Incidence and predictors of mortality among persons receiving second-line tuberculosis treatment in sub-Saharan Africa: A meta-analysis of 43 cohort studies

Dumessa Edessa1*, Fuad Adem1, Bisrat Hagos2, Mekonnen Sisay3

1 Department of Clinical Pharmacy, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia, 2 School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia, 3 Department of Pharmacology and Toxicology, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia

* jaarraa44@yahoo.com

Abstract

Background
Drug resistance remains among the most feared public health threats that commonly challenges tuberculosis treatment success. Since 2010, there have been rapid evolution and advances to second-line anti-tuberculosis treatments (SLD). However, evidence on impacts of these advances on incidence of mortality are scarce and conflicting. Estimating the number of people died from any cause during the follow-up period of SLD as the incidence proportion of all-cause mortality is the most informative way of appraising the drug-resistant tuberculosis treatment outcome. We thus aimed to estimate the pooled incidence of mortality and its predictors among persons receiving the SLD in sub-Saharan Africa.

Methods
We systematically identified relevant studies published between January, 2010 and March, 2020, by searching PubMed/MEDLINE, EMBASE, SCOPUS, Cochrane library, Google scholar, and Health Technology Assessment. Eligible English-language publications reported on death and/or its predictors among persons receiving SLD, but those publications that reported death among persons treated for extensively drug-resistant tuberculosis were excluded. Study features, patients’ clinical characteristics, and incidence and/or predictors of mortality were extracted and pooled for effect sizes employing a random-effects model. The pooled incidence of mortality was estimated as percentage rate while risks of the individual predictors were appraised based on their independent associations with the mortality outcome.

Results
A total of 43 studies were reviewed that revealed 31,525 patients and 4,976 deaths. The pooled incidence of mortality was 17% (95% CI: 15%-18%; I² = 91.40; P = 0.00). The studies
used varied models in identifying predictors of mortality. They found diagnoses of clinical conditions (RR: 2.36; 95% CI: 1.82–3.05); excessive substance use (RR: 2.56; 95% CI: 1.78–3.67); HIV and other comorbidities (RR: 1.96; 95% CI: 1.65–2.32); resistance to SLD (RR: 1.75; 95% CI: 1.37–2.23); and male sex (RR: 1.82; 95% CI: 1.35–2.44) as consistent predictors of the mortality. Few individual studies also reported an increased incidence of mortality among persons initiated with the SLD after a month delay (RR: 1.59; 95% CI: 0.98–2.60) and those persons with history of tuberculosis (RR: 1.21; 95% CI: 1.12–1.32).

Conclusions
We found about one in six persons who received SLD in sub-Saharan Africa had died in the last decade. This incidence of mortality among the drug-resistant tuberculosis patients in the sub-Saharan Africa mirrors the global average. Nevertheless, it was considerably high among the patients who had comorbidities; who were diagnosed with other clinical conditions; who had resistance to SLD; who were males and substance users. Therefore, modified measures involving shorter SLD regimens fortified with newer or repurposed drugs, differentiated care approaches, and support of substance use rehabilitation programs can help improve the treatment outcome of persons with the drug-resistant tuberculosis.

Trial registration number
CRD42020160473; PROSPERO

Introduction
Antimicrobial resistance to mycobacterium tuberculosis (TB) remains among the most feared public health threats that commonly challenges the TB treatment success [1]. In 2019, a total of 206,030 people across the world were detected and notified to have drug-resistant TB (DR-TB), with 177,099 of them enrolled for receiving treatments [2]. According to the World Health Organization’s (WHO) global estimate in 2017, from among the 558,000 people predicted to be infected with DR-TB, only 186,883 them were detected [2, 3]. This indicated that more than half of the DR-TB cases are left undetected, and a large number of these missed cases are likely to be in resource-limited settings. On top of this, treatment regimens received by persons with DR-TB are relatively complex, prolonged, costly, and associated with multiple toxicities that may lead to difficulties to complete the entire dosages [4]. The Global TB report of 2020 pertaining to a 2017 cohort of DR-TB patients indicated that 57% them completed the treatments successfully while 15% of them died, 16% of them lost from the follow-up, and 7% of them failed treatment [2]. In addition to the large number of missed DR-TB cases in Africa, the high proportion of unsuccessful outcomes linked with DR-TB patients will threaten the prospect of achieving the set target for the EndTB Strategy by 2035 [2, 5]. Accordingly, measuring the number of people who died from any cause during the follow-up period of standardized second-line anti-tuberculosis drugs (SLD) as the incidence of all-cause mortality and its predictors are the most informative ways of assessing the DR-TB treatment outcomes [6].

The mortality commonly occurs among the persons receiving SLD [7, 8]. Patient characteristics like older age, male sex, underweight, comorbid conditions including HIV-coinfection, and extra-pulmonary involvement are the frequent explanations to contribute to the increased incidence of mortality among the persons receiving SLD [9, 10]. Besides, a high incidence of
mortality was also reported among the DR-TB patients with previous history of TB and those patients with features involving undernutrition and excessive alcohol use [11, 12].

Since 2010, there has been a rapid evolution on the better use of more effective DR-TB treatment regimens, mainly in African and Asian patients [2]. There have also been progress in discovering novel drugs and approaches to the use of repurposed drugs, and some of the world countries have begun adding these medicines to the standardized SLD regimen [13–17]. Again, there have been advances with respect to rapid testing, detection, and effective treatment with shorter regimens for the DR-TB patients [18–22]. In line to these changes, the average annual all-cause mortality rate in resource-limited settings looked to mirror the global average, but it remained unacceptably high and reaches up to 30 percent or above for some of the resource-limited countries including sub-Saharan Africa (SSA) [2, 8, 23]. Indeed, a reduction in the mortality rate has been predicted in line with the various changes implemented in these countries as part of the EndTB Strategy target set for 2035 [2]. Accordingly, there appears to be other factors than the treatment features that could influence the all-cause mortality among persons receiving the SLD therapy. Understanding such potential factors can inform a policy priority for the SLD therapy alongside its fortifications with novel or repurposed drugs. As such, a focused evidence that considers the combined risks of behavioral, sociodemographic, and clinical features of patients with proven and consistent influences on the high incidence of mortality among persons receiving the SLD therapy is mandatory. This evidence can inform an appropriate and a context-led approach with the potential to contribute to the DR-TB treatment successes. We thus aimed to estimate a pooled incidence proportion of all-cause mortality and its predictors among the persons receiving SLD treatments in SSA.

Methods

A methodological protocol for this review was prepared according to a statement recommendation made by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) in 2015 [24]. The International Prospective Register of Systematic Reviews (PROSPERO) has registered the protocol with a trial registration number of CRD42020160473. Besides, we strictly followed the PRISMA flow diagram during the process of study selection [25].

Search strategy

We identified publications by systematic searches of PubMed/Medline, Embase, Scopus, Google Scholar, Heath Technology assessment and Cochrane Library, from February to March 15, 2020. The identified records were downloaded with an appropriate format and linked to the Endnote. The terms used for our search strategy included: second-line*, rifampicin-resistant, multidrug-resistant, tuberculosis, treatment outcome, unfavorable*, death, factor, and Africa, South of the Sahara. During the searches, we employed Boolean operators (AND, OR) and truncations as appropriate to identify and include more publications. A PubMed search strategy is added to the supporting information section as a (S1 Table).

Eligibility criteria

We applied several inclusion and exclusion criteria that were defined a priori to the records identified. Publications eligible for inclusion reported on the incidence of mortality and/or its predictors among individual patients treated for DR-TB (i.e., rifampicin-resistant TB (RR-TB) or multidrug-resistant TB (MDR-TB)) as a primary outcome, or secondary outcome. The mortality outcomes considered were those encounters reported following SLD therapy initiation that also included interim reports [26]. Again, publications of studies conducted in Africa,
South of the Sahara and published from January 2010 to March 15, 2020, were included. We excluded abstracts with unrelated data, non-English language studies, publications without original data (reviews, correspondence, guidelines, letters, and editorials), and original articles that reported insufficient or irrelevant information. We also excluded studies that reported results from a case series or case report, qualitative data, and mixed findings from pre-extensively or extensively drug-resistant (pre-XDR or XDR) TB and MDR-TB patients that did not separately report outcomes for the MDR-TB. The studies with treatment outcomes for the patients with XDR-TB were excluded to avoid confusions in observed outcomes of the standarized SLD therapy, for complicated cases of the XDR-TB were assumed as different conditions from the other forms of DR-TB [27].

**Study selection procedure**

Initially, we removed duplicates from the identified publications by the use of Endnote, version 8.2 (Thomson Reuters, Stamford, CT, USA) and manual screening. Next, two of us (BH and MS) independently appraised the titles and abstracts of the retained publications and selected relevant articles for possible inclusion in the review. Accordingly, the RR/MDR-TB studies with reported mortality outcome and/or its predicting factors were kept. With this, the RR-TB was defined as any resistance to rifampicin, in the form of mono-resistance, poly-resistance, or MDR but not XDR [27]. This definition included the MDR-TB [2] which is a resistance to both isoniazid and rifampicin [27]. We also considered studies that reported retreatment TB cases managed with SLD regimens among patients with failed treatment or defaulted. Finally, two of the authors (DE and FA) independently collected and evaluated full-text details of the remained articles for quality and eligibility assessment.

**Quality assessment**

Methodological quality of the retained publications were appraised by two independent authors using the Joanna Briggs Institute’s (JBI’s) checklist for cohort studies [28]. A third author’s appraisal score was considered in cases of disagreement between scores of the two authors. Finally, all studies that fulfilled at least 50% of the quality requirement as per the average positive score of the appraisers were considered for this review.

