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Protocol for systematic review and meta-analysis of treatment success rate among adult patients with tuberculosis in sub-Saharan Africa

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ABSTRACT

Introduction Tuberculosis (TB) is a leading cause of mortality globally. Despite being curable, treatment success rates (TSRs) among adult patients with bacteriologically confirmed pulmonary TB (BC-PTB) in sub-Saharan Africa (SSA) differ considerably. This protocol documents and presents an explicit plan of a systematic review and meta-analysis to summarise TSR among adult patients with BC-PTB in SSA.

Methods and analysis Two reviewers will search and extract data from MEDLINE, EMBASE, Ovid, Cumulative Index to Nursing and Allied Health Literature and Web of Science electronic databases. Observational and interventional studies published between 1 July 2008 and 30 June 2018, involving adult patients with BC-PTB will be eligible. Data abstraction disagreements will be resolved by consensus with a third reviewer, while percentage agreement computed with kappa statistics. TSR will be computed with Metaprop, a Stata command for pooling proportions using DerSimonian and Laird random effects model and presented in a forest plot with corresponding 95% CIs. Heterogeneity between included studies will be assessed with Cochran's Q test and quantified with I-squared values. Publication bias will be evaluated with funnel plots and tested with Egger's weighted regression. Time trends in TSR will be calculated with cumulative meta-analysis.

Ethics and dissemination No ethical approval will be needed because data from previous published studies in which informed consent was obtained by primary investigators will be retrieved and analysed. We will prepare a manuscript for publication in a peer-reviewed journal and present the results at conferences.

PROSPERO registration number CRD42018099151.

Strengths and limitations of this study

- First systematic review and meta-analysis of tuberculosis treatment success rate (TSR) for sub-Saharan Africa.
- Methodological design and statistical analysis plan are very strong and robust.
- Results will inform public health interventions and policy for improving tuberculosis programmes.
- The absence of data on TSR for paediatric and multidrug-resistant tuberculosis is a limitation.
- Restricting the review to published articles between July 2008 and June 2018 is a pitfall.

INTRODUCTION

Tuberculosis (TB) is the ninth leading cause of death globally, and presently the number one cause of death in HIV positive persons.[1] Estimates from WHO indicate that 1.3 million HIV negative, and another 374 000 HIV positive persons died of TB in 2016.[1] Sub-Saharan Africa (SSA) has the highest burden of TB in addition to having the most number of HIV negative TB cases.[2] Existing data indicate that 16 of the 30 high TB burden countries are in SSA.[3]

TB is curable with standardised short course regimens of proven and known bioavailability.[4] WHO recommends 85% cure and 90% treatment success rates (TSRs) for well-performing TB programmes,[5] which is adequate in reducing TB transmission, morbidity and mortality. To achieve the needed cure and TSR, WHO introduced the directly observed therapy short course (DOTS) strategy requiring patients with TB to take medications under the direct supervision of a treatment supporter. Following the scale up of DOTS, millions of patients with TB have been successfully treated, and the strategy has proven effective in TB control in low/middle-income countries.[6] Additionally, coverage, access and better treatment outcomes among patients with TB have dramatically improved.[7] One study in Nigeria showed an overall TSR of 84.1% among patients with TB treated under DOTS.[8] Another study showed that patients with TB who are not treated under DOTS were almost 17 times more likely to fail on TB treatment

or to relapse with TB disease compared with those treated under DOTS.[9]

Several epidemiological studies across TB programmes from the African continent show conflicting TSR as low as 71% in Ethiopia,[10] and as high as 80% and 85.4% in South Africa[11] and Nigeria,[12] respectively. So TSRs in SSA differ substantially, and at present, there is lack of summarised data particularly for adult patients with bacteriologically confirmed pulmonary TB (BC-PTB). To close this gap, we propose to undertake a systematic review and meta-analysis to summarise and synthesise TSR among adult patients with BC-PTB in SSA. The results of the study will be useful in generating evidence to inform public health interventions and policy for improving TB programme performance.

Objective of systematic review and meta-analysis

The primary objective of this systematic review and meta-analysis will be to summarise TSR among adult patients with BC-PTB (≥15 years of age), both new and retreatment in SSA for a decade.

METHODS AND ANALYSIS

Protocol design and registration

We will use a systematic review and meta-analysis study design to summarise observational and interventional studies published between 1 July 2008 and 30 June 2018. This study design is appropriate for summarising and synthesising research evidence to inform policy and practice by integrating results from several independent primary studies that are combinable.[13]

The development of this study protocol, the conduct and design, and the reporting of results will be in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol (PRISMA-P),[14 15] and Meta-analysis of Observational Studies in Epidemiology,[16] guidelines. This study protocol is registered with the International Registration of Systematic reviews (PROSPERO), a platform for the international registration of prospective systematic reviews,[1 7] and assigned the registration number CRD42018099151 (available at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018099151).[18] Registration reduces duplication of reviews and provides transparency in the review process, with the aim of minimising reporting bias.[19]

Table 1 provides WHO standard definitions for TB cases and treatment outcomes that have been adopted and used in this study.

Eligibility criteria

Studies that used observational (cross-sectional, case–control, prospective and retrospective cohorts) and interventional (randomised controlled trials, RCTs) epidemiological designs, involving adult new patients with BC-PTB treated with either the 6 months anti-TB regimen consisting of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) (2RHZE/4RH) or the 8 months anti-TB regimen (2RHZE/6HE) will be considered.

Retreatment BC-PTB cases treated with the 8 months anti-TB regimen containing streptomycin (S) (2RHZES/1RHZE/5RHE) will also be considered. Studies evaluating TB treatment outcomes on all patients with TB will be included, provided the reporting of results for new and retreatment adult patients with BC-PTB are clear.

We will consider articles published between 1 July 2008 and 30 June 2018. This time period is proposed for convenience because our aim is to review data that spanned for a decade, which we believe will be sufficient time frame for a demonstrable trend of events.

We will exclude systematic reviews and meta-analysis, and studies involving non-adult (children, below 15 years of age) TB cases, extra-PTB, clinically diagnosed PTB and multidrug-resistant TB cases. Also, eligible studies with unclear reporting of TSR (or contrary to WHO standard definition of TSR) and conducted outside the SSA will be excluded.

Search strategy and searching sources

A search strategy will be developed using key concepts in the research question: bacteriologically confirmed tuberculosis, adult, treatment success and sub-Saharan Africa. For each key concept, appropriate free-text words and Medical Subject Headings (MeSH) will be developed. To ensure a comprehensive search of appropriate electronic databases, certain text words will be truncated, while wildcards will be used for some. This will enable the retrieval of relevant articles that might have used different spellings for the same word. The free-text words (truncated or with wildcards) and MeSH terms will be combined using Boolean logic operators: AND, OR and NOT, appropriately. A pretest of the search strategy by coauthor, JI and verified by FB and RS will be performed in PubMed between 2 April 2018 and 29 June 2018. This will ensure the determination of the appropriateness of the search strategy in retrieving relevant articles and its subsequent modification.

Conversely, between 2 July 2018 and 30 November 2018, two independent reviewers (JI and RS) will implement the electronic search strategy in the following electronic databases: MEDLINE through PubMed, EMBASE, Cochrane Library, Ovid, Cumulative Index to Nursing and Allied Health Literature and Web of Science. The search term will be as follows; (Tuberculosis) AND (Treatment AND outcome OR (Successful AND Unsuccessful AND outcome)). Elsewhere (online supplementary material S1), the full electronic search strategy for MEDLINE through PubMed is presented.

Study selection

All citations identified by our search strategy will be exported to EndNote, a bibliographic management software and duplicates removed. The remaining citations will be screened by titles and abstracts by two

Table 1 WHO standard definitions

Bacteriologically confirmed pulmonary tuberculosis (PTB)	A patient with TB with a biological specimen that is positive on smear microscopy, culture or molecular test like GeneXpert.
Clinically diagnosed PTB	Patient who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or any other medical practitioner who has prescribed the patient a full course of anti-TB treatment. This also includes X-ray abnormalities or suggestive histology and EPTB cases without laboratory confirmation.
Cure	A patient with PTB with bacteriologically confirmed TB at the beginning of treatment, who is smear or culture negative in the last month of treatment and on at least one previous occasion.
Died	A patient with TB who dies for any reason before starting or during treatment.
Extra-PTB (EPTB)	Any bacteriologically confirmed or clinically diagnosed TB case involving organs other than the lungs, such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges among others.
HIV positive TB patient	A bacteriologically confirmed or clinically diagnosed TB case who is HIV positive at the time of TB diagnosis or any other evidence of enrolment into HIV care, such as enrolment into pre-ART (Anti-retroviral therapy) register or in ART register once ART has been started.
Lost to follow-up	Patients with TB who have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment (these were previously known as treatment after default patients).
New TB case	A patient who has never had treatment for TB, or had been on anti-TB treatment for less than 4 weeks in the past.
PTB	Refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. This also includes miliary TB. Patients with both PTB and EPTB are classified as PTB.
Retreatment TB case	These are patients with TB who have relapsed after, defaulted during or failed on first-line treatment.
TB relapse	Patient, who has previously been treated for TB, was declared cured or treatment completed at the end of their most recent course of treatment and is now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
Treatment completed	A patient with TB who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not performed, or results were unavailable.
Treatment failed	A patient whose sputum smear or culture is positive at month 5 or later during treatment.
Treatment success rate	Proportion of new smear-positive TB cases registered under directly observed therapy in a given year that successfully completed treatment, whether with bacteriological evidence of success (cured) or without (treatment completed).

