Title: Treatment Outcomes of Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis—An update

Registration: To be registered in Prospero

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Introduction:

Rationale:
One of the major threats to global tuberculosis (TB) control is the emergence of Multidrug resistant TB (MDRTB) (1)(2)(3). MDRTB is defined as resistance to at least rifampin and isoniazid (1,3,4). Extensively drug resistant TB (XDRTB) is defined as resistance to rifampin, isoniazid, a fluoroquinolone and at least one of the injectable second line agents (2,3,5). Both of these forms of drug resistant TB have been associated with worse clinical outcomes (3). Currently it is known that numerous comorbidities including HIV, Diabetes, Chronic kidney disease, and alcoholism amongst others negatively affect outcomes such as treatment success and completion in drug sensitive tuberculosis (3,6–9), but little is known about the outcomes related to these co-morbidities in MDRTB.

Goal:
To examine the influence of co-morbidities on MDR-TB treatment outcomes. To reach this goal, we will perform a systematic review of the published, peer-reviewed literature that reports an association between specific co-morbidities and MDRTB treatment outcomes.

Specific objective:
We plan to examine the association between co-morbidities including diabetes (DM), HIV, smoking, end-stage kidney disease (ESKD) and alcohol abuse on the treatment outcomes in MDRTB therapy. If appropriate, we will perform a meta-analysis to estimate a pooled effect estimate of each comorbid condition on specific treatment outcomes in MDRTB. Effect estimates will be pooled overall, and also stratified by key study characteristics, including type of MDRTB treatment regimen. Our primary objective is to compare the rate of the composite negative outcomes and the rate of positive outcomes when comparing patients with and without the previously stated comorbidities in a population with MDRTB. A positive outcome is defined as the composite or treatment success and completion and a negative outcome is the composite of death/default/transfer-out/unavailable date/relapse/failure. These definitions of outcomes are defined in (1,4). Our secondary objective is to look into the effect of specific comorbidities on the specific sub-outcomes such as death, relapse, failure as opposed to the composite negative outcome. The caveat is that this will only be done if the data available allows for us to calculate this reliably.

Methods:
Eligibility Criteria:
Our inclusion criteria include studies that report treatment outcomes in at least 50 patients with microbiologically confirmed MDRTB and/or XDRTB between January 1, 1980 and June 1, 2016. Eligible studies include case-control, retrospective cohort, prospective cohort or randomized control trials. Studies reported in the peer-reviewed literature in English, French, and Spanish will be included.

Exclusion criteria include studies with exclusive surgical/non-medical therapy, or exclusive use of standard first line therapy. Studies that do not report information required for calculation of an effect estimate (with confidence interval) for at least one of the comorbidities of interest will be excluded.

Quality criteria:
• We will only include studies with consecutive enrollment.
• We will exclude patients with >30% loss-to-follow-up, default, or with treatment outcomes otherwise unaccounted for from the final pooled analysis.
• Study quality will be assessed with the appropriate standardized quality reporting tools (e.g. Newcastle-Ottawa scale for cohort studies etc.)

Information sources: We will search MEDLINE, EMBASE, Cochrane Central Registrar of Controlled Trials and Cochrane Database of Systematic Reviews from January 1, 1980 to June 1, 2016. We will also search previous systematic reviews on MDRTB treatment outcomes(3,5,10) and search the bibliographies of papers chosen for full text review for additional references. Finally, we will search for and include relevant articles from the International Journal of Tuberculosis and Lung disease for relevant papers not detected by the above strategies.

Search Strategy: We will conduct the following searches for each of the listed databases.

MEDLINE via OVID SP
1. Exp Tuberculosis, Multidrug-Resistant/
2. MDRTB.mp.
3. MDR TB.mp.
4. MDR-TB.mp.
5. MDR Tuberculosis.mp.
6. Multi*drug resistant* TB.mp.
7. Multi*drug resistant* Tuberculosis.mp.
8. (tuberculosis adj5 multi* drug resistant*).mp.
9. (tuberculosis adj5 MDR).mp.
11. (TB adj10 multi* drug resistant*).mp.
12. extensive* drug resistant* tuberculosis.mp.
13. extensive* drug resistant* TB.mp.
EMBASE via OVID SP
1. exp multidrug resistant Tuberculosis/
2. MDRTB.mp.
3. MDR TB.mp.
4. MDR-TB.mp.
5. Multi*drug resistan* TB.mp.
7. MDR Tuberculosis.mp.
8. (tuberculosis adj10 MDR).mp.
9. (tuberculosis adj10 multi* drug resistan*).mp.
11. (TB adj10 multi* drug resistan*).mp.
12. exp extensively drug resistant tuberculosis/
13. extensive* drug resistan* TB.mp.
14. extensive* drug resistan* Tuberculosis.mp.
15. XDR Tuberculosis.mp.
16. XDRTB.mp.
17. XDR TB.mp.
18. XDR-TB.mp.
19. (tuberculosis adj10 extensive* drug resistan*).mp.
20. (tuberculosis adj10 XDR).mp.
21. (TB adj10 extensive* drug resistan*).mp.
22. (TB adj10 XDR).mp.
23. exp Treatment outcome/
24. outcome*.mp.
25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or
   18 or 19 or 20 or 21 or 22
26. 23 or 24
27. 25 AND 26
28. limit 27 to English, French or Spanish language, Humans and 1980-2016
26. 23 or 24
27. 25 AND 26