**Data extraction**

A data abstraction format prepared in a Microsoft excel sheet was employed to extract all relevant information for the systematic review and meta-analysis. Two non-blinded investigators (DE and FA) extracted the data independently, reviewed it for discrepancies, and finally reached a consensus through discussion. The following variables were extracted: name of the first author; year of the publication; number of deaths reported during the SLD therapy; design of the studies; settings; age category of patients (children, adults, children and adults); the WHO group of the SLD regimen used (group A, group B, group C); and details of the specific drugs used in the SLD regimen. We also extracted the number of persons exposed to the predictors of mortality, and the number died from those exposed and unexposed while receiving the SLD therapy. Additionally, predictors of mortality were extracted for studies that linked patient characteristics with this outcome. For detailed extraction of the drugs used, we abstracted the standardized SLD regimens that were fortified with a later generation fluoroquinolone, bedaquiline and linezolid as group A while the regimens that added cycloserine or terizidone and/or clofazimine were abstracted as group B. Likewise, regimens that included injectable aminoglycosides (kanamycin, capreomycin, or amikacin), ethambutol,
pyrazinamide, ethionamide, para-aminosalicylic acid, delamanid, etc. (i.e., to complete the therapy) were extracted as group C [29].

Outcome definitions
The definition we considered for mortality was in line with the WHO outcomes definition among the patients with DR-TB [26]. Accordingly, the sum of cure and treatment completion was considered as a successful outcome while failed treatment, death, lost to follow-up and unevaluated outcomes were assumed as unsuccessful. In this respect, the death outcome from any cause during the time period of SLD therapy was considered as the all-cause mortality and this was the primary outcome of interest [26].

Data analysis and synthesis
Statistical pooling for incidence proportion estimates was performed according to the random-effects model with generic inverse-variance methods, using Stata 15.0 (StataCorp. 2017, Stata Statistical Software: Release 15; College Station, TX: StataCorp LLC). The random-effects model of analysis was assumed since the studies identified were observational in nature and they had both clinical and methodological variabilities. The percentage rates of the mortality incidences were presented using forest plots. In this analysis, however, risk estimates for predictors were not pooled from individual studies as this approach would have not been feasible and valid given the high risk for bias [30]. To this end, we considered an approach suggested by Ross et al. and evaluated a given predictor with proven significant and independent association with the outcome of interest [31]. In determining the risk ratios, incidences of mortality among patients with HIV-coinfection and other comorbidities such as diabetes mellitus, myocardial infarction, congestive heart failure, asthma, hypertension, chronic pulmonary insufficiency, depression, epilepsy, etc. were pooled together. Again, the mortality incidence among persons diagnosed with anemia, underweight, pneumonia, pneumothorax, hemoptysis, nutritional problems, etc. were combined together as other clinical conditions. The forest plots were employed to present the pooled risk ratio of the factors associated with the incidence of mortality. The degree of heterogeneity for effect sizes among the studies was appraised using \( \chi^2 \) (I\(^2 \)) statistics. In line with this, subgroup analyses were carried out to explain few patient features with the potential to account for the differences in the effect sizes of the mortality incidence. Publication bias (or small-study effects) was assessed by a graphical inspection of funnel plot. Next, Egger’s regression and Begg’s correlation tests were performed to test the presence of publication bias. Lastly, all statistical tests were considered as significant for P-values less than 0.05.

Results
Study selection
There were 4,255 publications identified and eligibility appraised for this review. From among these 4,255 records we identified, 422 duplicates and 3,619 unrelated studies (i.e., 1,554 of them by screening titles and 2,065 of them by screening abstracts) were excluded. Next, 171 publications were excluded with reasons from among the 214 full-text details we appraised for quality and eligibility. Finally, 43 publications that met the priori eligibility and quality requirements for the review were included in the study (Fig 1 and S2 Table).
Study characteristics

From among the 43 studies that were included, a total of 31,525 persons receiving SLD were followed-up and 4,976 of them encountered the incidence of mortality. The study participants for four of these studies were children [32–35]; for 20 of the studies were adults [23, 36–54]; and for 19 of the studies were both adults and children [55–73]. Methodological design for nine of the studies was prospective cohort [23, 39, 42–46, 50, 63] while it was retrospective cohort for 34 of the remaining studies [32–38, 40, 41, 47–49, 51–62, 64–73]. In terms of regions of the SSA from where the data were originated, 25 of the studies were from the southern region [23, 32–34, 36–39, 41, 43, 45–47, 49, 51–56, 63, 66, 68, 71, 72]; 14 of the studies were from the eastern region [35, 40, 44, 48, 57, 58, 60–62, 65, 67, 69, 70, 73]; two of the studies were
from the central region \([42, 64]\); one of the study was from the western region \([59]\); and the remaining one study was from multi-sites in different SSA regions \([50]\). A total of 23 studies out of the 43 publications identified had reported the predictors of mortality among the persons receiving SLD therapy \([23, 32, 34, 35, 37–41, 44, 47, 49, 52, 54, 55, 57, 59–61, 64, 67, 69, 71]\). However, varied analytic models of analyses were used by these studies in their attempt to identify the potential predictors of mortality (Table 1 and S3 Table).

### Proportion of patients with the incidence of mortality

The pooled estimate for the incidence of mortality as a percentage rate was 17% (95% CI: 15% - 18%; \(I^2 = 91.40; P = 0.00\)). The effect sizes estimated for the individual studies ranged from 7% (95% CI: 3% - 16%) to 44% (95% CI: 39% - 50%) (Fig 2).

### Sensitivity analysis

To explore the source of heterogeneity among the included studies, we performed a sensitivity analysis by excluding two of the outliers \([41, 42]\). However, this resulted in a slight reduction to the degree of heterogeneity with a percentage decrease to the incidence of mortality that was already estimated (effect size: 16%; 95% CI: 15% - 18%; \(I^2 = 88.75\%\; P = 0.00\)) (Fig 3).

### Subgroup analyses

Since the variability among studies remained high even after the sensitivity analysis, we performed subgroup analyses to further explore the source of heterogeneity. We categorized the studies by groups of the SLD regimen, median duration of follow-up for the SLD therapy, and regions of the SSA as the key observational features. However, none of these subgroups appeared homogenous except the slight variabilities in the group-specific mortality estimates which were not statistically significant. The incidence proportion of mortality ranged from 13% (95% CI: 8%-17%) for studies with the median follow-up of less than 15 months to 18% (95% CI: 13%-19%) for studies with the median follow-up of 16–20 months. This was 13% (95% CI: 10%-17%) for group A, 15% (95% CI: 13%-17%) for group B, 19% (95% CI: 14%-24%) for group C and 21% (95% CI: 13%-29%) for non-specific SLD regimens. Again, the incidence proportion of mortality was 19% (95% CI: 17%-22%) for studies from the southern SSA region, 13% (95% CI: 11%-15%) for studies from the eastern SSA region, and 11% (95% CI: 6%-17%) for studies from mixed SSA regions (S1–S3 Figs).

### Predictors of mortality

A total of 23 studies had reported at least one predictor linked with the incidence of mortality among persons receiving the SLD therapy. Nineteen (19) of these studies reported HIV-infection and other comorbidities (i.e., diabetes mellitus, myocardial infarctions, hypertension, congestive heart failure, asthma, epilepsy, depression, chronic pulmonary insufficiency and pulmonary fibrosis) \([32, 34, 35, 37–41, 44, 49, 52, 54, 55, 59–61, 64, 67, 71]\) while ten of the studies reported diagnoses of clinical conditions such as anemia, underweight (BMI < 18.5 Kg/m2), pneumothorax, pneumonia, hemoptysis, opportunistic infections, cavitary changes and nutritional problems \([23, 32, 34, 44, 47, 51, 52, 57, 64, 69]\) as the key predictors of all-cause mortality. Besides, three of the studies specific to each feature had reported resistance to SLD \([54, 69, 71]\); male sex \([32, 49, 67]\); and excessive substance use \([61, 64, 69]\) as the predictors of all-cause mortality. Moreover, two of the studies reported delays (i.e., more than a month) in initiating SLD therapy \([59, 61]\); encounters of adverse drug events (ADEs) \([40, 41]\), and extrapulmonary involvement \([34, 41]\) as the predictors of the mortality outcome. Reports of
Table 1. Characteristics of identified publications and their analytic models of factor prediction for the SLD treatment outcomes.

| Study            | # died | Total size | Follow-up period | Design | Setting       | Age category       | Analytic model                     | Group of SLD regimen | Details of the drugs used                                    |
|------------------|--------|------------|------------------|--------|---------------|-------------------|-------------------------------------|----------------------|-------------------------------------------------------------|
| Adewumi (2012)   | 44     | 336        | 24 months        | RFU    | South Africa  | Adults and Children | $\chi^2$ test                      | Group B              | kanamycin, ethionamide, ofloxacin, cycloserine, pyrazinamide |
| Alakaye (2018)   | 83     | 343        | 18 months        | RFU    | Lesotho       | Adults and Children | Cox proportional hazards regression | Group C              | Amikacin, kanamycin, Capreomycin or any fluoroquinolone      |
| Alene (2017)     | 31     | 242        | 20 months        | RFU    | Ethiopia      | Adults and Children | Cox proportional hazards regression | Group B              | Pyrazinamide, capreomycin, levofloxacin, ethionamide, cycloserine |
| Ali (2019)       | 22     | 156        | 18 months        | RFU    | Sudan         | Adults and Children | Cox proportional hazards regression | Group B              | pyrazinamide, capreomycin, levofloxacin, ethionamide and cycloserine |
| Bajehson (2019)  | 38     | 147        | 20 months        | RFU    | Nigeria       | Adults and Children | Cox proportional hazards regression | Group B              | Capreomycin, levofloxacin, cycloserine, prothionamide and pyrazinamide |
| Borisov (2017)   | 17     | 113        | 18 months        | RFU    | South Africa  | Adults             | $\chi^2$ test                      | Group A              | Bedaquiline, linezolid, moxifloxacin, clofazimine and carbapenems |
| Brust (2010)     | 223    | 1209       | 24 months        | RFU    | South Africa  | Adults             | Multivariate logistic regression   | Group B              | Kanamycin, ofloxacin, pyrazinamide, ethambutol or cycloserine and thionamide |
| Brust (2018)     | 22     | 191        | 32 months        | RFU    | South Africa  | Adults             | Cox proportional hazards regression | Group B              | Kanamycin, moxifloxacin ethionamide, ethambutol and pyrazinamide |
| Cox (2014)       | 128    | 718        | 24 months        | RFU    | South Africa  | Adults/Adolescents | Cox proportional hazards regression | Group C              | Ofloxacin, kanamycin, ethambutol, ethionamide and pyrazinamide |
| Fantaw (2018)    | 30     | 164        | 13 months        | RFU    | Ethiopia      | Adults and Children | Cox proportional hazards regression | NS                   | Standardized SLD                                              |
| Farley (2011)    | 177    | 757        | 24 months        | FU     | South Africa  | Adults             | Cox proportional hazards regression | Group C              | Pyrazinamide, ethambutol, ethionamide, ofloxacin, and either amikacin or kanamycin. |
| Getachew (2013)  | 29     | 188        | 14 months        | RFU    | Ethiopia      | Adults and Children | Cox proportional hazards regression | NS                   | Standardized SLD                                              |
| Girum (2017)     | 13     | 154        | 24 months        | RFU    | Ethiopia      | Adults             | Cox proportional hazards regression | Group B              | Capreomycin, amikacin, ethionamide, levofloxacin and cycloserine |
| Hall (2017)      | 69     | 423        | 24 months        | RFU    | South Africa  | Children           | Cox proportional hazards regression | Group C              | A fluoroquinolone and second-line injectables                |
| Hicks (2014)     | 8      | 68         | 18 months        | RFU    | South Africa  | Children           | Multivariate logistic regression   | Group B              | pyrazinamide, ethambutol, terizidone, kapromycin, ofloxacin and ethambutol |
| Hirases (2018)   | 37     | 240        | 12 months        | FU     | South Africa  | Adults             | Cox proportional hazards regression | NS                   | Standardized SLD                                              |
| Huerga (2017)    | 21     | 145        | 24 months        | RFU    | Kenya         | Adults and Children | Multivariate logistic regression   | Group B              | kanamycin or capreomycin, levofloxacin, prothionamide, cycloserine, para-aminosalicylic acid |
| Jikjela (2018)   | 147    | 332        | 24 months        | RFU    | South Africa  | Adults             | Multivariate logistic regression   | NS                   | Standardized SLD                                              |

(Continued)
Table 1. (Continued)

| Study                | # died | Total size | Follow-up period | Design | Setting       | Age category         | Analytic model                     | Group of SLD regimen | Details of the drugs used                                                                                                                                 |
|----------------------|--------|------------|------------------|--------|---------------|----------------------|------------------------------------|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kapata (2017)        | 12     | 71         | 20 months        | FU     | Zambia        | Adults and Children  | Cox proportional hazards regression | Group B              | kanamycin, levofloxacin, ethionamide, cycloserine and pyrazinamide                                                                                           |
| Kashongwe (2017)     | 18     | 199        | 6 months         | RFU    | Congo         | Adults and Children  | Multivariate logistic regression | NS                  | Standardized SLD                                                                                                                                             |
| Kuaban (2015)        | 10     | 150        | 12 months        | FU     | Cameroon      | Adults               | Multivariate logistic regression | Group B              | gatifloxacin, clofazimine, prothionamide, ethambutol and pyrazinamide                                                                                       |
| Leveri (2019)        | 56     | 332        | 24 months        | RFU    | Tanzania      | Adults and Children  | Multivariate logistic regression | Group B              | Amikacin or kanamycin, ofloxacin or levofloxacin, pyrazinamide, ethionamide, cycloserine, and ethambutol                                               |
| Loveday (2015)       | 223    | 1549       | 24 months        | FU     | South Africa  | Adults               | Cox proportional hazards regression | Group B              | Kanamycin, pyrazinamide, ethambutol, ethionamide, ofloxacin and cycloserine                           |
| Marais (2013)        | 65     | 324        | 24 months        | RFU    | South Africa  | Adults and Children  | Multivariate logistic regression | Group B              | kanamycin, pyrazinamide, ofloxacin, ethionamide and terizidone or ethambutol                             |
| Meressa (2015)       | 85     | 612        | 24 months        | FU     | Ethiopia      | Adults               | Cox proportional hazards regression | Group B              | Three of levofloxacin, ethionamide, cycloserine or para-aminosalicylic acid, pyrazinamide and amikacin or kanamycin or capreomycin |
| Mibe (2016)          | 18     | 205        | 20 months        | RFU    | Kenya         | Adults and Children  | Multivariate logistic regression | Group B              | kanamycin, levofloxacin, cycloserine, ethionamide and pyrazinamide                                      |
| Mohr (2015)          | 123    | 757        | 18 months        | RFU    | South Africa  | Adults and Children  | Multivariate logistic regression | NS                  | second-line anti-TB drugs                                                                                                                                       |
| Mollalign (2015)     | 37     | 342        | 16 months        | RFU    | Ethiopia      | Adults and Children  | Cox proportional hazards regression | Group C              | Ethambutol, streptomycin, kanamycin, amikacin and capreomycin                                                                                                   |
| Moll (2019)          | 29     | 201        | 20 months        | RFU    | Tanzania      | Adults and Children  | Multivariate logistic regression | Group B              | amikacin or kanamycin, ofloxacin, cycloserine, ethionamide, pyrazinamide and ethambutol                 |
| Ndjeke (2018)        | 25     | 200        | 24 months        | FU     | South Africa  | Adults               | Multivariate logistic regression | Group A              | Bedaquiline, clofazimine, levofloxacin, linezolid, kanamycin                                                                                                    |
| Padayatchi (2014)    | 7      | 23         | 18 months        | FU     | South Africa  | Adults               | Multivariate Poison regression | Group C              | kanamycin, ofloxacin, pyrazinamide, ethambutol or cycloserine and ethionamide                           |
| Satti (2012)         | 46     | 134        | 24 months        | RFU    | Lesotho       | Adults               | Cox proportional hazards regression | Group B              | fluoroquinolone, prothionamide or ethionamide, cycloserine, pyrazinamide, para-aminosalicylic acid, etc.                                                   |
| Schnippel (2015)     | 2165   | 15339      | 24 months        | RFU    | South Africa  | Adults and Children  | Multivariate Poison regression | Group B              | Kanamycin or amikacin, ethambutol or ethionamide, terizidone, and pyrazinamide                         |
| Seddon (2012)        | 13     | 111        | 24 months        | RFU    | South Africa  | Children             | Multivariate logistic regression | Group B              | Amikacin, capreomycin, ofloxacin, ethionamide, para-aminosalicylic acid, terizidone, linezolid, etc.    |
| Shibabaw (2018)      | 19     | 235        | 24 months        | RFU    | Ethiopia      | Adults               | Cox proportional hazards regression | Group B              | At least three of oral agents (pyrazinamide, levofloxacin, ethionamide, protonamide, cycloserine or para-aminosalicylic acid) and an injectable agent (amikacin, kanamycin, capreomycin) |

(Continued)
individual studies also indicated multiple other drugs than SLD [41]; previous episode of TB [71]; previous history of failed treatment [23], and under five aged children [35] as the predictors of mortality.

We combined risk ratio estimates for at least three of the studies that reported similar predictors of all-cause mortality and found its significant increases among persons receiving the SLD and with certain characteristics. These features included diagnoses of newer clinical conditions (RR: 2.36; 95% CI: 2.82–3.05); substance use (RR: 2.56; 95% CI: 1.78–3.67); presence of HIV-coinfection and other comorbidities (RR: 1.96; 95% CI: 1.65–2.32); resistance to SLD (RR: 1.75; 95% CI: 1.37–2.23); and male sex (RR: 1.82; 95% CI: 1.35–2.44) (Fig 4). The resistance to SLD regimen was defined by the studies as any resistance to fluoroquinolones or at least one injectable aminoglycoside (i.e., capreomycin, kanamycin and amikacin) [54, 69, 71].

### Publication bias

Graphical visualization of the funnel plot found its symmetrical appearance which gave us hint about absence of the publication bias. This visual inspection was further tested by using Egger’s regression and it also showed no evidence of the small-study effects (effect estimate: 1.40; 95% CI: -0.14–2.94; P = 0.073). Additionally, Begg’s correlation test revealed no evidence of the publication bias (Z = 0.96; P = 0.34) (Fig 5).

---

**Table 1. (Continued)**

| Study          | # died | Total size | Follow-up period | Design | Setting | Age category | Analytic model                        | Group of SLD regimen | Details of the drugs used                                   |
|----------------|--------|------------|------------------|--------|---------|--------------|----------------------------------------|---------------------|-------------------------------------------------------------|
| Shin (2017)    | 118    | 588        | 24 months        | RFU    | Botswana| Adults       | Multivariate Poison regression         | Group B             | amikacin, levofloxacin, ethionamide, cycloserine, and pyrazinamide |
| Tola (2020)    | 18     | 155        | 36 months        | RFU    | Ethiopia| Children     | Cox proportional hazards regression    | Group B             | levofloxacin, ethionamide, cycloserine, para-aminosalicylic acid, pyrazinamide, prothionamide, linezolid, clofazimine, amikacin, kanamycin and capreomycin |
| Trebecq (2018) | 78     | 1006       | 24 months        | FU     | 9 Africa countries| Adults | Multivariate logistic regression      | Group B             | moxifloxacin, clofazimine, ethambutol, pyrazinamide, kanamycin, prothionamide and high-dose isoniazid |
| Umanah (2015a)| 181    | 947        | 24 months        | RFU    | South Africa | Adults | Multivariate logistic regression      | Group B             | Kanamycin/Amikacin, Moxifloxacin, Ethionamide, Terizidone, Ethambutol and/or pyrazinamide |
| Umanah (2015b)| 258    | 1137       | 24 months        | RFU    | South Africa | Adults | Multivariate Poison regression       | Group B             | kanamycin/amikacin, moxifloxacin, ethionamide, terizidone, and pyrazinamide |
| Van der Walt (2016) | 123 | 393        | 24 months        | RFU    | South Africa | Adults and Children | χ² test NS | Standardized SLD                                                                 |
| Verdecchia (2018) | 37  | 174        | 18 months        | RFU    | Eswatini | Adults | Cox proportional hazards regression | Group B             | Levofloxacin, ethionamide, terizidone or cycloserine, pyrazinamide, kanamycin/amikacin with/without para-aminosalicylic acid |
| Woldeyohannes (2019) | 73    | 415        | 20 months        | RFU    | Ethiopia | Adults and Children | Cox proportional hazards regression | Group B             | Pyrazinamide, Ethambutol, Capreomycin, Levofloxacin, Ethionamide, Cycloserine; and others |

Total 4,976 31,525

Note

#, number; NS, not specified; and χ², chi-squared.

https://doi.org/10.1371/journal.pone.0261149.t001
Discussion

More than one-sixths of the persons receiving SLD for DR-TB managements in SSA had died during the last decade. A relatively lower incidence proportion of the mortality was found among the DR-TB patients treated with group A or B regimens compared with those patients treated with group C regimens. The pooled risk ratio estimate for the identified predictors found increased incidences of mortality among persons with features of established comorbidities, diagnoses of newer clinical conditions, resistance to SLD, substance use, and male sex.

The pooled incidence proportion of mortality among the DR-TB patients treated with SLD in SSA was 17%. No significant differences were found by subgroup analyses that considered the median time period of treatment follow-up, specific regimen groups for SLD and regions of the SSA. However, the pooled estimate of mortality was as high as 19% in southern SSA and as low as 13% among the patients treated with group A SLD. It was also estimated to be 15% among the patients treated with group B regimens. Essentially, these estimates are promising and can hint as though this setting is on a right track to achieving the EndTB strategy target of
90% mortality reduction by 2030 [2]. A study report also revealed similar benefits of using SLD regimens that contained linezolid, a later generation fluoroquinolones (levofloxacin or moxifloxacin), bedaquiline, clofazimine, or capreomycin [74]. Most of these drugs are the essential medicines that are usually added to groups A, B, or shorter SLD regimens. A similar meta-analysis also reported that there have been no significant differences in survival benefits with respect to specific drugs used and the time period of the treatment follow-up [75]. Again, most of the specific drugs added to group A, B or C regimens were part of the DR-TB treatment advances in the last decade [76]. Similar benefits were reported by the use of repurposed drugs, newer drugs, later generation fluoroquinolones, ethionamide or prothionamide, four or more effective drugs in intensive phase, and three or more likely effective drugs in continuation phase of the DR-TB treatment [76]. Most of the DR-TB patients included in this review also used SLD regimens that added the later generation fluoroquinolones, repurposed agents, newer drugs, and injectable aminoglycosides. Besides, these drugs had appeared to have strong association with treatment success and survival benefits [77].
Moreover, most of the DR-TB patients in SSA had already initiated newer agents and shorter SLD regimens as part of the response to EndTB Strategy and WHO recommendation [76]. These shorter regimens appeared to be effective in treating MDR-TB [78]. With this, the type of drug added to the SLD regimen is considerable for optimal benefits [79]. To this end, the global average mortality of 15% among the cohort of DR-TB patients treated with SLD mirrors the percentage rate this study found (17%) for a similar setting (i.e., SSA) [2]. About
half of countries (n = 21) from among 48 countries with high burden of DR-TB patients included in the cohort were from SSA, for which the estimated treatment successes ranged from zero percent (in Angola) to 88% (in Congo). For this cohort, majorities of the SSA countries achieved a success rate of around 65% [2]. Individual studies that participated DR-TB patients during their SLD therapy follow-up in India, Malaysia, and Pakistan also found 16%, 15.3%, and 17.4% mortality rates, respectively [80–82].

HIV and other comorbidities were the most common predictors of mortality which were frequently reported among persons receiving SLD therapy. The mortality was 1.96 times higher among the patients with comorbidities than those patients free of these conditions. Similarly, in reference to patients free of comorbidities, the risk of mortality among the

Fig 5. Funnel plot of standard error by effect size for publication bias.

https://doi.org/10.1371/journal.pone.0261149.g005
patients with various comorbid conditions while on SLD therapy was variably increased by 1.96 (95% CI: 1.35–3.85), 2.33 (95% CI: 1.34–4.05), 2.6 (95% CI: 1.82–3.70), 5.42 (95% CI: 2.66–11.04), and 6.82 (95% CI: 2.16–21.50) folds [9, 12, 80, 83]. Again, several other studies indicated a varied but increased likelihood of mortality by 1.46 (95% CI: 1.05–1.96), 1.50 (95% CI: 1.20–1.90), 1.70 (95% CI: 1.20–3.10), 1.89 (95% CI: 1.02–3.52), 2.97 (95% CI: 1.41–6.24), 3.18 (95% CI: 1.05–9.69), 3.47 (95% CI: 1.02–11.64), 4.22 (95% CI: 2.65–6.72), and 5.6 (95% CI: 3.2–9.7) times higher among the HIV-infected patients than HIV-uninfected ones [83–91]. A meta-analysis also reported 1.8 (95% CI: 1.5–2.2) times higher odds of mortality among the HIV-positive patients on antiretroviral therapy (ART) than those who did not receive the ART [92], but majorities of the studies included in our review did not report mortality by the ART status and we were unable to explore this difference by the ART treatment. Another meta-analysis also stressed on a closer link between HIV-infection and MDR-TB and found that the MDR-TB was 2.28 times more likely in HIV-infected people than those people who were HIV-uninfected [93]. In the current review, the risk of mortality was somewhat lower than the likely risks reported by several of the previous studies. Unarguably, the MDR-TB management approach of countries (in the last decade) had involved early and rapid diagnosis with genotype testing; prompt treatment with appropriate regimens based on drug-susceptibility testing; preference for shorter regimens by using newer or repurposed drugs; a patient-centered approach; and strong infection-control measures. All these strategies might have helped the mortality reduction among the DR-TB patients with comorbidities including HIV-coinfection [94]. Also, the use of a differentiated care approach, the demand created for effective TB/HIV service delivery, the establishment of HIV/TB coordination mechanisms, the rapid scale-up of facilities with decentralization of treatment services, the regular joint supervision, and monitoring might have contributed to the successes [95, 96].

In another way round, CD4 values lower than 50 cells/mm³ (HR, 4.64; P = 0.01) and 51–200 cells/mm³ (HR, 4.17; P = 0.008) among the treated DR-TB patients were found as the independent risk factors of mortality compared with those patients with CD4 values >200 cells/mm³ [97]. A higher susceptibility to opportunistic infections (OIs) due to the lower immune status (indicated by the low CD4 levels) can justify this finding. Previous OIs among patients treated with SLD therapy were also related to a 3.13 (95% CI: 1.64–5.96) times higher hazards of mortality than those without the OIs episode [90]. Again, patients with previous TB history and treated with SLD for about 2–6 months had 1.46 times higher risks of mortality compared to the patients without previous TB episodes [98]. In addition, history of previous TB increased the risk of death by 1.61 fold among patients with the episode compared to those patients free of the episode [12]. A study finding also implicated numbers of the previous TB episodes to have direct links with the increased risks of death [83].

Resistance to SLD was another predictor of mortality with about 75% increased risks of death among the patients who experienced drug resistance. Consistent with this finding, a study in Brazil found that MDR-TB patients who developed resistance to SLD had 74% higher risks of death than those patients who did not experience resistance [84]. Another study also reported resistance to the SLD as a key predictor of poor outcome (OR: 2.61; 95% CI: 1.61–4.21) [81]. Besides, a 31.4% incidence proportion of mortality was reported among the cohort of patients with any form of resistance to SLD therapy [99]. This mortality could reach more than 50% among under-treated patients with the resistant strains [100]. Again, MDR-TB patients with any form of resistance to SLD were found to have the lowest success rate (29.3%) [101]. In line with this, delay in initiating the SLD regimens or substituting the regimen components with resistance could be the likely reason for extending to a further resistance. About two-fold increased odds of dying was reported with the delay in starting SLD treatment [102]. Again, near to 30% increased risk of unfavorable outcome was explained with more than a
month delay in initiation of SLD after the resistance detection [103]. Delay in the resistance detection was also reported to increase the probability of mortality by 8.3% among the patients treated with SLD therapy [104].

In this review, the risk of mortality was 2.36-fold increased among the cohorts of patients diagnosed with clinical conditions than those patients free of the conditions. Underweight and anemia were the most frequent diagnosis that the studies reported. Similarly, other studies also revealed underweight to be 1.30 (95% CI: 1.0–1.50), 2.50 (95% CI: 2.10–2.90), 2.50 (95% CI: 1.70–3.5), and 3.39 (95% CI: 1.20–9.45) times more likely related with unfavorable outcomes than the patients with normal body weight [11, 91, 105, 106]. Besides, there were pieces of evidence that reported findings of baseline underweight among most MDR-TB patients (i.e., up to 86.6%), in which anemia was the most common clinical condition (i.e., up to 73.83%) [107–109]. Besides, underweight patients had a 90% increased incidence of mortality than the patients with normal body weight [110]. In fact, severe anemia and malnutrition were known as the independent predictors of early mortality in TB patients [111].

The DR-TB patients who used excessive substances (cigarette and alcohol) and male patients had 2.56 and 1.82 times higher risks of mortality than the patients who did not use the substances and who were females, respectively. Consistently, patients with excessive substance uses tended to have poor MDR-TB treatment outcomes [112]. In a study report, patients with alcohol misuse had a 1.45 (95% CI: 1.21–1.75) times higher risks of unsuccessful outcomes than the patients who did not drink alcohol [113]. Again, MDR-TB patients with habits of cigarette smoking were found to have 5.44 (95% CI: 1.09–27.19) times higher odds of mortality than those patients who were non-smokers [89]. In line with this, a two-fold increased odds of substance abuse disorders were correlated with male sex [114]. And, the risk of mortality was 1.4 (95% CI: 1.1–1.7) and 2.0 (95% CI: 1.27–3.14) times higher among males than females on SLD therapy follow-up [9, 106].

Despite the large size of aggregate data pooled together for summary effects in this systematic review and meta-analysis, it is not without limitations. First, the studies considered for the meta-analysis were observational by nature. This selection might have resulted in a higher degree of heterogeneity with a range of potential biases. However, we employed a random-effects model to account for the anticipated heterogeneity. Second, there were some inconsistencies in the studies included in terms of the median time period of follow-up for the SLD therapy, but we assumed the intention-to-treat approach and considered deaths reported at any time during the follow-up period. Third, the retrospective cohort studies included in our review did not adjust for mortality in patients with lost follow-up and failed treatment. Due to the aggregate data meta-analysis approach and a limited control over the data, these deaths could not be accounted for, and this gap might have under-estimated the incidence of all-cause mortality. Fourth, we included articles written in the English language, and this restriction could have under- or over-estimated the pooled incidence of mortality and its predictors while on the SLD therapy. Fifth, there appeared some overlaps of included patients in four of the South Africa studies reporting national treatment register and community-based programs, but we were unable to avoid such overlaps for we do not have clear knowledge of the data source. Therefore, interpretations for the findings in this review need to be aligned and seen in contexts of these limitations.

Conclusions
We found about one in six persons who received SLD in SSA had died in the last decade. This pooled incidence proportion of mortality while on the SLD therapy follow-up among the patients in SSA mirrors the global average mortality. Several measures including fortification
of newer or repurposed drugs and the initiation of shorter regimens were among the essential components for this acceptable mortality rate we estimated which was in line with the set target of EndTB Strategy. Nonetheless, the incidence of mortality was considerably high among DR-TB patients with comorbidities; diagnoses of other clinical conditions; resistance to SLD therapy; male sex; and excessive substance use. Therefore, modified measures involving shorter SLD regimens fortified with newer or repurposed drugs, differentiated care approaches, and support of substance use rehabilitation programs can help improve the treatment outcome of persons with the drug-resistant tuberculosis.

Supporting information

S1 Fig. Forest plot of mortality proportion by median duration of SLD therapy.
(TIF)

S2 Fig. Forest plot of mortality proportion by group of SLD regimen.
(TIF)

S3 Fig. Forest plot of mortality proportion by SSA regions.
(TIF)

S1 Table. PubMed search strategy and results.
(DOCX)

S2 Table. Quality assessment for the included studies.
(DOCX)

S3 Table. Completed PRISMA checklist.
(DOC)

Acknowledgments

We extend our acknowledgment to Tara Wilfong (Ph.D.) for her editorial supports in this manuscript preparation.

Author Contributions

Conceptualization: Dumessa Edessa.
Data curation: Dumessa Edessa, Fuad Adem, Bisrat Hagos, Mekonnen Sisay.
Formal analysis: Dumessa Edessa, Fuad Adem, Bisrat Hagos, Mekonnen Sisay.
Investigation: Dumessa Edessa, Fuad Adem, Bisrat Hagos, Mekonnen Sisay.
Methodology: Dumessa Edessa, Fuad Adem, Bisrat Hagos, Mekonnen Sisay.
Software: Dumessa Edessa.
Supervision: Dumessa Edessa, Fuad Adem, Bisrat Hagos, Mekonnen Sisay.
Validation: Dumessa Edessa, Fuad Adem, Bisrat Hagos, Mekonnen Sisay.
Writing – original draft: Dumessa Edessa.
Writing – review & editing: Dumessa Edessa, Fuad Adem, Bisrat Hagos, Mekonnen Sisay.
References

1. Lange C, Chesov D, Heyckendorf J, Leung CC, Udawadia Z, Dheda K: Drug-resistant tuberculosis: An update on disease burden, diagnosis and treatment. Respirology (Carlton, Vic) 2018, 23(7):656–673. https://doi.org/10.1111/resp.13304 PMID: 29641838

2. WHO: Global Tuberculosis Report. Accessed March 29, 2021 2020.

3. WHO: MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB) 2018 UPDATE. 2018.

4. Meintjes G: Management of drug-resistant TB in patients with HIV co-infection. J Int AIDS Soc 2014, 17(4 Suppl 3):19508. https://doi.org/10.7448/IAS.17.4.19508 PMID: 25394017

5. Ismail N, Ismail F, Omar SV, Blows L, Gardee Y, Koornhof H, et al: Drug resistant tuberculosis in Africa: Current status, gaps and opportunities. African journal of laboratory medicine 2018, 7(2):781. https://doi.org/10.4102/ajlm.v7i2.781 PMID: 30568900

6. WHO: Mortality rate (per 100 000 population). 2021.

7. Schnippel K, Ndjeika N, Maartens G, Meintjes G, Master I, Ismail N, et al: Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. The Lancet Respiratory medicine 2018, 6(9):699–706. https://doi.org/10.1016/S2213-2600(18)30235-2 PMID: 30001994

8. Kanwal S, Akhtar AM, Ahmed A: Factors associated with mortality to drug-resistant tuberculosis and their programmatic management in treatment centres of Punjab, Pakistan. JPMJ The Journal of the Pakistan Medical Association 2017, 67(6):858–862. PMID: 28585882

9. Balabanova Y, Ignatyeva O, Fiebig L, Riekstina V, Danilovits M, Jaama K, et al: Survival of patients with multidrug-resistant TB in Eastern Europe: what makes a difference? Thorax 2016, 71(9):854–861. https://doi.org/10.1136/thoraxjnl-2015-207638 PMID: 27012887

10. Khan I, Ahmad N, Khan S, Muhammad S, Ahmad Khan S, Ahmad I, et al: Evaluation of treatment outcomes and factors associated with unsuccessful outcomes in multidrug resistant tuberculosis patients in Baluchistan province of Pakistan. J Infect Public Health 2019, 12(6):809–815. https://doi.org/10.1016/j.jiph.2019.04.009 PMID: 31056438

11. Abdelbary BE, Garcia-Viveros M, Ramirez-Oropesa H, Rahbar MH, Restrepo BI: Predicting treatment failure, death and drug resistance using a computed risk score among newly diagnosed TB patients in Tamaulipas, Mexico. Epidemiol Infect 2017, 145(14):3020–3034. https://doi.org/10.1017/S0950268817001911 PMID: 28903800

12. Wang JJ, Zhou ML, Chen C, Wu G, Zhuo YP, Ren X, et al: [Survival time and influencing factors in multi-drug-resistant tuberculosis patients in Wuhan, 2006–2014]. Zhonghua liu xing bing xue za zhi = Zhonghua luxingbingxue zazhi 2019, 40(11):1409–1413. https://doi.org/10.3760/cma.j.issn.0254-6450.2019.11.013 PMID: 31838813

13. Cheepsattayakorn A, Cheepsattayakorn R: Novel compounds and drugs and recent patents in treating multidrug-resistant and extensively drug-resistant tuberculosis. Recent Pat Antinfect Drug Discov 2012, 7(2):141–156. https://doi.org/10.2174/157489112801619683 PMID: 22670838

14. Furin J, Bridgen G, Lessem E, Becerra MC: Novel pediatric delivery systems for second-line anti-tuberculosis medications: a case study. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease 2013, 17(9):1239–1241. https://doi.org/10.5888/tijhd.13.0196 PMID: 23827936

15. Giovagnoli S, Marenzoni ML, Nocchetti M, Santi C, Blasi P, Schoubben A, et al: Synthesis, characterization and in vitro extracellular and intracellular activity against Mycobacterium tuberculosis infection of new second-line antitubercular drug-palladium complexes. The Journal of pharmacy and pharmacology 2014, 66(1):106–121. https://doi.org/10.1111/jphp.12162 PMID: 24341950

16. Gupta R, Wells CD, Hittel N, Hafkin J, Geiter LJ: Delamanid in the treatment of multidrug-resistant tuberculosis. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease 2016, 20(12):33–37.

17. Kakkar AK, Daihya N: Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. Tuberculosis (Edinburgh, Scotland) 2014, 94(4):357–362. https://doi.org/10.1016/j.tube.2014.04.001 PMID: 24841672

18. Ahmad S, Mokaddas E: Current status and future trends in the diagnosis and treatment of drug-susceptible and multidrug-resistant tuberculosis. J Infect Public Health 2014, 7(2):75–91. https://doi.org/10.1016/j.jiph.2013.09.001 PMID: 24216518

19. Evans J, Segal H: Novel multiplex allele-specific PCR assays for the detection of resistance to second-line drugs in Mycobacterium tuberculosis. The Journal of antimicrobial chemotherapy 2010, 65(5):897–900. https://doi.org/10.1093/jac/dkq047 PMID: 20185419
20. Field SK, Fisher D, Jarand JM, Cowie RL: New treatment options for multidrug-resistant tuberculosis. *Therapeutic advances in respiratory disease* 2012, 6(5):255–268. https://doi.org/10.1177/175346812452193 PMID: 22763676

21. Garcia-Prats AJ, Schaaf HS, Hesseling AC: The safety and tolerability of the second-line injectable antituberculosis drugs in children. *Expert opinion on drug safety* 2016, 15(11):1491–1500. https://doi.org/10.1080/14740338.2016.1223623 PMID: 27548570

22. Singh AK, Maurya AK, Kant S, Umravo J, Kushwaha RA, Nag VL, et al: Rapid detection of drug resistance and mutational patterns of extensively drug-resistant strains by a novel GenoType® MTBDRsl assay. *Journal of postgraduate medicine* 2013, 59(3):179–185. https://doi.org/10.4103/0022-3859.118034 PMID: 24029194

23. Hirasen K, Berhanu R, Evans D, Rosen S, Sanne I, Long L: High rates of death and loss to follow up by 12 months of rifampicin resistant TB treatment in South Africa. *PLoS ONE* 2018, 13(10). https://doi.org/10.1371/journal.pone.0205463 PMID: 30300403

24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015, 4:1. https://doi.org/10.1186/s40843-016-0025-3 PMID: 25554246

25. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England)* 2010, 8(5):336–341. https://doi.org/10.1016/j.isu.2010.02.007 PMID: 20171303

26. WHO: Definitions and reporting framework for tuberculosis—2013 revision (updated December 2014 and January 2020). *Accessed March 31, 2021* 2013.

27. WHO: Tuberculosis: TB drug resistance types. *Accessed April 3 (2021)* 2021.

28. Moola S, Munn Z, Tufanaru C, Aromatiris E, Sears K, Sfetcu R, et al: Chapter 7: Systematic reviews of etiology and risk. In: Aromatiris E, Munn Z (Editors). The Joanna Briggs Institute Reviewer’s Manual. The Joanna Briggs Institute 2017, Available from https://reviewersmanual.joannabriggs.org/.

29. WHO: WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019.

30. D’Ascenzo F, Bollati M, Clementi F, Castagno D, Lagerqvist B, de la Torre Hernandez JM, et al: Incidence and predictors of coronary stent thrombosis: evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses. *International journal of cardiology* 2013, 167(2):575–584. https://doi.org/10.1016/j.ijcard.2012.01.080 PMID: 22360945

31. Ross JS, Mulvey GK, Stauffer B, Patlolla V, Bernheim SM, Keenan PS, et al: Statistical models and patient predictors of readmission for heart failure: a systematic review. *Arch Intern Med* 2008, 168(13):1371–1386. https://doi.org/10.1001/archinte.168.13.1371 PMID: 18625917

32. Hall EW, Morris SB, Moore BK, Erasmus L, Odendaal R, Menzies H, et al: Treatment Outcomes of Children With HIV Infection and Drug-resistant TB in Three Provinces in South Africa, 2005–2008. *The Pediatric infectious disease journal* 2017, 36(12):e322. https://doi.org/10.1097/INF.0000000000001691 PMID: 28746263

33. Hicks RM, Padayatchi N, Shah NS, Wolf A, Werner L, Sunkari VB, et al: Malnutrition associated with unfavorable outcome and death among South African MDR-TB and HIV co-infected children. *International Journal of and Lung Disease* 2014, 18(9):1074–1079. https://doi.org/10.5588/ijtld.14.0231 PMID: 25189555

34. Seddon JA, Hesseling AC, Willems M, Donald PR, Schaaf HS: Culture-confirmed multidrug-resistant tuberculosis in children: clinical features, treatment, and outcome. *Clin Infect Dis* 2012, 54(2):157–166. https://doi.org/10.1093/cid/cir772 PMID: 22052896

35. Tola HH, Holakouie-Naieni K, Mansournia MA, Yaseri M, Tesfaye E, Mahamed Z, et al: Low enrollment and high treatment success in children with drug-resistant tuberculosis in Ethiopia: A ten years national retrospective cohort study. *PLoS ONE* 2020, 15(2).

36. Borisov SE, Dheda K, Enverem M, Leyet RR, D’Ambrosio L, Centis R, et al: Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR and XDR-TB: a multicentre study. *European Respiratory Journal* 2017, 49(5):170387. https://doi.org/10.1183/13993003.00387-2017 PMID: 28652905

37. Brust JC, Gandhi NR, Carrara H, Osburn G, Padayatchi N: High treatment failure and default rates for patients with multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa, 2000–2003. *The international journal of tuberculosis and lung disease* 2010, 14(4):413–419. PMID: 20202298

38. Brust JCM, Shah NS, Mlisana K, Moodley P, Allana S, Campbell A, et al: Improved Survival and Cure Rates with Concurrent Treatment for Multidrug-Resistant Tuberculosis-Human Immunodeficiency Virus Coinfection in South Africa. *Clinical Infectious Diseases* 2018, 66(8):1246–1253. https://doi.org/10.1093/cid/cix1125 PMID: 29293906
39. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, et al: Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. *PLoS One* 2011, 6(7):e20436. https://doi.org/10.1371/journal.pone.0020436 PMID: 21799728

40. Girum T, Tairku Y, Dessu S: Survival status and treatment outcome of multidrug resistant tuberculosis (MDR-TB) among patients treated in treatment initiation centers (TIC) in South Ethiopia: a retrospective cohort study. *Annals of medical and health sciences research* 2017, 7(5).

41. Jikijela O: Clinical characteristics and treatment outcomes of multi-drug resistant tuberculosis patients attending a hospital in Buffalo City Metropolitan Municipality, Eastern Cape. 2018.

42. Kuaben C, Noeske J, Rieder HL, Ait-Khaled N, Abana Foe JL, Trebuch A: High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *International Journal of and Lung Disease* 2015, 19(5):517–524. https://doi.org/10.5588/ijtld.14.0535 PMID: 25868018

43. Loveday M, Wallengren K, Brust J, Roberts J, Voce A, Margot B, et al: Community-based care vs. centralised hospitalisation for MDR-TB patients, KwaZulu-Natal, South Africa. *The International Journal of Tuberculosis and Lung Disease* 2015, 19(2):163–171. https://doi.org/10.5588/ijtld.14.0369 PMID: 25574914

44. Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, et al: Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study. *Thorax* 2015, 70(12):1181–1188. https://doi.org/10.1136/thoraxjnl-2015-207374 PMID: 26506854

45. Ndjeka N, Schnippel K, Master I, Meinjjes G, Maartens G, Romero R, et al: High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. *The European respiratory journal* 2018, 52(6). https://doi.org/10.1183/13993003.01528-2018 PMID: 30361246

46. Padayatchi N, Abdool Karim SS, Naidoo K, Grobler A, Friedland G: Improved survival in multidrug-resistant tuberculosis patients receiving integrated tuberculosis and antiretroviral treatment in the SAPIT trial. *International journal of tuberculosis and lung disease* 2014, 18(2):147-154. https://doi.org/10.5588/ijtld.13.0632 PMID: 24429305

47. Satti H, McLaughlin MM, Hedt-Gauthier B, Atwood SS, Omotayo DB, Ntlamelle L, et al: Outcomes of multidrug-resistant tuberculosis treatment with early initiation of antiretroviral therapy for HIV co-infected patients in Lesotho. *PLoS One* 2012, 7(10):e46943. https://doi.org/10.1371/journal.pone.0046943 PMID: 23115633

48. Shibabaw A, Gelaw B, Wang S-H, Tessema B: Time to sputum smear and culture conversions in multidrug-resistant tuberculosis at University of Gondar Hospital, Northwest Ethiopia. *PloS one* 2018, 13(6):e0198080. https://doi.org/10.1371/journal.pone.0198080 PMID: 29944658

49. Shin SS, Modongo C, Boyd R, Caiphus C, Kuate L, Kgwaadira B, et al: High treatment success rates among HIV-infected multidrug-resistant tuberculosis patients after expansion of antiretroviral therapy treatment. *The European respiratory journal* 2019, 54(4):861–867. https://doi.org/10.1183/13993003.0046943 PMID: 27525155

50. Trebuch A, Schwoebel V, Kashongwe Z, Bakayoko A, Kuaban C, Noeske J, et al: Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease* 2018, 22(1):17–25. https://doi.org/10.5588/ijtld.17.0498 PMID: 29149917

51. Umanah T, Ncyaiyana J, Nyasulu P: Predictors of cure among human immunodeficiency virus co-infected multidrug-resistant tuberculosis patients at Sizwe Tropical Disease Hospital Johannesburg, South Africa. *Transactions of The Royal Society of Tropical Medicine and Hygiene*, trv025 2015. https://doi.org/10.1093/trstmh/trv025 PMID: 25787727

52. Umanah T, Ncyaiyana J, Padanilam X, Nyasulu PS: Treatment outcomes in multidrug resistant tuberculosis-human immunodeficiency virus Co-infected patients on anti-retroviral therapy at Sizwe Tropical Disease Hospital Johannesburg, South Africa. *BMC Infect Dis* 2015, 15:478. https://doi.org/10.1186/s12879-015-1214-3 PMID: 26511616

53. Verdecchia M, Keus K, Blankley S, Yambe D, Ssonko C, Piening T, et al: Model of care and risk factors for poor outcomes in patients on multi-drug resistant tuberculosis treatment at two facilities in eSwatini (formerly Swaziland), 2011–2013. *PloS one* 2018, 13(10):e0205601. https://doi.org/10.1371/journal.pone.0205601 PMID: 30334452

54. Cox H, Hughes J, Daniels J, Azevedo V, McDermid C, Poolman M, et al: Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease* 2014, 18(4):441–448. https://doi.org/10.5588/ijtld.13.0742 PMID: 24670700
55. Adewumi AO: Treatment outcomes in patients infected with multidrug resistant tuberculosis and in patients with multidrug resistant tuberculosis coinfected with human immunodeficiency virus at Bre- welskloof Hospital. 2012.

56. Alakaye OJ: Time to sputum culture conversion of Multidrug-Resistant tuberculosis in HIV positive versus HIV negative patients in Lesotho. University of Pretoria; 2018.

57. Alene KA, Viney K, McBryde ES, Tsegaye AT, Clements AC: Treatment outcomes in patients with multidrug-resistant tuberculosis in north-west Ethiopia. *Tropical medicine & international health*. TM & IH 2017, 22(3):351–362. https://doi.org/10.1111/tmi.12826 PMID: 27978594

58. Ali MH, Alrasheedy AA, Kibuule D, Godman B, Hassali MA, Ali HMH: Assessment of multidrug-resistant tuberculosis (MDR-TB) treatment outcomes in Sudan; findings and implications. *Expert review of anti-infective therapy* 2019(just-accepted). https://doi.org/10.1080/14787210.2019.1689818 PMID: 31689134

59. Bajehson M, Musa BM, Gidado M, Nsa B, Sani U, Habibu AT, et al: Determinants of mortality among patients with drug-resistant tuberculosis in northern Nigeria. *PLoS One* 2019, 14(11):e0225165. https://doi.org/10.1371/journal.pone.0225165 PMID: 31743358

60. Fantaw D: Assessment of the Survival Status and Risk Factors for the Mortality of Multidrug Resistant Tuberculosis Patients at Adama and Bishoftu General Hospitals, Oromia, Ethiopia. Addis Ababa University; 2018.

61. Getachew T, Bayray A, Weldearegay B: Survival and predictors of mortality among patients under multi-drug resistant tuberculosis treatment in Ethiopia: St. Peter’s specialized tuberculosis hospital, Ethiopia. *Int J Pharm Sci Res* 2013, 4(2):776.

62. Huerga H, Bastard M, Kamene M, Wanjala S, Arnold A, Oucho N, et al: Outcomes from the first multi-drug-resistant tuberculosis programme in Kenya. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease* 2017, 21(3):314–319. https://doi.org/10.5588/ijtld.16.0661 PMID: 28225342

63. Kapata N, Grobusch MP, Chongwe G, Chanda-Kapata P, Ngosa W, Tembo M, et al: Outcomes of multidrug-resistant tuberculosis in Tanzania: a cohort analysis. *Infection* 2017, 45(6):831–839. https://doi.org/10.1007/s15010-016-1054-8 PMID: 27779436

64. Kashongwe MI, Mbulula L, Umba P, Lepira FB, Kaswa M, Kashongwe ZM: Factors Associated with Mortality among Multidrug Resistant Tuberculosis MDR/RR-TB Patients in Democratic Republic of Congo. *Journal of Tuberculosis Research* 2017, 5(04):276.

65. Leveri TH, Lekule I, Mollel E, Lyamuwa F, Kilonzo K: Predictors of treatment outcomes among multi-drug resistant tuberculosis patients in Tanzania. *Tuberculosis research and treatment* 2019, 2019. https://doi.org/10.1155/2019/3569018 PMID: 30891315

66. Marais E, Mlambo CK, Lewis JJ, Rastogi N, Zozio T, Grobusch MP, et al: Treatment outcomes of multidrug-resistant tuberculosis patients in Gauteng, South Africa. *Infection* 2014, 42(2):405–413. https://doi.org/10.1007/s15010-013-0572-2 PMID: 24363208

67. Mbele DJ, Kiarié JW, Wairia A, Kamene M, Okumu ME: Treatment outcomes of drug-resistant tuberculosis patients in Kenya. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease* 2016, 20(11):1477–1482. https://doi.org/10.5588/ijtld.15.0915 PMID: 27776588

68. Mohr E, Cox V, Wilkinson L, Moyo S, Hughes J, Daniels J, et al: Programmatic treatment outcomes in HIV-infected and uninfected drug-resistant TB patients in Khayelitsha, South Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2015, 109(7):425–432. https://doi.org/10.1093/trstmh/trv037 PMID: 25979526

69. Molalign S, Wencheke E: Risk factors of mortality in patients with multi-drug resistant TB. *Ethiop J Health Dev* 2015, 29.

70. Mollel E, Lekule I, Lynen L, Decroo T: Effect of reliance on Xpert MTB/RIF on time to treatment and multidrug-resistant tuberculosis treatment outcomes in Tanzania: a retrospective cohort study. *Int Health* 2019, 11(6):520–527. https://doi.org/10.1093/inthealth/ihz005 PMID: 30806660

71. Schnippel K, Shearer K, Evans D, Berhanu R, Djamin S, Ndjeka N: 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. *International Journal of Infectious Diseases* 2015, 39:89–94. https://doi.org/10.1016/j.ijid.2015.09.002 PMID: 26358856

72. Van Der Walt M, Lancaster J, Shean K: Tuberculosis Case Fatality and Other Causes of Death among Multidrug-Resistant Tuberculosis Patients in a High HIV Prevalence Setting, 2000–2008, South Africa. *PLoS one* 2016, 11(3):e0144249–e0144249. https://doi.org/10.1371/journal.pone.0144249 PMID: 26950554
73. Woldeyohannes D, Assefa T, Aman R, Tekalegn Y, Hailmariam Z: Predictors of time to unfavorable treatment outcomes among patients with multidrug resistant tuberculosis in Oromia region, Ethiopia. *PloS One* 2019, 14(10). https://doi.org/10.1371/journal.pone.0224025 PMID: 31665154

74. Ahmad N, Ahuja SD, Akkerman OW, Alfenaa JR, Anderson LF, Baghai P, et al: Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018, 392(10150):821–834. https://doi.org/10.1016/S0140-6736(18)31644-1 PMID: 30215381

75. Bastos ML, Lan Z, Menzies D: An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis. *The European respiratory journal* 2017, 49(3). https://doi.org/10.1183/13993003.00803-2016 PMID: 28331031

76. Chang KC, Nuerberger E, Sojgjui G, Leung CC: New drugs and regimens for tuberculosis. *Respirology (Carlton, Vic)* 2018, 23(11):978–990. https://doi.org/10.1111/resp.13345 PMID: 29917287

77. Isaakidis P, Casas EC, Das M, Tseretopoulou X, Nzani EE, Ford N: Treatment outcomes for HIV and MDR-TB co-infected adults and children: systematic review and meta-analysis. *The international journal of tuberculosis and lung disease: the official journal of the International Union Against Tuberculosis and Lung Disease* 2015, 19(6):969–978. https://doi.org/10.5588/ijtld.15.0123 PMID: 26162364

78. Ahmad Khan F, Salim MAH, du Cros P, Casas EC, Khamraev A, Sikhondze W, et al: Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *The European respiratory journal* 2017, 50(1). https://doi.org/10.1183/13993003.00661-2017 PMID: 28751411

79. Fox GJ, Benedetti A, Cox H, Koh WJ, Viiklepp P, Ahuja S, et al: Group 5 drugs for multidrug-resistant tuberculosis: individual patient data meta-analysis. *The European respiratory journal* 2017, 49(1). https://doi.org/10.1183/13993003.00993-2016 PMID: 28049171

80. Mohd Shariff N, Shah SA, Kamaludin F: Predictors of death among drug-resistant tuberculosis patients in Kuala Lumpur, Malaysia: A retrospective cohort study from 2009 to 2013. *J Glob Antimicrob Resist* 2016, 6:102–107. https://doi.org/10.1016/j.jgar.2016.04.005 PMID: 27330850

81. Javaid A, Ullah I, Masud H, Basit A, Ahmad W, Butt ZA, et al: Predictors of poor treatment outcomes in multidrug-resistant tuberculosis patients: a retrospective cohort study. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2018, 24(6):612–617. https://doi.org/10.1111/jcmi.13345 PMID: 28973158

82. Gupta N, Jorwal P: Treatment Outcomes Associated with Multidrug-resistant Tuberculosis. *Journal of global infectious diseases* 2018, 10(3):125–128. https://doi.org/10.4103/jgid.jgid_96_17 PMID: 30166810

83. Chung-Delgado K, Guileen-Bravo S, Revilla-Montag A, Bernabe-Ortiz A: Mortality among MDR-TB cases: comparison with drug-susceptible tuberculosis and associated factors. *PloS One* 2015, 10(3):e0119332. https://doi.org/10.1371/journal.pone.0119332 PMID: 25790076

84. Gayoso R, Dalcolmo M, Braga JU, Barreira D: Predictors of mortality in multidrug-resistant tuberculosis patients from Brazilian reference centers, 2005 to 2012. *The Brazilian journal of infectious diseases: an official publication of the Brazilian Society of Infectious Diseases* 2018, 22(4):305–310. https://doi.org/10.1016/j.bjid.2018.07.002 PMID: 30086258

85. Mutembo S, Mutanga JN, Musokotwane K, Kanene C, Dobbin K, Yao X, et al: Urban-rural disparities in treatment outcomes among recurrent TB cases in Southern Province, Zambia. *BMC Infect Dis* 2019, 19(1):1087. https://doi.org/10.1186/s12879-019-4709-5 PMID: 31888518

86. Olayeye AO, Beke AK: Survival of smear-positive multidrug resistant tuberculosis patients in Witbank, South Africa: A retrospective cohort study. *Infectious diseases (London, England)* 2016, 48(6):422–427. https://doi.org/10.3109/23744235.2016.1153806 PMID: 26954520

87. Kurbatova EV, Taylor A, Gammino VM, Bayona J, Becerra M, Danilovitz M, et al: Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. *Tuberculosis (Edinburgh, Scotland)* 2012, 92(5):397–403. https://doi.org/10.1016/j.tube.2012.06.003 PMID: 22789497

88. Manda SO, Masenyelets Lj, Lancaster JL, van der Walt ML: Risk of Death among HIV Co-Infected Multidrug Resistant Tuberculosis Patients, Compared To Mortality in the General Population of South Africa. *J AIDS Clin Res* 2013, Suppl 3:7.

89. Mollle EW, Chilongola JO: Predictors for Mortality among Multidrug-Resistant Tuberculosis Patients in Tanzania. *J Trop Med* 2017, 2017:9241238. https://doi.org/10.1155/2017/9241238 PMID: 28808447

90. Mannheimer SB, Sepkowitz KA, Stoeckle M, Friedman CR, Hafner A, Riley LW: Risk factors and outcome of human immunodeficiency virus-infected patients with sporadic multidrug-resistant tuberculosis in New York City. *The international journal of tuberculosis and lung disease: the official journal of the International Union Against Tuberculosis and Lung Disease* 1997, 1(4):319–325. PMID: 9432387
91. Suryawanshi SL, Shewade HD, Nagaraja SB, Nair SA, Parmar M: Unfavourable outcomes among patients with MDR-TB on the standard 24-month regimen in Maharashtra, India. *Public Health Action* 2017, 7(2):116–122. https://doi.org/10.5588/pha.17.0013 PMID: 28695084

92. Bisson GP, Bastos M, Campbell JR, Bang D, Brust JC, Issaikidis P, et al: Mortality in adults with multidrug-resistant tuberculosis and HIV by antiretroviral therapy and tuberculosis drug use: an individual patient data meta-analysis. *Lancet* 2020, 396(10248):402–411. https://doi.org/10.1016/S0140-6736(20)31316-7 PMID: 32771107

93. Mesfin YM, Hailemariam D, Biadgilign S, Kibret KT: Association between HIV/AIDS and multi-drug resistance tuberculosis: a systematic review and meta-analysis. *PLoS One* 2014, 9(1):e82235. https://doi.org/10.1371/journal.pone.0082235 PMID: 24416139

94. Singh A, Prasad R, Balasubramaniv V, Gupta N: Drug-Resistant Tuberculosis and HIV Infection: Current Perspectives. *HIV/AIDS (Auckland, NZ)* 2020, 12:9–31. https://doi.org/10.2147/HIV.S193059 PMID: 32021483

95. González Fernández L, Casas EC, Singh S, Churchyard GJ, Brigden G, Gotuzzo E, et al: New opportunities in tuberculosis prevention: implications for people living with HIV. *J Int AIDS Soc* 2020, 23(1): e25438. https://doi.org/10.1002/jia2.25438 PMID: 31913556

96. Deshmukh R, Shah A, Sachdeva KS, Sreenivas AN, Gupta RS, Khaparde SD: Scaling up of HIV-TB collaborative activities: Achievements and challenges in India. *The Indian journal of tuberculos* 2016, 63(1):4–7. https://doi.org/10.1016/j.ijtb.2016.02.003 PMID: 27235937

97. Gandhi NR, Andrews JR, Brust JC, Montreuil R, Weissman D, Heo M, et al: Risk factors for mortality among MDR- and XDR-TB patients in a high HIV prevalence setting. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease* 2012, 16(1):90–97.

98. Field N, Lim MS, Murray J, Dowdeswell RJ, Glynn JR, Sonnenberg P: Timing, rates, and causes of death in a large South African tuberculosis programme. *BMC Infect Dis* 2014, 14:3858. https://doi.org/10.1186/s12879-014-0679-9 PMID: 25528248

99. Chavan VV, Dalal A, Nagaraja S, Thekkur P, MANSoor H, Meneguim A, et al: Ambulatory management of pre- and extensively drug resistant tuberculosis patients with imipenem delivered through port-a-cath: A mixed methods study on treatment outcomes and challenges. *PLoS One* 2020, 15(6): e0234651. https://doi.org/10.1371/journal.pone.0234651 PMID: 32944714

100. Zürcher K, Ballif M, Fenner L, Borrell S, Keller PM, Gonkoroko J, et al: Drug susceptibility testing and mortality in patients treated for tuberculosis in high-burden countries: a multicentre cohort study. *Lancet Infect Dis* 2019, 19(3):298–307. https://doi.org/10.1016/S1473-3099(18)30673-x PMID: 30744962

101. Kim DH, Kim HJ, Park SK, Kong SJ, Kim YS, Kim TH, et al: Treatment outcomes and survival based on drug resistance patterns in multidrug-resistant tuberculosis patients with imipenem delivered through port-a-cath: A mixed methods study on treatment outcomes and challenges. *Am J Respir Crit Care Med* 2010, 182(1):113–119. https://doi.org/10.1164/rcrm.200911-1656OC PMID: 2024066

102. Ngabonziza JS, Habimana YM, Decroo T, Migambi P, Dushime A, Mazariati JB, et al: Reduction of diagnostic and treatment delays reduces rifampicin-resistant tuberculosis mortality in Rwanda. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease* 2020, 24(3):329–339. https://doi.org/10.5588/ijtld.19.0298 PMID: 3228764

103. Nair D, Navneethapandian PD, Tripathy JP, Harries AD, KJ Lipon JS, Watson B, et al: Impact of rapid molecular diagnostic tests on time to treatment initiation and outcomes in patients with multidrug-resistant tuberculosis, Tamil Nadu, India. *Trans R Soc Trop Med Hyg* 2016, 110(9):534–541. https://doi.org/10.1093/trstmh/trw060 PMID: 27738284

104. Eliseev P, Balantcev G, Nikishova E, Gaida A, Bogdanova E, Enarson D, et al: The Impact of a Line Probe Assay Based Diagnostic Algorithm on Time to Treatment Initiation and Treatment Outcomes for Multidrug Resistant TB Patients in Arkhangelsk Region, Russia. *PLoS One* 2016, 11(4):e0152761. https://doi.org/10.1371/journal.pone.0152761 PMID: 27055269

105. Chiang SS, Starke JR, Miller AC, Cruz AT, Del Castillo H, Valdivia WJ, et al: Baseline Predictors of Treatment Outcomes in Children With Multidrug-Resistant Tuberculosis: A Retrospective Cohort Study. *Clin Infect Dis* 2016, 63(8):1063–1071. https://doi.org/10.1093/cid/ciw489 PMID: 27485026

106. Nair D, Velayutham B, Kannan T, Tripathy JP, Harries AD, Natrajain M, et al: Predictors of unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India. *Public Health Action* 2017, 7(1):32–38. https://doi.org/10.5588/pha.16.0055 PMID: 28775941

107. Jain S, Varudkar HG, Julika A, Singapurwala M, Khosla S, Shah B: Socio-economical and Clinico-Radiological Profile of 474 MDR TB Cases of a Rural Medical College. *The Journal of the Association of Physicians of India* 2018, 66(12):14–18. PMID: 31315318
108. Mukati S, Julka A, Varudkar HG, Singapurwala M, Agrawat JC, Bhandari D, et al: A study of clinical profile of cases of MDR-TB and evaluation of challenges faced in initiation of second line Anti tuberculosis treatment for MDR-TB cases admitted in drug resistance tuberculosis center. *The Indian journal of tuberculosis* 2019, 66(3):358–363. https://doi.org/10.1016/j.ijtb.2016.11.031 PMID: 31439180

109. Venkatesh U, Srivastava DK, Srivastava AK, Tiwari HC: Epidemiological profile of multidrug-resistant tuberculosis patients in Gorakhpur Division, Uttar Pradesh, India. *Journal of family medicine and primary care* 2018, 7(3):589–595. https://doi.org/10.4103/jfmpc.jfmpc_99_17 PMID: 30112315

110. Podewils LJ, Holtz T, Riekstina V, Skripconoka V, Zarovska E, Kirvelaitė G, et al: Impact of malnutrition on clinical presentation, clinical course, and mortality in MDR-TB patients. *Epidemiol Infect* 2011, 139(1):113–120. https://doi.org/10.1017/S0950268810000907 PMID: 20429966

111. Singla R, Raghu B, Gupta A, Caminero JA, Sethi P, Tayal D, et al: Risk factors for early mortality in patients with pulmonary tuberculosis admitted to the emergency room. *Pulmonology* 2020. https://doi.org/10.1016/j.pulmoe.2020.02.002 PMID: 32127307

112. Pradipta IS, Van’t Boveneind-Vrublevskaya N, Akkerman OW, Alffenara JC, Hak E: Treatment outcomes of drug-resistant tuberculosis in the Netherlands, 2005–2015. *Antimicrobial resistance and infection control* 2019, 8:115. https://doi.org/10.1186/s13756-019-0561-z PMID: 31338162

113. Samuels JP, Sood A, Campbell JR, Ahmad Khan F, Johnston JC: Comorbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. *Scientific reports* 2018, 8(1):4980. https://doi.org/10.1038/s41598-018-23344-z PMID: 29563561

114. Messer T, Lammers G, Müller-Siecheneder F, Schmidt RF, Latifi S: Substance abuse in patients with bipolar disorder: A systematic review and meta-analysis. *Psychiatry research* 2017, 253:338–350. https://doi.org/10.1016/j.psychres.2017.02.067 PMID: 28419959