independent reviewers (JI and RS), and ineligible studies will be excluded. The full texts of selected articles will be retrieved and read thoroughly to ascertain the suitability prior to data extraction. A hand search will be performed on the reference lists of selected articles in order to include studies that will not be identified by the search strategy. In addition, a deliberate hand search of the *International Journal of Tuberculosis and Lung Disease*, WHO and the World Bank websites will be conducted. Experts in TB care and research will be consulted for additional research papers as well. For grey literature, we will search LILACS, OpenGrey, dissertations/thesis and reports. In each electronic database, RS will use an iterative process to refine the search strategy and incorporate new search terms. The search process will be presented in a PRISMA flow chart.

Data collection/extraction process and data items

Data will be extracted by two independent reviewers (JI and DS) using a standardised data abstraction form, developed according to the sequence of variables required from the primary studies. Disagreements in data abstraction between JI and DS will be resolved by a third independent reviewer, FB.

Data will be extracted on the following: author's first name, publication date, location (country in which the research was conducted), study design (cross-sectional, case–control, prospective and retrospective cohort, and interventional studies), sample size, HIV serostatus (HIV positive and HIV negative), TB treatment regimen (2RHZE/4RH, 2RHZE/6HE and 2RHZES/1RHZE/5RHE), TB treatment category (new or retreatment TB cases), and TB treatment outcomes (number of patients with TB who got cured, completed TB treatment or were successfully treated, died, defaulted and failed treatment).

In studies comparing TSR in two or more arms, each study arm will be considered as a single study. Data will be

extracted separately from each study arm on the outcome of interest and then added to obtain a single outcome measure.

The degree of agreement between the two independent data extractors (JI and DS) will be computed using kappa statistics to indicate the difference between observed and expected agreements between JI and DS, at random or by chance only. Kappa values will be interpreted as follows: (1) less than 0 equals less than chance agreement, (2) 0.01–0.20: slight agreement, (3) 0.21–0.40: fair agreement, (4) 0.41–0.60: moderate agreement, (5) 0.61–0.80: substantial agreement and (6) 0.8–0.99: almost perfect agreement.[20]

Dealing with missing outcome data

We will contact and request first authors through electronic mails to provide missing outcome data, perform sensitivity analysis to assess the robustness of meta-analytic results, and discuss the potential impact of missing data on the review findings.[21]

We will not use any one of the several statistical approaches (available case analysis, analysis of worst and best case scenarios, last observation carried forward and data imputation in sensitivity analysis to explore impact of missing data) for dealing with missing outcome data because none is effective. Besides, they cannot reliably compensate for missing data and are less recommended in meta-analysis.[22]

Data processing

Extracted data will then be entered in EpiData V.3.1 (EpiData Association, Odense, Denmark),[23] with quality control measures (skipping, alerts, range and legal values) to ensure data quality.

Quality assessment

Two reviewers (JI and DS) will assess the quality of data in included studies. We will use the National Institute of Health (NIH) quality assessment tools.[24 25] The NIH tool will be preferred because it is more comprehensive and thus enables an exhaustive assessment of quality of included studies. The overall quality of included studies will be rated as good, fair and poor. The rates will be incorporated in the meta-analytic results.

Primary outcome

The primary outcome will be TSR, which will be the proportion of new and retreatment smear-positive TB cases registered under DOT in a given year that successfully completed treatment, whether with bacteriological evidence of success (cured) or without (treatment completed). The numerator will be the number of adult new and retreatment patients with BC-PTB who have either got cured or who have completed TB treatment, while the denominator will be the number of patients initiating TB treatment.

Statistical analysis

Data will be analysed in Stata V.15.1 (StataCorp). We will present data from eligible studies in evidence table and summarise using descriptive statistics. The effect measure, TSR, will be computed using the Metaprop command for the meta-analysis of proportions in Stata. Metaprop allows the inclusion of studies with proportions equal to 0 or 100% and avoids CIs surpassing the 0 to 1 range, where normal approximation procedures often breaks down. It achieves this by using the binomial distribution to model within-study variability or by allowing Freeman-Tukey double arcsine transformation to stabilise the variances.[26] In this study, TSR will be calculated together with the corresponding 95% CI using the Wald method executed with the cimethod (score) command.

A forest plot will be generated to show the individual and pooled TSR, 95% CI, the author's name, publication year and study weights (both for primary studies and this systematic review/meta-analysis).

Prediction intervals

After performing meta-analysis, we will compute prediction interval (PI) to reflect the variation of TSR in different settings, including the direction of evidence in future studies.[27] PI shows the range in which the point estimate (TSR) of future studies will fall, assuming true effect sizes are normally distributed. Reporting PI ensures informative inference in meta-analyses. However, PI is only appropriate when studies included in meta-analysis have low risk of bias.[28]

Testing for heterogeneity

Heterogeneity between the results of the primary studies will be assessed using the Cochran's Q test and quantified with the I-squared statistic. Probability value less than 0.1 ($p<0.1$) will be considered to suggest statistically significant heterogeneity. Heterogeneity will be considered low, moderate and high when the values are below 25%, between 25% and 75%, and above 75%, respectively.[29] Statistical heterogeneity occurs when differences between study results are beyond those attributable to chance only. Heterogeneity may arise from the study setting, the study participant type, the implementation of intervention, among others.

In statistical analysis, the random-effects model is frequently used to incorporate heterogeneity in meta-analyses.[30] Consequently, we will use the DerSimonian and Laird random effects model for pooling TSR since the studies are anticipated to be heterogeneous. This accounts for heterogeneity among study results beyond the variation associated with fixed-effects model.[31]

We will then investigate the sources of heterogeneity with the random-effects meta-regression analysis based on the primary study characteristics: study design, publication year, setting of the study and TB regimen. The meta-regression analysis will be weighted to account for both within-study variances of treatment effects and the residual between-study heterogeneity (ie, heterogeneity not explained by the covariates in the regression).[32]

Assessment of publication bias

Publication bias, the tendency of publishing studies with beneficial outcome or studies that demonstrate statistically significant findings,[33] will be assessed using a funnel plot (a plot of effect estimates against sample sizes). Based on the shape of the graph, a symmetrical graph will be interpreted to suggest absence of publication bias, whereas an asymmetrical graph will be interpreted to indicate presence of publication bias.[34 35] Egger's weighted regression will be used to test for publication bias, with p<0.1 considered indicative of statistically significant publication bias.[34] Where publication bias exists, we will perform Duval and Tweedie non-parametric 'trim and fill' analysis to formalise use of funnel plot, estimate number and outcome of missing studies, and adjust for theoretically missing studies.

Cumulative meta-analysis

To determine the 10-year time trends in TSR across SSA, a cumulative meta-analysis (defined as the performance of an updated meta-analysis every time a new trial appears) which is critical in evaluating the results of primary studies in a continuum will be performed. In cumulative meta-analysis, one primary study will be added at a time according to publication date and the results will be summarised until all primary studies will have been added.[36] Cumulative meta-analysis will therefore retrospectively identify the point in time at which treatment effect, in this case TSR, first reached conventional levels of significance. In doing so, cumulative meta-analysis will represent in a compelling way the trends in the evolution of summary (effect size) and will assess the impact of a specific study on the overall conclusion.[37]

Sensitivity analysis

We will perform sensitivity analysis to reflect the extent to which the meta-analytical results and conclusions are altered as a result of changes in analysis approach.[21] This helps in assessing the robustness of study conclusion and the impact of methodological quality, sample size and analysis methods on the meta-analytical results. In particular, the leave-one-out jackknife sensitivity analysis in which one primary study is excluded at a time will be used. We will then compare the new pooled TSR with that of the original TSR.

If the new pooled TSR will lie outside of the 95% CI of the original pooled TSR, we will conclude that the excluded study has a significant effect in the study and should be excluded from the final analysis.

Subgroup analysis

We will perform subgroup analysis on TSR based on several study characteristics: HIV serostatus (HIV positive, HIV negative or both HIV positive and negative TB patients), type of patient with BC-PTB (new, retreatment or both new and retreatment), SSA region (Northern, Southern, Eastern, Central and Western Africa), study designs (cross-sectional, case–control, cohort and RCT), interventional versus observational studies, study setting (rural, urban, and both rural and urban) and the recent United Nations Development Programme Human Development Index for included countries (very high, high, medium, and low human development index), where feasible.

Ethics and dissemination

No human subject participants will be involved. On completion of the analysis, we will prepare a manuscript for publication in a peer-reviewed journal and present the results at conferences.

Implications of the review

The aim of this systematic review and meta-analysis will be to summarise TSR among adult patients with BC-PTB in SSA, a region heavily burdened by TB and having the highest TB case fatality rate. The review results may impact on practice, policy and research. Healthcare providers, managers and policy-makers can use the findings to improve the performance of TB programmes by developing strategies and initiating deliberate steps for addressing gaps in TB care. Second, it may provide a foundation for prospective research on TSR among patients with BC-PTB in SSA.

Patient and public involvement

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

Contributors JI is the first and corresponding author; JI and FB conceived and designed the study; JI, DS and FB will acquire data; JI and FB will analyse and interpret data; JI, DS, RS, IKT and FB drafted the initial and final manuscripts; JI, DS, RS, IKT and FB performed critical revisions of the manuscript. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical approval will not be required because this study will retrieve and synthesise data from already published studies.

Provenance and peer review Not commissioned; externally peer reviewed.

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