Cochrane Database of Systematic reviews via OVID
1. Multi*drug resistan* tuberculosis.mp.
2. Extensive* drug resistan* tuberculosis.mp.
3. XDR-TB.mp.
4. XDR TB.mp.
5. MDR TB.mp.
6. MDR-TB.mp.
7. (tuberculosis adj10 MDR).mp.
8. (tuberculosis adj10 multi* drug resistan*).mp.
9. (TB adj10 multi* drug resistan*).mp.
11. (tuberculosis adj10 XDR).mp.
12. (tuberculosis adj10 extensive* drug resistan*).mp.
14. (TB adj10 extensive* drug resistan*).mp.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

Cochrane Central Register of Controlled Trials via OVID
1. exp Tuberculosis, Multidrug-Resistant/
2. exp Extensively Drug-Resistant Tuberculosis/
3. extensive* drug resistan* Tuberculosis.mp.
4. extensive* drug resistan* TB.mp.
5. XDRTB.mp.
6. XDR-TB.mp.
7. XDR TB.mp.
8. XDR Tuberculosis.mp.
9. MDRTB.mp.
10. MDR-TB.mp.
11. MDR TB.mp.
12. MDR Tuberculosis.mp.
15. (tuberculosis adj10 extensive* drug resistan*).mp.
17. (tuberculosis adj10 MDR).mp.
18. (tuberculosis adj10 multi* drug resistan*).mp.
20. (TB adj10 extensive* drug resistan*).mp.
21. (TB adj10 multi* drug resistan*).mp.
22. (TB adj10 MDR).mp.
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. Limit 19 to English, French or Spanish Languages and 1980-2016

**Selection Process:**
The above search strategy has been verified with one of our institutions medical librarians, and has been reviewed by two authors with systematic review experience (FAK/JCJ). Two authors will carry out the search strategy in parallel (JS/AS). Discrepancies will be resolved by a third author (JCJ).

1. We will review all titles and non-relevant publications will be excluded (and reasons for exclusion recorded).
2. We will review abstracts and non-relevant publications will be excluded (and reasons for exclusion recorded).
3. We will identify and review all full text articles identified by both reviewers.
4. The bibliographies of all full text articles and prior systematic reviews on MDRTB treatment will be reviewed for further full text articles.
5. Full text articles will be assessed according to the above mentioned exclusion and inclusion criteria. This process will be documented on a flow sheet.

**Data Collection:**
A data sheet has been created and piloted prior to the initiation of our study. It will collect data on the following:
- First author, publication date
- Funding source
- Study country(ies)
- Study dates
- Study design (prospective cohort, retrospective cohort, RCT, case control, case series)
- Duration of study
- Median/mean length of follow up post-treatment
- Number of subjects
- Number/proportion of subjects with smear positivity
- Number/proportion of subjects with cavitary disease
- Number/proportion of subjects with pulmonary/extrapulmonary disseminated/meningeal disease
- Number/proportion of patients with XDRTB
- Number/proportion of patients with surgical therapy/prior first line therapy/standardized vs individualized therapy
- Number/proportion of subjects with cure/treatment completion/failure/relapse/death/transfer out/default/data not recorded
- Number/proportion of subjects with DM, HIV, smoking, ESRD, Alcoholism
- Number/proportion of subjects with treatment outcomes reported for the above co-morbidities
• Effect estimate (with confidence intervals) of the association of each identified co-morbidity with each treatment outcomes as defined in (1,4); plus details on the effect estimate (type, eg. Odds vs Risk vs Hazard; adjusted vs crude; variables adjusted for).

• The outcomes will be recorded in terms of end of treatment and end of follow up outcomes.

Data Analysis:
For each predefined comorbidity we will plot our effect estimates with confidence interval of the composite negative outcome onto a Forrest plot and combine the data via a Random effects model which assumes within and between study variability. Heterogeneity will be tested with the I-squared test. Lastly an assessment of publication bias will be done through a funnel plot and performing a Begg’s/Egger’s test. Additionally, we will look at outcomes in this manner as defined in the introduction in terms of end of treatment outcomes as well as end of follow-up outcomes. We will perform a pooled analysis of end of follow up outcomes from studies that have less than 30% default/transfer-out/unavailable data/loss to follow-up. We are primarily concerned with the difference in the composite negative outcome but if the data allows we will examine the rate of specific sub-outcomes (i.e difference in rate of failure, death, relapse in those with specific comorbidities in addition to the composite outcome). For each study we will document associated factors such as smear positivity, cavitary disease, pulmonary vs non-pulmonary disease, but will likely not be able to stratify outcomes based on the data since the information would likely not be complete enough in the studies.

Reporting:
The final report will conform to the recommendations set out by the PRISMA-IPD checklist(11). Reasons for inclusion and exclusion of studies will be clearly detailed in a flow chart. Characteristics and details of included studies will be tabulated, assessment of study quality will be shown, methods will be clearly presented and results will be detailed. Pooled outcomes will be presented in forest plots with relevant outcomes and statistics clearly shown. Funnel plots will also be reported along with statistics for publication bias (Beggs/Eggers tests).

References:


