren, Germany)	INH, RMP, SM, EMB, PZA, ETH, OFX, CPM, AMK, MOX, 4-aminosalicylic acid
Temple 2008 (40)	July 2003 – November 2006	Uganda	Cohort study Subnational study NTLP clinic Mulonga Hospital in Kampala	Consecutive treatment-experienced patients with TB >18 years	410	1	BACTEC 460, BACTEC MGIT 960, Middle Brook 7H10 agar	INH, RMP, SM, EMB, PZA, ETH, OFX, KAN, CPM, para-amino salicylic acid

Abbreviations; TB= tuberculosis, NIH= National Institute of Hygiene, NTLP=National Tuberculosis and Leprosy Programme, DST= drug susceptibility testing, DS-TB=drug susceptible tuberculosis, DR-TB= drug-resistant tuberculosis, INH=Isoniazid, RMP=rifampicin, SM=streptomycin, EMB= ethambutol, PZA= pyrazinamide, ETH= ethionamide, OFX= Ofloxacin, KAN= kanamycin, CPM = Capreomycin, AMK= Amikacin, MOX= moxifloxacin, CPX= ciprofloxacin

Table 4: Characteristics of excluded studies

Author	Study tittle	Reason for exclusion
XDR-TB diagnosis		
Meriki 2013	Drug Resistance Profiles of Mycobacterium tuberculosis Complex and Factors Associated with Drug Resistance in the Northwest and Southwest Regions of Cameroon	No case of XDR-TB was detected
Diarra 2016	Tuberculosis drug resistance in Bamako, Mali, from 2006 to 2014	
Hoza 2015	Anti-TB drug resistance in Tanga, Tanzania: A cross sectional facility-base prevalence among pulmonary TB patients	
Lukoye 2013	Anti-Tuberculosis Drug Resistance among New and Previously Treated Sputum Smear-Positive Tuberculosis Patients in Uganda: Results of the First National Survey	
Lukoye 2011	Rates of Anti-Tuberculosis Drug Resistance in Kampala- Uganda Are Low and Not Associated with HIV Infection	
Kapata 2017	Outcomes of multidrug-resistant tuberculosis in Zambia: a cohort analysis	
Kaswa 2014	Pseudo-Outbreak of Pre-Extensively Drug-Resistant (Pre-XDR) Tuberculosis in Kinshasa: Collateral Damage Caused by False Detection of Fluoroquinolone Resistance by GenoType MTBDRsl	
Umubyeyi 2008	Low levels of second-line drug resistance among multidrug-resistant Mycobacterium tuberculosis isolates from Rwanda	

Ibrahim 2017	Pattern of prevalence, risk factors and treatment outcomes among Egyptian patients with multidrug resistant tuberculosis	
Veldsman 2009	The prevalence of isoniazid and rifampicin resistance of *Mycobacterium tuberculosis*	
Study includes children		
Bhembe 2014	Molecular detection and characterization of resistant genes in Mycobacterium tuberculosis complex from DNA isolated from tuberculosis patients in the Eastern Cape province South Africa	Results included age group <20 years.
Agonafir 2010	Phenotypic and genotypic analysis of multidrug-resistant tuberculosis in Ethiopia	Included participants aged 10-75 years. Results did not differentiate children.
Osei-Wusu 2018	Second-line anti-tuberculosis drug resistance testing in Ghana identifies the first extensively drug-resistant tuberculosis case	Minimum age of participants was 13 years.
Schnippel 2015	Predictors of mortality and treatment success during treatment for rifampicin-resistant tuberculosis within the South African National TB Programme, 2009 to 2011: a cohort analysis of the national case register	Results included <15year age group.
Avalos 2015	Prevalence and Risk Factors of Drug Resistant Mycobacterium Tuberculosis in a Multisite Cohort Study	Included patients of at least 5 years of age.

Said 2012	Molecular characterization and second-line anti-TB drug-resistance patterns of multidrug resistant tuberculosis isolates from the northern region of South Africa	Included participants aged 6 to 69 years. Results do not differentiate children
Calver 2010	Emergence of Increased Resistance Tuberculosis Despite Treatment and Extensively Drug-Resistant Adherence, South Africa	Assumed included children ("All mine employees and dependents with drug-resistant TB" were included in the study)
Loveday 2017	Drug-resistant tuberculosis in patients with minimal symptoms: favorable outcomes in the absence of treatment	Included participants aged 14 years.
Gadallah 2015	Prognostic factors of treatment among patients with multidrug-resistant tuberculosis in Egypt	Included participants aged 7 to 76 years. Results do not differentiate children
Seung 2009	Early Outcomes of MDR-TB Treatment in a High HIV- Prevalence Setting in Southern Africa	Included participants aged 3-62.Results do not differentiate children
Schnippel 2016	Severe adverse events during second-line tuberculosis treatment in the context of high HIV Co-infection in South Africa: a retrospective cohort study	Included participants <15 years
Study design		
Andrews 2010	Predictors of Multidrug- and Extensively Drug-Resistant Tuberculosis in a High HIV Prevalence Community	Case-control study

Gandhi 2010	HIV Coinfection in Multidrug- and Extensively Drug-Resistant Tuberculosis Results in High Early Mortality	XDR-TB diagnosis already known at enrolment into the study
O'Donell 2011	Extensively drug-resistant Tuberculosis in Women,KwaZulu-Natal, South Africa	Case-control study
Millan-Lou 2016	Mycobacterial diversity causing multi- and extensively drug- resistant tuberculosis in Djibouti, Horn of Africa	Genotypic lineage study
Van der Plas 2011	High prevalence of comorbidity and need for up-referral among inpatients at a district-level hospital with specialist tuberculosis services in South Africa – the need for specialist support	Cross-sectional hospital based study interrogating typical patient types, including co-morbidities. No diagnostic tests carried out.
Age range of participants not stated		
Gandhi 2006	Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa	Age range not stated. Age range cannot be implied from results.
Olle-Goig 2011	Resistance to anti-tuberculosis medications in the Horn of Africa	
Moodley 2011	Spread of Extensively Drug-Resistant Tuberculosis in KwaZulu-Natal Province, South Africa	
Saleri 2010	Extensively Drug-Resistant Tuberculosis in Burkina Faso	
Mlambo 2008	Genotypic diversity of extensively drug-resistant tuberculosis (XDR-TB) in South Africa	
Results include extra-pulmonary TB cases		
Shin 2017	High Treatment Success Rates Among HIV-Infected Multidrug-Resistant Tuberculosis Patients After Expansion of Antiretroviral Therapy in Botswana, 2006–2013	

Evans 2017	Treatment initiation among persons diagnosed with drug resistant tuberculosis in Johannesburg, South Africa	
Loveday 2012	Comparing early treatment outcomes of MDR-TB in decentralised and centralised settings in KwaZulu-Natal, South Africa	Results include extra-pulmonary TB
Chingonzoh 2018	Risk factors for mortality among adults registered on the routine drug resistant tuberculosis reporting database in the Eastern Cape Province, South Africa, 2011 to 2013	Specimen type not stated. Results could include extra-pulmonary TB
Full text not available		
Allanana 2012	Prevalence of mycobacterium tuberculosis infection among Jos prison inmates and comparison three diagnostic methods	
Sanogo 2017	Acquisition of proper treatment for Extensively Drug Resistant tuberculosis patients in Mali: Where is the issue?	Full text not available
Multi-country studies with un-stratified results		
Bastard 2018	Outcomes of HIV-infected versus HIV-non- infected patients treated for drug-resistance tuberculosis: Multicenter cohort study	Multiple country study. Results not stratified per country included in study.
Cegielski 2014	Extensive Drug Resistance Acquired During Treatment of Multidrug-Resistant Tuberculosis	
Non-African study setting		
Batbold 2017	Double-blind, placebo-controlled, 1:1 randomized Phase III clinical trial of Immunoxel honey lozenges as an adjunct immunotherapy in 269 patients with pulmonary tuberculosis	Study conducted in Ukraine and Mongolia

Study reports estimates		
Ismail 2018	Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey	Estimates reported versus actual number of XDR-TB cases detected.

3.3. Assessment of risk of bias in included studies

The quality of cross-sectional studies, cross-sectional surveys and population based studies were assessed using an quality assessment tool by Hoy et al. 2012 (27) as adapted by Wefarli et al. 2014 (28) (Table 5). Most of the articles were of moderate risk; one study was considered as low risk (34) and none were of high risk. Three studies (35,36,39) did not state the sampling method used and three (34,37,38) had a high risk of non-response bias, since the response rate was less than 75% in these studies. All studies collected data from the patients directly. The case definition of XDR-TB was determined before the commencement of the studies.

Table 5: Assessing risk of bias in included studies

Study ID	External validity				Internal validity						Quality score	Risk of bias
	A1	A2	A3	A4	B1	B2	B3	B4	B5	B6		
Bantubani 2014 (68)	1	1	1	0	1	1	1	1	1	1	9	Low
Cox 2010 (35)	1	0	UN	1	1	1	1	1	1	1	8	Moderate
Dalton 2012 (36)	0	1	UN	1	1	1	1	1	1	1	8	Moderate
Ennassiri, 2017 (38)	1	1	1	0	1	1	1	UN	UN	1	7	Moderate
Jacobson 2017 (37)	1	1	UN	0	1	1	1	1	1	1	8	Moderate
Sanchez-Padilla 2012 (39)	1	1	UN	1	1	1	1	1	UN	1	8	Moderate
EXTERNAL VALIDITY: A1, Representative of the target population; A2, Appropriate recruitment of the participants, A3 Appropriate sampling frame, A4 Minimal non-response bias INTERNAL VALIDITY:B1 Data collected directly from the subjects (as opposed to a proxy), B2 Acceptable case definition, B3 valid and reliable study instrument, B4 same mode of data collection used for all subjects, B5 Appropriate shortest prevalence period for the parameter of interest, B6 Appropriate numerator(s) and denominator(s) for the parameter of interest. SCORE: 1 indicates the study met the criteria; 0 indicates the study did not meet the criteria, UN indicates the response was unclear.											
INTERPRETATION Quality score**:** 0-5 high risk of bias; 6-8 moderate risk of bias; >8 Low risk of bias												

Cohort studies were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control studies (41) (Table 6). The only study with a cohort study design (40) had a high-risk quality score as there was no control or comparison group. XDR-TB cases were already diagnosed at enrolment, not during the study.

Table 6: Assessment of risk of bias for cohort studies

Study ID	Selection				Comparability	Outcome			Quality score (per study)	Risk of bias
	A1	A2	A3	A4	B1	C1	C2	C3		
Temple 2008 (40)	0	0	1	UN	0	1	1	0	3	High
A. SELEECTION OF THE STUDY GROUPS (A1 Representativeness of the exposed cohort, A2 selection of the non-exposed cohort, A3 ascertainment of exposure, A4 Demonstration that outcome of interest was not present at the start of the study); B. Comparability (B1 comparability of the cohorts on the basis of the design and analysis) C. Outcome ascertainment of the exposure (C1 Assessment of outcome C2 Was follow-up long enough for outcome to occur C3 Adequacy of follow up of cohorts)										
Quality score: 0-5 High risk of bias, 6-8 Low risk of bias										

3.4. Synthesis of results

3.4.1. Prevalence of XDR-TB in Africa

All seven studies reported on the proportion of XDR-TB cases among the study population. Studies differed regarding study design, study population and reporting format necessitating subgroup analysis of the studies included in the quantitative analysis of XDR-TB prevalence in Africa.

The size of cohorts, diagnosed with pulmonary TB, in the 7 studies ranged from 155 – 658 adults (Table 7). The proportion of individuals diagnosed with DS-TB (34,35,39) is not

reflected in Table 7 as the objective of the systematic review was to determine the prevalence of XDR-TB.

Six (6) studies reported the number of participants, as ranging from 104 to 497 per study, with resistance to any first- and / or second-line anti-tuberculosis drug. Six (6) studies reported the number of participants with MDR-TB, which ranged from 18 to 155 per study (Table 7).

All 7 studies conducted second-line anti-tuberculosis DST on a total of 1243 participants, a range of 51 to 472 patients per study. However, only four (4) studies (35,37–39) reported results indicating resistance to any second-line anti-TB drug. A range of 8 – 98 individuals, per study, were resistant to any second-line anti-tuberculosis drugs (Table 7).

All studies reported on the number of XDR-TB participants, ranging from 1 – 31 per study (Table 7). A total of 61 XDR-TB patients were identified among 1243 participants who were tested for second-line anti-tuberculosis drug resistance.

Table 7: Comparison of XDR-TB prevalence among various TB cohorts based on second-line anti-TB drug resistance testing.

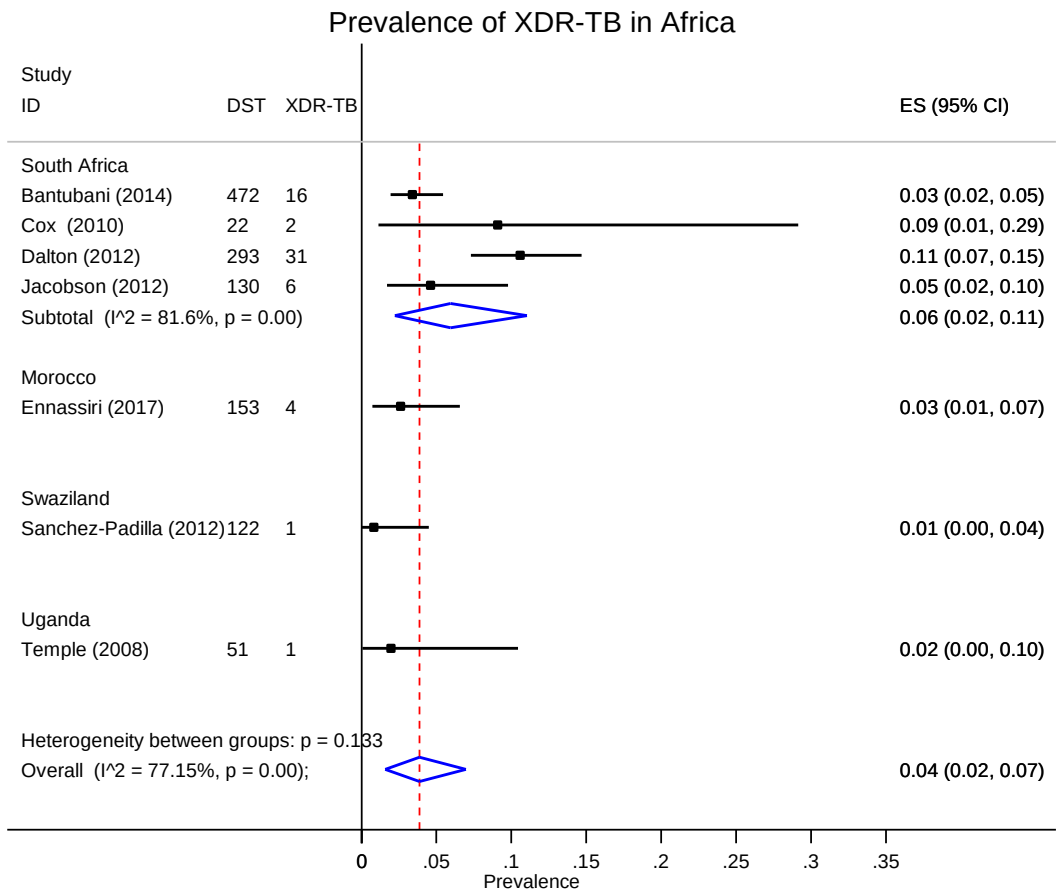
Study ID	Study year	Country	Study design description	Study population description	Participants with TB	Participants with drug resistant TB resistant to any (first and/or second-line) anti-TB drug	No of participants with MDR-TB	Participants tested for resistance to second-line anti-TB drugs	Participants resistant to second-line anti-TB drugs	No of participants with XDR-TB
Bantubani 2014 (34)	2007-2009	South Africa	Cross-sectional study Subnational study Conducted in Hospitals in Kwa-Zulu Natal	Adult inpatients reporting "coughing" >18 years Age median 37 (30-48)	543	104	84	472	Not stated	16
Cox 2010 (35)	2008	South Africa	Cross-sectional survey Subnational survey Conducted in two large primary care clinics in Khayelitsha, Cape Town	Clinic attendees suspected of pulmonary tuberculosis Not currently on treatment > 18 years	535	105	18	22	8	2
Dalton 2012 (36)	2005 - 2008	Multi-country including South Africa	Population based study Subnational study Conducted in four provinces of South Africa (Eastern Cape, KwaZulu Natal,	Adults within the catchment areas including locally confirmed, pulmonary MDR-TB who started treatment with second-line drugs >18 years	293	Not stated	142	293	Not stated	31

			Mpumalanga, and Northwest)							
Ennassiri, 2017 (38)	2015	Morocco	Cohort study National	MDR-TB patients amongst suspected DR-TB patients whose strain were sent to National Tuberculosis Reference Laboratory (NTRL) in the National Institute of Hygiene (NIH) (Rabat, Morocco) Age range 15-72 years	155	155	155	153	22	4
Jacobson 2017 (37)	2012 -2013	South Africa	Prospective observational study Conducted in 3 provinces (Eastern Cape, Gauteng, and Free State)	Adults diagnosed with RIF-resistant MTB by Xpert ≥18 years)	497	497	Not stated	130	98	6
Sanchez-Padilla 2012 (39)	2009 - 2010	Eswatini (formerly Swaziland)	Cross-sectional survey National survey	Consecutive smear-positive patients who were given a new diagnosis of TB >14 years of age Age median 33 (27-41)	658	193	122	122	72	1

Temple 2008 (40)	2003 – 2006	Uganda	Cohort study Subnational NTLP clinic Mulonga Hospital in Kampala	Consecutive treatment-experienced patients with TB >18 years	410	115	52	51	Not stated	1
Note: No of participants with TB= refers to participants diagnosed with pulmonary mycobacterium tuberculosis No of participants with resistant to any (first- and/or second-line) anti-TB drug= refers to participants who are resistant to at least one anti-TB drug No of participants with MDR-TB= refers to participants who are diagnosed with MDR-TB No of participants with second-line resistance= refers to participants who are resistant to at least one second-line anti-TB drug No of participants with XDR-TB= refers to participants diagnosed with XDR-TB										
Abbreviations; TB= tuberculosis, DST= drug susceptibility testing, DR-TB=drug-resistant tuberculosis, MDR-TB= multi drug-resistant tuberculosis, XDR-TB= extensively drug-resistant tuberculosis										

3.4.2. Prevalence of XDR-TB amongst participants tested for second-line anti-TB drug resistance

The pooled prevalence of XDR-TB in those tested for second-line anti-TB drug resistance is 4% [95% Confidence Interval (CI), 2% to 7%; n=1243 adults; I^2 = 77.15%] (Figure 2). By country, South Africa had the highest prevalence at 6% (95% CI, 2% to 11%; n=972; I^2 = 81.6%).

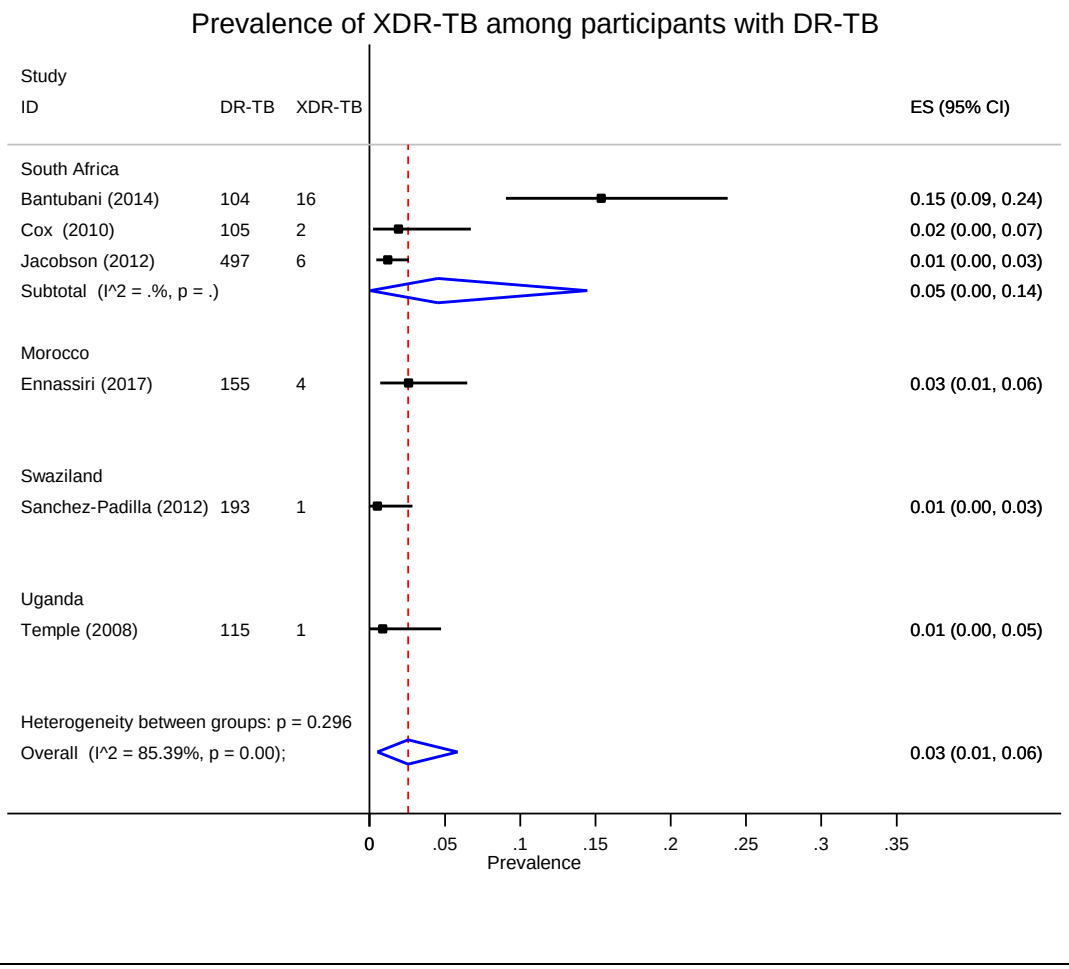


ES= estimated prevalence, CI=confidence interval, MDR-TB =multi drug-resistant tuberculosis, XDR-TB = extensively drug-resistant tuberculosis

Figure 2: Subgroup analysis of the prevalence of XDR-TB amongst participants tested for second-line anti-TB drug resistance.

3.4.3. Prevalence of XDR-TB amongst participants with DR-TB

The pooled prevalence of XDR-TB in those with DR-TB is 3% (95% CI, 1% to 6%; n=1169; I^2=85.39% (Figure 3). By country, South Africa had the highest prevalence at 5% (95% CI, 0% to 14%; n=706)

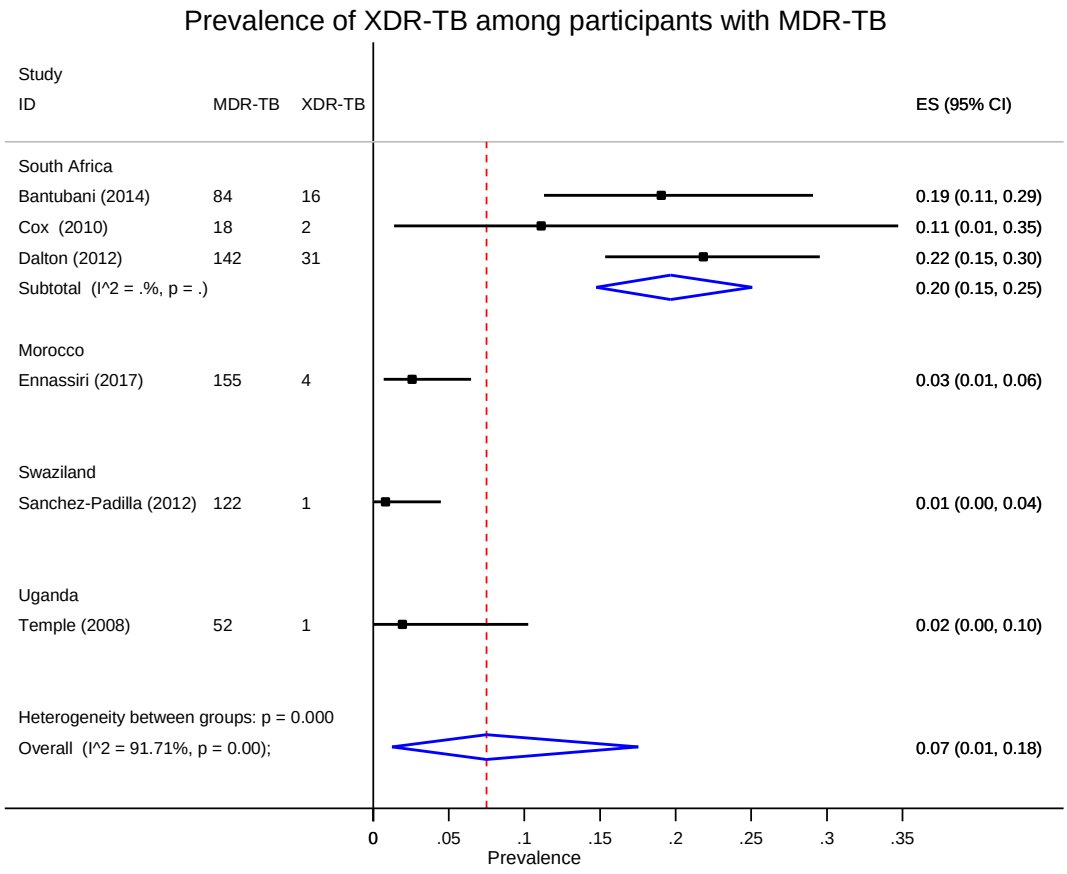


ES= estimated prevalence, CI=confidence interval, DR-TB =drug-resistant tuberculosis, XDR-TB = extensively drug-resistant tuberculosis.

Figure 3: Subgroup analysis of the prevalence of XDR-TB amongst participants with resistance to at least one anti-TB drug

3.4.4. Prevalence of XDR-TB amongst participants with MDR-TB

The pooled prevalence of XDR-TB in those with MDR-TB is 7% (95% CI, 1% to 18%; n=573; I^2=91.71% (Figure 4). By country, South Africa had the highest prevalence at 20% (95% CI, 15% to 25%; n=244).

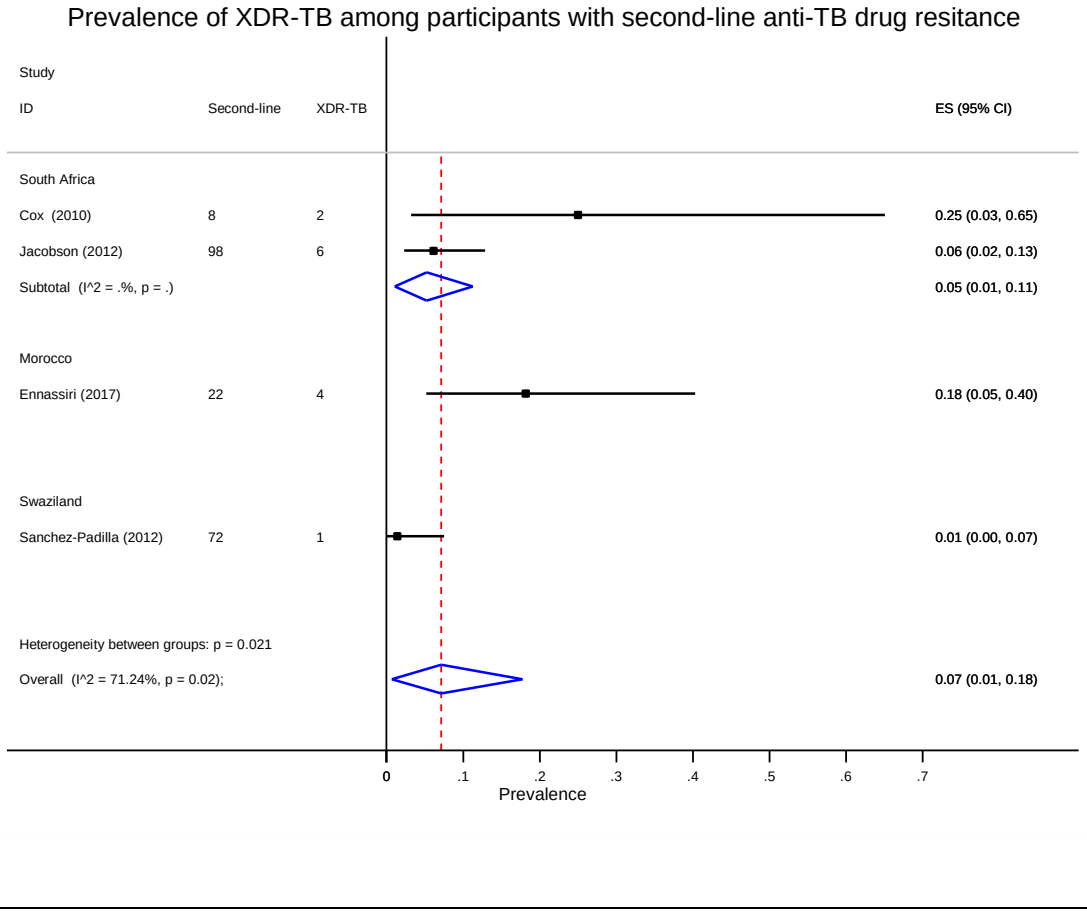


ES= estimated prevalence, CI=confidence interval, MDR-TB =multi drug-resistant tuberculosis, XDR-TB = extensively drug-resistant tuberculosis.

Figure 4: Subgroup analysis of the prevalence of XDR-TB amongst participants with MDR-TB

3.4.5. Prevalence of XDR-TB amongst participants with resistance to at least one second-line anti-tuberculosis drug

The pooled prevalence of XDR-TB in countries with resistance to at least one second-line anti-TB drug is 7% (95% CI, 1% to 18%; n=200; I^2=71.24% (Figure 5). By country, Morocco had the highest prevalence at 18% (95% CI, 5% to 40%; n=22).

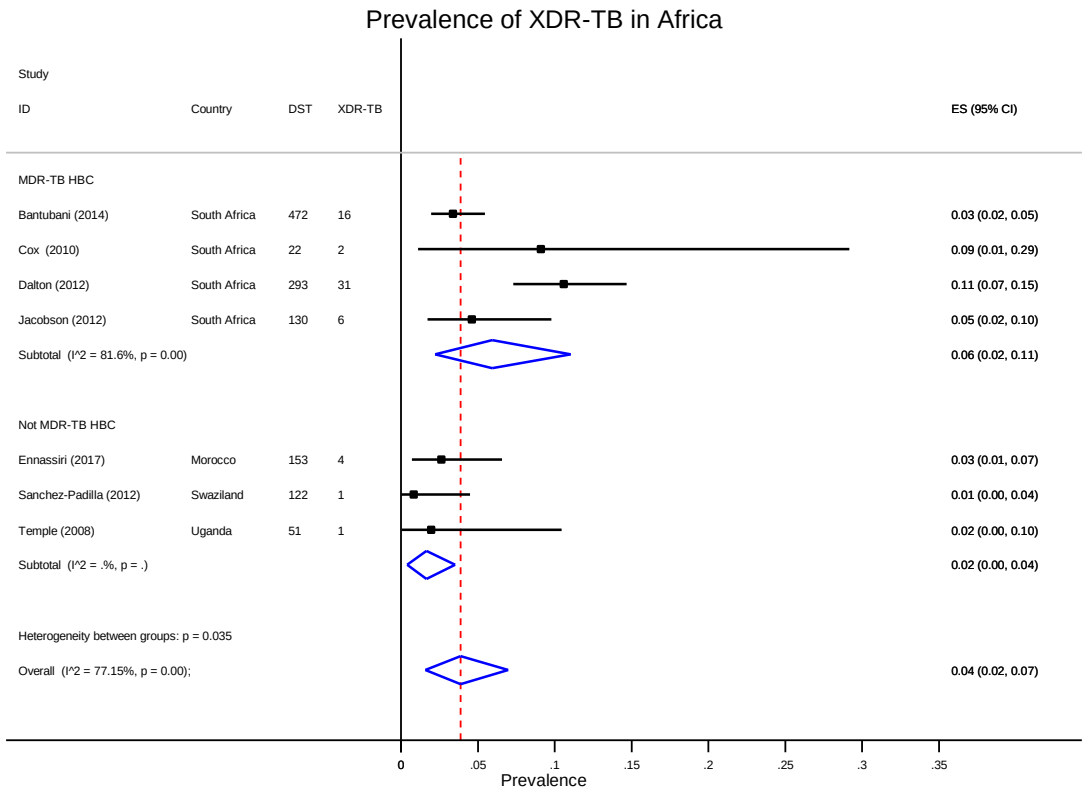


ES= estimated prevalence, CI=confidence interval, second-line= second-line anti-tuberculosis drug resistance, XDR-TB = extensively drug-resistant tuberculosis.

Figure 5: Subgroup analysis of the prevalence of XDR-TB amongst participants with resistance to at least one second-line anti-tuberculosis drug.

3.4.6. Subgroup analysis of the prevalence of XDR-TB in Africa according to WHO TB high burden country categories

The pooled prevalence of XDR-TB in those countries with a high burden of MDR-TB is 6% (95% CI, 2% to 11%; n=917; I^2=81.6% (Figure 6). The pooled prevalence of XDR-TB in those countries with a low burden of MDR-TB is 2% (95% CI, 0% to 4%; n=326; I^2=81.6%).

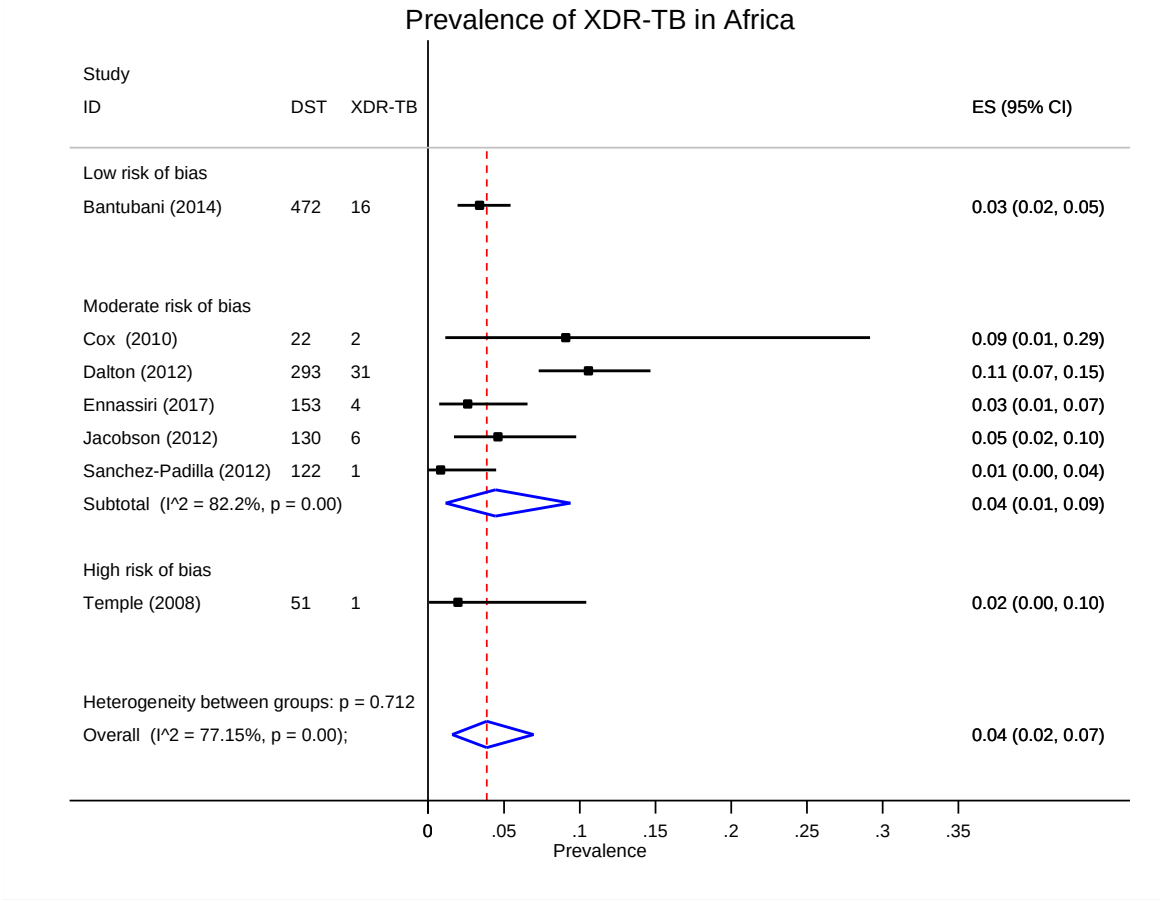


ES= estimated prevalence, CI=confidence interval, DST= drug susceptibility testing, MDR-TB= multi drug resistant tuberculosis XDR-TB = extensively drug-resistant tuberculosis, HBC= high burden country.

Figure 6: Subgroup analysis of the prevalence of XDR-TB in Africa as per MDR-TB HBC.

3.4.7. Subgroup analysis of the prevalence of XDR-TB in Africa by studies quality score categories.

The pooled prevalence of XDR-TB in studies with a low risk of bias is 3% (95% CI, 2% to 5%; n=472), moderate risk of bias is 4% (95% CI, 1% to 9%; n=720; I^2=82.2%), and in studies with a high risk of bias is 2% (95% CI, 0% to 10%; n=51) (Figure 7).

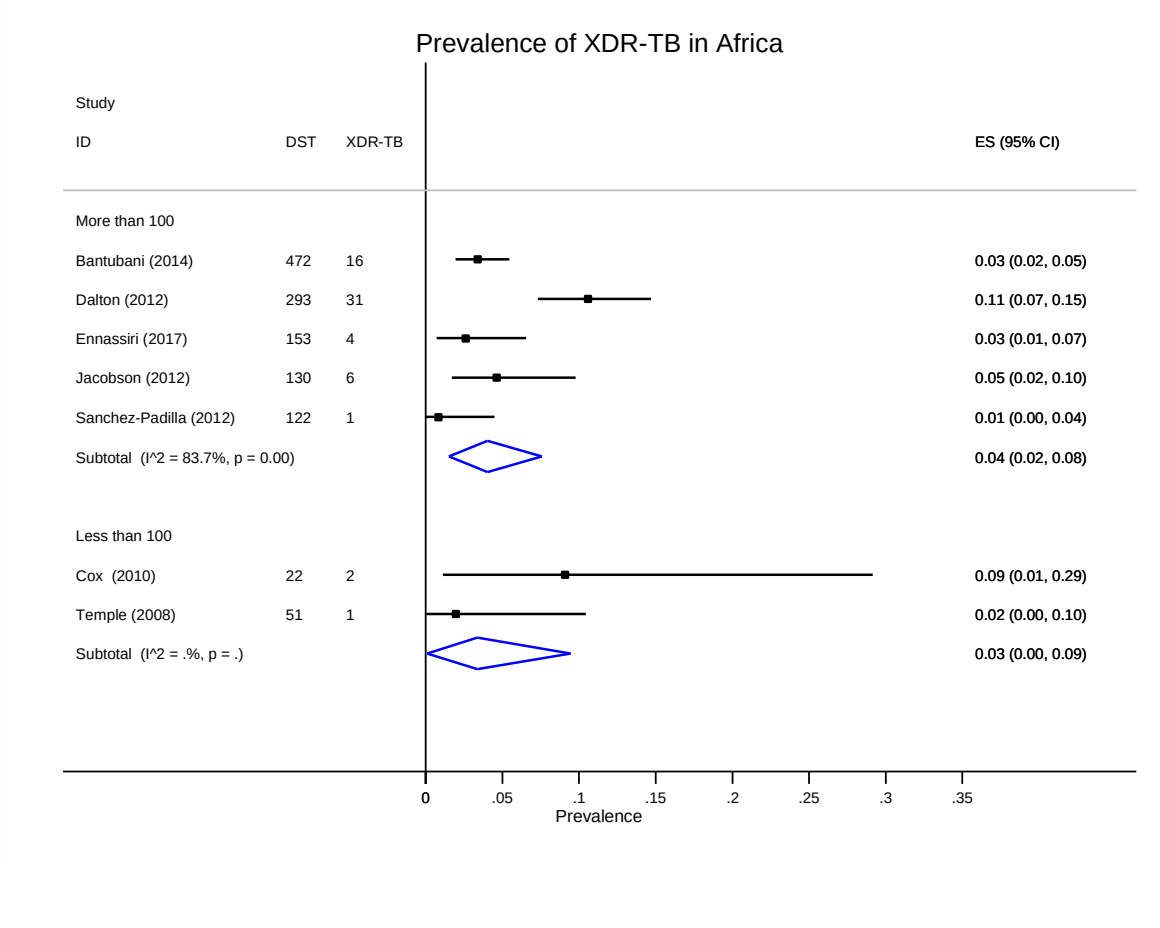


ES= estimated prevalence, CI=confidence interval, DST =drug susceptibility testing, XDR-TB = extensively drug-resistant tuberculosis

Figure 7: Subgroup analysis of the prevalence of XDR-TB in Africa by studies quality score categories.

3.4.8. Subgroup analysis of the prevalence of XDR-TB in Africa by sample size categories.

The pooled prevalence of XDR-TB in those studies with a sample size greater than 100 is 4% (95% CI, 2% to 8%; n=1170; I^2=83.7%) (Figure 8). The pooled prevalence of XDR-TB in those studies with a sample size less than 100 is 3% (95% CI, 2% to 7%; n=73).



ES= estimated prevalence, CI=confidence interval, DST =drug susceptibility testing, XDR-TB = extensively drug-resistant tuberculosis, Sample Size= The number of people tested for second-line anti-TB drug resistance per study

Figure 8: Subgroup analysis of the prevalence of XDR-TB in Africa by sample size categories.

3.4.9. Factors associated with the prevalence of XDR-TB in Africa

Among studies reporting on the prevalence of XDR-TB two (34,38) reported on factors, HIV status and previous TB treatment, associated with the prevalence of XDR-TB in Africa (Table 8). All participants were HIV infected in the one study that reported HIV status of XDR-TB participants (38). History of previous TB treatment was reported in 9/16 (56.5%) and 4/4 (100%) participants respectively (34,38).

Table 8: Summary of factors reported associated with the prevalence of XDR-TB in Africa

Factor associated with XDR-TB prevalence	Study reporting on this factor	Summary value (%)
HIV status	(38)	4/4 (100%)
History of previous TB treatment	(34,38)	9/16 (56.5%) 4/4 (100%)

3.5. Heterogeneity in included studies

There is considerable heterogeneity (I^2=77.15%) among included studies as expected with prevalence studies given clinical heterogeneity, different study procedures and study populations. Additionally, the high heterogeneity among the included studies could have been influenced by chance, different outcome measure and diagnostic tests. To account for this, we applied the Freeman-Tukey Double Arcsine Transformation (*ftt*) method to estimate the random effects pooled prevalence of XDR-TB in the various groups and subgroups studied. We were unable to generate a funnel plot to examine for publication bias, given the small number of studies.

3.6. Grading the quality of evidence

We were unable to apply GRADE because of limited information about factors associated with the prevalence of XDR-TB reported.

4. DISCUSION

This systematic review found a prevalence of XDR-TB in Africa of 4% amongst participants tested for second line anti-TB drug resistance, 3% among participants with DR-TB, and 7% among participants with MDR-TB. This suggests that the burden of XDR-TB is high among the people infected with MDR-TB compared to adults infected with DR-TB. HIV infection and the history of previous TB treatment are factors associated with the prevalence of XDR-TB in Africa.

The pooled prevalence of XDR-TB among those with drug resistance is close to the reported burden of 3.9% of XDR-TB among MDR/RR-TB cases (1). The WHO reported global prevalence (6.2%) of XDR-TB among MDR-TB (1) is close to the one found by this review among participants with MDR-TB. The similarity of XDR-TB prevalence in those with MDR-TB and those with resistance to second-line anti-TB drugs could be due to the fact that second-line anti-TB drugs are used in the treatment of MDR-TB (42). The pooled prevalence of XDR-TB in South Africa among participants with MDR-TB is high compared to the reported prevalence of XDR-TB at 4.9% among confirmed MDR-TB cases in SA (43). The factors associated with XDR-TB prevalence identified by this review have also been associated with XDR-TB in other studies conducted in Africa (20,44).

Among the countries included in this systematic review, South Africa is the only country that is categorized as an MDR-TB high burden country while both Uganda and Swaziland are listed as a TB/HIV high burden country. Morocco, although having a high prevalence of XDR-TB

amongst participants with resistance to any second-line anti-TB drug (Figure 5), is not part of any TB related HBC category (1). Moreover, South Africa is the only triple high burden country included in this systematic review. The pooled prevalence of subgroup analysis by MDR-TB burden categories show a that MDR-TB high burden countries is 4% higher than in countries not categorized as MDR-TB high burden. Subgroup analysis show that the prevalence of XDR-TB is two times higher at 20%) in South Africa than the overall prevalence of XDR-TB at amongst participants with MDR-TB. This suggest that South Africa has a high burden of XDR-TB among participants with MDR-TB compared to other countries in Africa.

The prevalence of XDR-TB in Africa in the quality score subgroup category of studies with a moderate risk of bias is 4% which is the same as the overall pooled estimate prevalence of XDR-TB in Africa. The quality score subgroup category of studies with a high risk of bias is 2% which is low than the overall pooled prevalence estimates of XDR-TB in Africa. This consequently reduces the likelihood of an overestimation influence on the overall pooled prevalence of XDR-TB in Africa by studies with a high risk of bias. The estimated pooled prevalence of XDR-TB in Africa is 1% higher in studies with sample sizes greater than 100 compared to studies with less than 100 participants. In exploring the sensitivity of the overall pooled estimate of the prevalence of XDR-TB in Africa we conducted multiple subgroup analysis and compared the subgroup estimates with the overall pooled estimate and observed that the overall pooled estimate prevalence was sensitive during subgroup analysis by country and by WHO HBC.

We found a dearth of studies measuring the prevalence of pulmonary XDR-TB whereas the few studies that did measure the prevalence of XDR-TB reported a combined prevalence inclusive of both pulmonary and extra-pulmonary TB. Moreover, some papers lacked information about the age range of participants and specimens collected. The lack of this information in papers made it difficult for us to know the age range and type of TB infecting the study participants. Consequently, the papers lacking the information required for study inclusion into this review were excluded. Furthermore, attempts to get additional information from study authors were unsuccessful. As only two studies reported factors associated with XDR-TB prevalence, a meta-regression was not done. The limited data about factors associated with XDR-TB in this review could be explained by the fact that most study authors do not report characteristics of participants stratified by DR-TB but rather report on characteristics of all participants in the study as a whole.

This review covered a period of 10 years during which major changes regarding XDR-TB diagnosis, given new-generation diagnostic tools, were introduced. These changes are expected to have had an influence on XDR-TB prevalence. This review included few studies; thus, it is possible that the calculated pooled prevalence estimate of XDR-TB in Africa could be an underestimation of the true prevalence of XDR-TB in Africa. This review only considered articles published in English potentially increasing the possibility of publication bias potentially causing an overestimation of the calculated pooled estimate of XDR-TB in Africa. To our knowledge, this is the first study to review the prevalence of pulmonary XDR-TB amongst adults in Africa.

5.CONCLUSIONS

5.1. Implications for practice

This systematic reviews' results show that the prevalence of XDR-TB is high in participants with MDR-TB. Thus, it would be advisable for mandatory second-line anti-TB DST to be done in all patients diagnosed with MDR-TB at commencement 2

of treatment. This will allow for the early detection and treatment of XDR-TB. Although there is limited data on the factors associated with XDR-TB prevalence, patients receiving treatment for DR-TB who present with HIV infection and history of previous TB treatment must be assessed for XDR-TB infection as these are factors are associated with XDR-TB. The assessment of these patients is to allow for the diagnosis and treatment of XDR-TB thus potentially resulting in the reduction of XDR-TB burden in Africa. Due to the high heterogeneity among studies included in this systematic review and meta-analysis, the estimated prevalence of XDR-TB in Africa should be used with caution when developing healthcare policy.

5.2. Implications for research

We observed that some authors do not report on all demographic information regarding study participants. It would be advantageous if study authors report all demographic information about the study participants and the proportion of XDR-TB cases in comparison to DR-TB and MDR-TB cases. Such information is paramount for health research, including systematic reviews, not only as a reliable reflection of the burden of XDR-TB disease in Africa but more so to work towards End TB in Africa by 2035. Since this review found limited information about factors associated with the prevalence of XDR-TB in Africa since only two of the

included studies reported on these factors. A systematic review and meta-analysis about factors associated with pulmonary XDR-TB amongst adults in Africa is needed.

6. FUNDING

This review study was not funded.

7. COMPETING INTEREST

None to declare.

8. AUTHOR CONTRIBUTIONS

Conceptualization: PK, EP, JN, ME

Data curation: PK, EP, JN, ME

Formal analysis: PK,

Investigation: PK, EP

Methodology: PK, EP, JN, ME

Software: PK, ME

Supervision: JN, ME

Validation: PK, EP

Visualization: PK,

Writing – original draft: PK

Writing – review and editing: PK, EP, JN, ME

9. REFERENCES

1. World Health Organisation. Global Tuberculosis Report 2017. World Health Organization. 2017.

2. WHO. Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. Wkly Epidemiol Rec. 2006;81(45):430–2.

3. World Health Organisation. MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB). 2017.

4. Peter R. Donald PD van H. The Global Burden of Tuberculosis — Combating Drug Resistance in Difficult Times. N Engl J Med. 2009;360(23):2393–5.

5. World Health Organisation. Global Tuberculosis Report 2013. World Health Organization. 2013.

6. Minime-Lingoupou F, Manirakiza A, Yango F, Zandanga G, Faou A Le, Rigouts L. Relatively low primary resistance to anti-tuberculosis drugs in Bangui and Bimbo, Central African Republic. Int J Tuberc Lung Dis. 2011;15(5):657–61.

7. Hamusse SD, Teshome D, Suaudi Hussen M, Demissie M, Lindtjørn B. Primary and secondary anti-tuberculosis drug resistance in Hitossa District of Arsi Zone, Oromia Regional State, Central Ethiopia. BMC Public Health. 2016;16:593.

8. Ndung W, Kariuki S, Ng ’ang ’ Z, Revathi G, Ndung ’u W, Ng ’ang ’a Z. Resistance patterns of Mycobacterium tuberculosis isolates from pulmonary tuberculosis patients in Nairobi. J Infect Dev Ctries. 2012;6(1):33–9.

9. Lukoye D, Adatu F, Musisi K, Kasule GW, Were W, Odeke R, et al. Anti-Tuberculosis Drug Resistance among New and Previously Treated Sputum Smear-Positive Tuberculosis Patients in Uganda: Results of the First National Survey. PLoS

One. 2013;8(8):e70763.

10. Tessema B, Beer J, Emmrich F, Sack U, Rodloff AC. First-and second-line anti-tuberculosis drug resistance in Northwest Ethiopia. Int J Tuberc Lung Dis. 2012;16(6):805–11.

11. Abubakar S. Hoza SGMM, Konig B. Anti-TB drug resistance in Tanga, Tanzania: A cross sectional facility-base prevalence among pulmonary TB patients. Asian Pac J Trop Med. 2015;8(11):907–13.

12. Gehre F, Otu J, Kendall L, Forson A, Kwara A, Kudzawu S, et al. The emerging threat of pre-extensively drug-resistant tuberculosis in West Africa: preparing for large-scale tuberculosis research and drug resistance surveillance. BMC Med. 2016;14(160).

13. Gudo PS, Cuna Z, Coelho E, Maungate S, Borroni E, Miotto P, Ahmadova S, Brouwer M, Migliori GB, Zignol M CD. Is MDR-TB on the rise in Mozambique? Results of a national drug resistance survey. Eur Respir J. 2011;38(1):222–4.

14. Lukoye D, Cobelens FGJ, Ezati N, Kirimunda S, Adatu FE, Lule JK, et al. Rates of Anti-Tuberculosis Drug Resistance in Kampala- Uganda Are Low and Not Associated with HIV Infection. PLoS One. 2011;6(1):e16130.

15. Saleri N, Badoum G, Ouedraogo M, Dembélé SM, Nacanabo R, Bonkoungou V, et al. Extensively Drug-Resistant Tuberculosis, Burkina Faso. Emerg Infect Dis. 2010;16(5):840–2.

16. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar S V, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779–87.

17. Hind Satti, Kwonjune Seung, Salmaan Keshavjee and JF. Extensively Drug-Resistant

Tuberculosis, Lesotho. Emerg Infect Dis. 2008;14(6):992–3.

18. Diarra B, Toloba Y, Konate B, Sanogo M, Combo A, Togo G, et al. Extensively drug resistant tuberculosis in Mali: a case report. BMC Res Notes. 2017;10(1):561.

19. Pietersen E, Ignatius E, Streicher EM, Mastrapa B, Padanilam X, Pooran A, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014;383(9924):1230–9.

20. Andrews JR, Shah NS, Weissman D, Moll AP, Friedland G, Gandhi NR. Predictors of Multidrug-and Extensively Drug-Resistant Tuberculosis in a High HIV Prevalence Community. PLoS One. 2010;5(12):e15735.

21. Gandhi NR, Moll A, Sturm W, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368:1575–80.

22. Shah NS, Auld SC, Brust JC, Mathema B, Ismail N, Moodley P, Mlisana K, Allana S, Campbell A, Mthiyane T MN. Transmission of Extensively Drug-Resistant Tuberculosis in South Africa. N Engl J Med. 2017;376(3):243–53.

23. Musa BM, Adamu AL, Galadanci NA, Zubayr B, Odoh CN, Aliyu MH. Trends in prevalence of multi drug resistant tuberculosis in sub-Saharan Africa: A systematic review and meta-analysis. PLoS One. 2017;12(9):e0185105.

24. Lukoye D, Ssengooba W, Musisi K, Kasule GW, Cobelens FGJ, Joloba M, et al. Variation and risk factors of drug resistant tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis. BMC Public Health. 2015;15(1):291.

25. World Health Organisation. Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs. 2008.

26. World Health Organisation. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: Policy guidance. 2016.

27. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65:934–9.

28. Werfalli M, Musekiwa A, Engel ME, Ross I, Kengne AP, Levitt NS, et al. The prevalence of type 2 diabetes mellitus among older people in Africa: a systematic review study protocol. BMJ Open. 2014;4(6):e004747.

29. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5.

30. Wells GA, Shea B, O'connell D, Peterson J, Welch V, Losos M TP. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. [cited 2017 Dec 6]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

31. Nyaga VN, Arbyn M, Aerts M. Metaprop: A Stata command to perform meta-analysis of binomial data. Arch Public Heal. 2014;72(1):1–10.

32. Deeks JJ, Higgins JPT AD. Cochrane Handbook: General Methods For Cochrane Reviews: Ch 9: Analysing data and undertaking meta-analyses. In: Cochrane Handbook for Systematic Reviews of Interventions. 2011. p. 243–96.

33. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097.

34. Bantubani N, Kabera G, Connolly C, Rustomjee R, Reddy T, Cohen T, et al. High rates of potentially infectious tuberculosis and multidrug-resistant tuberculosis (MDR-TB) among hospital inpatients in KwaZulu Natal, South Africa indicate risk of nosocomial transmission. PLoS One. 2014;9(3):1–7.

35. Cox HS, Mcdermid C, Azevedo V, Muller O, Coetzee D, Simpson J, et al. Epidemic Levels of Drug Resistant Tuberculosis (MDR and XDR-TB) in a High HIV Prevalence Setting in Khayelitsha, South Africa. South Africa PLoS ONE. 2010;5(11):e1371.

36. Dalton T, Cegielski P, Akksilp S, Asencios L, Caoili JC, Cho SN, Erokhin VV, Ershova J, Gler MT, Kazennyy BY KH. Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. Lancet. 2012;380(9851):1406–17.

37. Jacobson KR, Barnard M, Kleinman MB, Streicher EM, Ragan EJ, White LF, et al. Implications of failure to routinely diagnose resistance to second-line drugs in patients with rifampicin-resistant tuberculosis on Xpert MTB/RIF: A multisite observational study. Clin Infect Dis. 2017;64(11):1502–8.

38. Ennassiri W, Jaouhari S, Cherki W, Charof R, Filali-Maltouf A, Lahlou O. Extensively drug-resistant tuberculosis (XDR-TB) in Morocco. J Glob Antimicrob Resist. 2017;11:75–80.

39. Sanchez-Padilla E, Dlamini T, Ascorra A, Rüsch-Gerdes S, Tefera ZD, Calain P, et al. High prevalence of multidrug-resistant tuberculosis, Swaziland, 2009-2010. Emerg Infect Dis. 2012;18(1):29–37.

40. Temple B, Ayakaka I, Ogwang S, Nabanjja H, Kayes S, Nakubulwa S, et al. Rate and Amplification of Drug Resistance among Previously-Treated Patients with Tuberculosis in Kampala, Uganda. Clin Infect Dis. 2008;47(9):1126–34.

41. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. Newcastle-Ottawa Quality Assessment Form for Cohort Studies. Ottawa Hosp Res Inst. 2014;17–8.

42. World Health Organisation. WHO treatment guidelines for drug- resistant tuberculosis 2016. 2016;(October).

43. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar S V., Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779–87.

44. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368(9547):1575–80.

PART D: APPENDIX CONTENTS

APPENDIX 1: African Search Filter

Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Canary Islands OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Democratic Republic of Congo OR Djibouti OR Egypt OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Ivory Coast OR "Cote d'Ivoire" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR St Helena OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe

*****the search was done using text word fields

APPENDIX 2: Search strategy

*strategy developed in MEDLINE

#1	Tuberculosis, Multidrug-Resistant [MeSH] OR XDR Tuberculosis OR MDR tuberculosis OR Multi-Drug Resistant Tuberculosis OR Drug-Resistant Tuberculosis OR Multidrug-Resistant Tuberculosis OR Extensively Drug Resistant Tuberculosis OR XDR TB OR MDR TB OR Mycobacterium tuberculosis
#2	Prevalence [MeSH] OR prevalence OR proportion OR rate OR statistic OR epidemiology OR epidemiological OR frequency
#3	Africa search filters (see Appendix 2)
#4	#1 AND #2 AND #3 (for prevalence of XDR-TB in Africa)
#5	Risk Factors [MeSH] OR Risk OR associated OR association OR associations OR predict OR prediction OR predictors OR probability OR odds ratios OR correlation OR determinant
#6	#1 AND #3 AND #5 (represents risk predictors of XDR-TB in Africa)

*strategy can be modified for use in different electronic databases.

APPENDIX 3: Data extraction form

1. General Information

Study ID *(e.g Kosmas, 2018)*			
Reviewers details			
Review date *(dd/mm/yyyy)*			
Study title			
Study author(s)			
Year of publication			
Article Citation			
Publication type	Abstract	Yes	No
	Scientific paper	Yes	No
	Full report (Country generated)	Yes	No
	Grey literature	Yes	No
	Thesis (Master / PhD)	Yes	No
	Other (specify):		
Articles referenced to follow up			
Authors contact details	Email address:		
	Telephone number:		
Notes			

2. Study eligibility

	Eligibility criteria	Specify		Eligibility criteria met	Location in text
	Study included the following			*(Yes/No/ Unclear/ Not applicable)*	*(page #)*
Study setting	Country in Africa *(see protocol for list of African countries)*				
Study design *(see protocol for list of eligible study design)*	Observational study	Yes	No		
	Population-based study	Yes	No		
	Cross-sectional surveys	Yes	No		
	Baseline cohort studies data	Yes	No		
	Baseline cases control study data	Yes	No		
	Baseline experimental study data	Yes	No		
	Other study design: (specify)				
Condition of interest	Pulmonary XDR-TB	Yes	No		
Publication date	Was the article published within the review period (01/01/2006-31/07/2018)?	Yes	No		
Age	Adults only	Yes	No		
	Adults and children	Yes	No		
	Adult and children studies: results differentiate children <15?	Yes	No		
Diagnostic test	Based on any WHO recommended laboratory procedures?	Yes	No		
Case definition	Generic XDR-TB definition?	Yes	No		
TB Population	Only XDR-TB population	Yes	No		
Type of outcome measure	Outcome reported	Prevalence			
		Other (specify):			
Ethical approval	Authors' state ethical approval obtained?	Yes	No		
Decision regarding study	Reasoning for inclusion:				
	Reasoning for exclusion:				
Notes					

3. Study characteristic

	Descriptions as reported in paper			Location in text *(page #)*
Study objective				
Country of study				
Study design	Observational study	Yes	No	
	Population-based study	Yes	No	
	Cross-sectional surveys	Yes	No	
	Baseline cohort studies data	Yes	No	
	Baseline cases control study data	Yes	No	
	Baseline experimental study data	Yes	No	
	Other study design: (specify)			
Sampling method				
Study start date				
Study end date				
Study period *(duration of study e.g. 1 yr)*				
Data sources				
Notes				

4. Participants characteristics

	Descriptions as reported in paper			Location in text *(page #)*
Population description				
Inclusion criteria				
Exclusion criteria				
Site of recruitment of participants	Clinic	Yes	No	
	Hospital	Yes	No	
	Community	Yes	No	
	Other (specify):			
Age	Mean/median			
	Range			
	15-29	Number	%	
	30-45	Number	%	
	46-60	Number	%	
	61-75	Number	%	
	>75	Number	%	
Gender	Male	Number	%	
	Female	Number	%	
Notes				

5. Outcomes and Results

Outcome 1: XDR-TB Prevalence

Outcome 1: Prevalence	**Description as reported in paper**			**Location in text** (page #)
Total cohort included studied				
No of cohort diagnosed with TB				
No of cohort diagnosed with DS-TB				
No of cohort diagnosed with DR-TB				
No diagnosed with MDR-TB				
No of XDR-TB				
No of XDR in cohort compared to	TB	DR-TB	MDR-TB	
% of XDR in cohorts				
XDR in cohorts ***(95% confidence intervals)***				
Notes				

Outcome 2: Factors associated with the prevalence of XDR-TB in Africa

Factors / variable		Total	Value (%)	Location in text (*page #*)
HIV status	Positive			
	Negative			
	Unknown			
History of previous TB treatment	Yes			
	No			
	Unknown			
Previous TB treatment status	Cured			
	Treatment completed			
	Default			
	Failure			
	Transferred out			
Hospitalization history	Previous year			
	Never hospitalised			
CD4 count (cell/ ms^2**)**	<200 cell/ms^2			
	>200 cell/ms^2			
	Mean CD4 count			
Weight (kg)	<50kg			
	>50kg			
	Mean weight			
Smoking status	Yes			
	No			
	Unknown			
Diabetic	Yes			
	No			
	Unknown			
Age	Mean/ median			
	Range			
Gender	Male			
	female			
Other				

6. Other information

	Description as reported in paper	Location in text *(page #)*
Limitations of article		
Study funding sources *(including funders influence)*		
Possible conflicts of interests *(for study authors)*		
Notes		

APPENDIX 4: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

APPENDIX 5: PLOS ONE instruction to authors

Submission Guidelines for PLOS ONE journal

Length	Manuscripts can be any length. There are no restrictions on word count, number of figures, or amount of supporting information. We encourage you to present and discuss your findings concisely.
Font	Use a standard font size and any standard font, except for the font named "Symbol". To add symbols to the manuscript, use the Insert → Symbol function in your word processor or paste in the appropriate Unicode character.
Headings	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout and spacing	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page and line numbers	Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).
Footnotes	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
Language	Manuscripts must be submitted in English. You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text.

Keep abbreviations to a minimum.

Reference PLOS uses "Vancouver" style, as outlined in the ICMJE sample references

Manuscript Organization

Manuscripts should be organized as follows. Instructions for each element appear below the list.

Beginning section: The following elements are required in the following order:

- Title page: List title, authors, and affiliations as first page of manuscript
- Abstract
- Introduction

Middle section: The following elements can be renamed as needed and presented in any order:

- Materials and Methods
- Results
- Discussion
- Conclusions (optional)

Ending section: The following elements are required, in order:

- Acknowledgments
- References
- Supporting information captions (if applicable)

Other elements

- Figure captions are inserted immediately after the first paragraph in which the figure is cited.
- Figure files are uploaded separately.
- Tables are inserted immediately after the first paragraph in which they are cited.
- Supporting information files are uploaded separately.

Systematic reviews and meta-analyses

A systematic review paper, as defined by The Cochrane Collaboration, is a review of a clearly formulated question that uses explicit, systematic methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. These reviews differ substantially from narrative-based reviews or synthesis articles. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies.

Reports of systematic reviews and meta-analyses must include a completed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist and flow diagram to accompany the main text.

Authors must also state in their "Methods" section whether a protocol exists for their systematic review, and if so, provide a copy of the protocol as supporting information and provide the registry number in the abstract.

If your article is a systematic review or a meta-analysis you should:

- State this in your cover letter
- Select "Research Article" as your article type when submitting
- Include the PRISMA flow diagram as Fig 1 (required where applicable)
- Include the PRISMA checklist as supporting information

APPENDIX 6: Ethics waiver

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 October 2018

HREC REF: 680/2018

A/Prof Mark Engel
Medicine
J-Floor
OMB

Dear A/Prof Engel

PROJECT TITLE: EXTENSIVELY DRUG RESISTANT TUBERCULOSIS IN AFRICA; PREVALENCE AND FACTORS ASSOCIATED; A SYSTEMATIC REVIEW AND META-ANALYSIS (Masters Candidate - Mr. P. N. Kosmas)

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC note that the proposed study is a systematic review and meta-analysis.

As the systematic review involves published literature available through publically accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: *"Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research."*

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015)

Yours sincerely

signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE