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Linezolid for drug-resistant pulmonary tuberculosis (Review)

Singh B, Cocker D, Ryan H, Sloan DJ

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[Intervention Review]

Linezolid for drug-resistant pulmonary tuberculosis

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ABSTRACT

Background

Linezolid was recently re-classified as a Group A drug by the World Health Organization (WHO) for treatment of multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), suggesting that it should be included in the regimen for all patients unless contraindicated. Linezolid use carries a considerable risk of toxicity, with the optimal dose and duration remaining unclear. Current guidelines are mainly based on evidence from observational non-comparative studies.

Objectives

To assess the efficacy of linezolid when used as part of a second-line regimen for treating people with MDR and XDR pulmonary tuberculosis, and to assess the prevalence and severity of adverse events associated with linezolid use in this patient group.

Search methods

We searched the following databases: the Cochrane Infectious Diseases Specialized Register; CENTRAL; MEDLINE; Embase; and LILACS up to 13 July 2018. We also checked article reference lists and contacted researchers in the field.

Selection criteria

We included studies in which some participants received linezolid, and others did not. We included randomized controlled trials (RCTs) of linezolid for MDR and XDR pulmonary tuberculosis to evaluate efficacy outcomes. We added non-randomized cohort studies to evaluate adverse events.

Primary outcomes were all-cause and tuberculosis-associated death, treatment failure, and cure. Secondary outcomes were treatment interrupted, treatment completed, and time to sputum culture conversion. We recorded frequency of all and serious adverse events, adverse events leading to drug discontinuation or dose reduction, and adverse events attributed to linezolid, particularly neuropathy, anaemia, and thrombocytopenia.

Data collection and analysis

Two review authors (BS and DC) independently assessed the search results for eligibility and extracted data from included studies. All review authors assessed risk of bias using the Cochrane 'Risk of bias' tool for RCTs and the ROBINS-I tool for non-randomized studies. We contacted study authors for clarification and additional data when necessary.

We were unable to perform a meta-analysis as one of the RCTs adopted a study design where participants in the study group received linezolid immediately and participants in the control group received linezolid after two months, and therefore there were no comparable data from this trial. We deemed meta-analysis of non-randomized study data inappropriate.

Main results

We identified three RCTs for inclusion. One of these studies had serious problems with allocation of the study drug and placebo, so we could not analyse data for intervention effect from it. The remaining two RCTs recruited 104 participants. One randomized 65 participants to receive linezolid or not, in addition to a background regimen; the other randomized 39 participants to addition of linezolid to a background regimen immediately, or after a delay of two months. We included 14 non-randomized cohort studies (two prospective, 12 retrospective), with a total of 1678 participants.

Settings varied in terms of income and tuberculosis burden. One RCT and 7 out of 14 non-randomized studies commenced recruitment in or after 2009. All RCT participants and 38.7% of non-randomized participants were reported to have XDR-TB.

Dosing and duration of linezolid in studies were variable and reported inconsistently. Daily doses ranged from 300 mg to 1200 mg; some studies had planned dose reduction for all participants after a set time, others had incompletely reported dose reductions for some participants, and most did not report numbers of participants receiving each dose. Mean or median duration of linezolid therapy was longer than 90 days in eight of the 14 non-randomized cohorts that reported this information.

Duration of participant follow-up varied between RCTs. Only five out of 14 non-randomized studies reported follow-up duration.

Both RCTs were at low risk of reporting bias and unclear risk of selection bias. One RCT was at high risk of performance and detection bias, and low risk for attrition bias, for all outcomes. The other RCT was at low risk of detection and attrition bias for the primary outcome, with unclear risk of detection and attrition bias for non-primary outcomes, and unclear risk of performance bias for all outcomes. Overall risk of bias for the non-randomized studies was critical for three studies, and serious for the remaining 11.

One RCT reported higher cure (risk ratio (RR) 2.36, 95% confidence interval (CI) 1.13 to 4.90, very low-certainty evidence), lower failure (RR 0.26, 95% CI 0.10 to 0.70, very low-certainty evidence), and higher sputum culture conversion at 24 months (RR 2.10, 95% CI 1.30 to 3.40, very low-certainty evidence), amongst the linezolid-treated group than controls, with no differences in other primary and secondary outcomes. This study also found more anaemia (17/33 versus 2/32), nausea and vomiting, and neuropathy (14/33 versus 1/32) events amongst linezolid-receiving participants. Linezolid was discontinued early and permanently in two of 33 (6.1%) participants who received it.

The other RCT reported higher sputum culture conversion four months after randomization (RR 2.26, 95% CI 1.19 to 4.28), amongst the group who received linezolid immediately compared to the group who had linezolid initiation delayed by two months. Linezolid was discontinued early and permanently in seven of 39 (17.9%) participants who received it.

Linezolid discontinuation occurred in 22.6% (141/624; 11 studies), of participants in the non-randomized studies. Total, serious, and linezolid-attributed adverse events could not be summarized quantitatively or comparatively, due to incompleteness of data on duration of follow-up and numbers of participants experiencing events.

Authors' conclusions

We found some evidence of efficacy of linezolid for drug-resistant pulmonary tuberculosis from RCTs in participants with XDR-TB but adverse events and discontinuation of linezolid were common. Overall, there is a lack of comparative data on efficacy and safety. Serious risk of bias and heterogeneity in conducting and reporting non-randomized studies makes the existing, mostly retrospective, data difficult to interpret. Further prospective cohort studies or RCTs in high tuberculosis burden low-income and lower-middle-income countries would be useful to inform policymakers and clinicians of the efficacy and safety of linezolid as a component of drug-resistant TB treatment regimens.

PLAIN LANGUAGE SUMMARY

Linezolid for managing people with drug-resistant tuberculosis

What is drug-resistant tuberculosis, and how might linezolid work?

Tuberculosis is caused by infection with *Mycobacterium tuberculosis* bacteria. When there are symptoms or signs of illness, this is called active tuberculosis. An estimated one-third of the world's population are infected with tuberculosis, and around 1.4 million people died from active tuberculosis in 2015.

Bacteria that cause tuberculosis can develop resistance to the drugs most commonly used to treat tuberculosis, also called first-line antibiotics. This is an increasing problem that makes treatment more difficult, because second-line tuberculosis treatment drugs are less powerful against the bacteria, and more likely to cause harmful effects. Standard treatment for drug-resistant tuberculosis requires patients to take multiple antibiotics for nearly two years. Linezolid is a second-line drug that laboratory studies have found to be good at killing bacteria that cause tuberculosis, but that can also cause frequent, serious harmful effects.

The review question

Recent international guidelines recommend trying to include linezolid in the treatment of all patients with multi-drug resistant tuberculosis, but there is concern about whether enough good evidence exists to tell us how well it works, what dose is best, and how safe it is for people who take it.

Study characteristics

We searched for evidence up to 13 July 2018. We analysed data from two trials, one of which randomly allocated 65 people with drug-resistant tuberculosis to either a linezolid-containing or linezolid-free drug combination, and another that randomly allocated 39 participants to receive linezolid as part of their treatment from the start or have it added after a delay of two months. We also included 14 studies, including 1678 people, in which some participants received linezolid but others did not, but this was not determined at random.

What are the main results of the review?

One trial showed a higher likelihood of cure and lower risk of treatment failure in participants receiving linezolid compared to those who did not. The second trial showed that participants who received linezolid immediately had a higher chance of tuberculosis being cleared from their sputum four months after the start of the study than those who added linezolid after a two-month delay.

When they examined safety, the first trial found a higher risk of developing low red blood cell counts, nausea and vomiting, and nerve damage in people receiving linezolid. From 11 of the non-randomized studies that reported this, 22.6% of people had to stop linezolid due to adverse effects (side effects), though further comparisons of harmful effects were not possible due to incomplete reporting in the non-randomized studies.

Overall, although there is some evidence of benefit, we have very low certainty in its accuracy. More high-quality studies are required before we can be certain how effective and safe linezolid is for drug-resistant tuberculosis.

How up-to-date is this review?

This review is current up to 13 July 2018.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Linezolid compared to no linezolid for drug-resistant pulmonary tuberculosis

Patient or population: drug-resistant pulmonary tuberculosis
Setting: one study (Tang 2015): China; all adults; all extensively drug resistant; no participants with HIV (excluded)
Intervention: linezolid
Comparison: no linezolid

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with no linezolid	Risk with linezolid				
Death	9 per 100	6 per 100 (1 to 34)	RR 0.65 (0.12 to 3.62)	65 (1 RCT)	⊕◯◯◯ **Very low**[a,b,c,d] due to risk of bias, imprecision, and indirectness	We are uncertain whether or not linezolid reduces death
Treatment failure	47 per 100	12 per 100 (5 to 33)	RR 0.26 (0.10 to 0.70)	65 (1 RCT)	⊕◯◯◯ **Very low**[a,b,d,e] due to risk of bias, imprecision, and indirectness	We are uncertain whether or not linezolid reduces treatment failure
Cure	22 per 100	52 per 100 (25 to 100)	RR 2.36 (1.13 to 4.90)	65 (1 RCT)	⊕◯◯◯ **Very low**[a,b,d,f] due to risk of bias, imprecision, and indirectness	We are uncertain whether or not linezolid increases cure
Treatment interrupted	9 per 100	12 per 100 (3 to 50)	RR 1.29 (0.31 to 5.33)	65 (1 RCT)	⊕◯◯◯ **Very low**[a,b,c,d] due to risk of bias, imprecision, and indirectness	We are uncertain whether or not linezolid reduces treatment interruption

Treatment completed	13 per 100	18 per 100 (6 to 59)	RR 1.45 (0.45 to 4.68)	65 (1 RCT)	⊕○○○ **Very low**[a,b,c,d] due to risk of bias, imprecision, and indirectness	We are uncertain whether linezolid increases treatment completion as the certainty of the evidence is very low
Sputum culture conversion at 24 months	38 per 100	79 per 100 (49 to 100)	RR 2.1 (1.3 to 3.4)	65 (1 RCT)	⊕○○○ **Very low**[b,d,f] due to risk of bias, imprecision, and indirectness	We are uncertain whether or not linezolid increases sputum culture conversion
Total adverse events[g]	28 (32 participants) in no-linezolid group; 74 (33 participants) in linezolid group[g]		-	65 (1 RCT)	⊕○○○ **Very low**[a,d,h,i] due to risk of bias, imprecision, and indirectness	We are uncertain whether or not linezolid reduces total adverse events
Serious adverse events	-	-	-	-	-	Not reported
Antituberculous treatment discontinuation[j]	3 per 100	6 per 100 (1 to 64)	RR 1.94 (0.18 to 20.35)	65 (1 RCT)	⊕○○○ **Very low**[a,b,d,k] due to risk of bias, imprecision, and indirectness	We are uncertain whether or not linezolid reduces antituberculous treatment discontinuation
Linezolid discontinuation[l]	2/33 participants receiving linezolid had permanent discontinuation of linezolid		-	65 (1 RCT)	-	Comparison is not possible for this outcome

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] No serious inconsistency: only one study was included.
[b] Downgraded by one level for serious indirectness: the population (drug-resistant tuberculosis), though meeting criteria for inclusion in the review, only included adults, who had extensively drug-resistant tuberculosis, and tested negative for HIV infection. Recruitment was from only one country (China). Participants were excluded if they could not afford linezolid.
[c] Downgraded by two levels for very serious imprecision: the CI is wide, and the event rate is low.
[d] Downgraded by two levels for risk of bias: random sequence generation and allocation concealment were not described, therefore leading to unclear risk of bias. There was no blinding, nor placebo control, so there was a high risk of performance and detection bias.
[e] Serious imprecision, due to small sample size.
[f] Downgraded by two levels for very serious imprecision: the CI is wide and sample size is small.
[g] Due to lack of reporting of follow-up duration, we were unable to calculate a risk ratio.
[h] Downgraded by one level for serious indirectness: due to lack of follow-up duration data, we were unable to perform comparative analysis for this outcome.
[i] Downgraded by two levels for very serious imprecision, due to inability to calculate risk ratio.
[j] Antituberculous treatment (ATT): a further two participants in each group discontinued ATT due to inability to afford the drugs. We included only discontinuations due to clinical reasons in the results, for the purpose of the review.
[k] Downgraded by two levels for very serious imprecision: number of events was small, with a resulting wide CI, ranging from very large increase to an 82% decrease in discontinuation.
[l] Some participants discontinued linezolid temporarily, but the number of those was not reported. Participants discontinuing linezolid due to being unable to afford it (n = 2) are not included in this number.

BACKGROUND

Description of the condition

Tuberculosis is caused by infection with bacteria of the *Mycobacterium tuberculosis* complex. It remains one of the leading infectious causes of death worldwide; there were 1.4 million deaths from tuberculosis worldwide in 2015, with an additional 0.4 million deaths from tuberculosis amongst people living with HIV (WHO 2016b). Pulmonary tuberculosis is the most common form of tuberculosis, and the most important from a public health perspective because tuberculosis is transmitted by aerosolized droplets from people with active pulmonary tuberculosis when they cough (Vashishtha 2013). It is estimated that around one third of the world's population are infected with tuberculosis, although of these only one in ten will develop active tuberculosis disease (WHO 2009).

Most people with tuberculosis are infected with strains of *M tuberculosis* that are treatable with the standard first-line drugs recommended by the World Health Organization (WHO) guidelines: rifampicin, isoniazid, pyrazinamide, and ethambutol (WHO 2010). Early diagnosis and treatment with effective drugs is a mainstay of tuberculosis disease control, as well as being a life-saving intervention for people with tuberculosis.

Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis disease that is caused by *M tuberculosis* strains that have acquired resistance to two important drugs in the first-line regimen: rifampicin and isoniazid (Sharma 2006). Rifampicin-monoresistant tuberculosis is often managed as MDR-TB (WHO 2016a). Extensively drug-resistant tuberculosis (XDR-TB), occurs when *M tuberculosis* strains are resistant to rifampicin, isoniazid, and any of the antibiotics in the fluoroquinolone class, as well as any of the three injectable drugs used in the second-line treatment of tuberculosis: amikacin, kanamycin, and capreomycin (WHO 2016a).

The WHO estimates that 480,000 cases of MDR-TB occurred in 2015, with 190,000 deaths worldwide, and an estimated 9.5% of people with MDR-TB actually having XDR-TB (WHO 2016b). Detection of drug-resistant tuberculosis is challenging and currently requires costly laboratory services. Access to effective treatment is far from universal. Despite rapid progress, only 12% of new tuberculosis cases were tested for drug resistance in 2014, with case detection at only 41% (WHO 2015a). Over the last decade treatment success rates have remained static at around 50% (WHO 2015a), and the international tuberculosis community has recognized that new drugs and regimens with improved efficacy are urgently needed to improve cure rates. The WHO End TB Strategy outlines measures for post-2015 tuberculosis control; these include a goal to detect and treat everyone with drug-resistant tuberculosis, which will require significant scaling up of resources and efforts (WHO 2014).

Constructing drug-resistant tuberculosis chemotherapy regimens is difficult; several of the available agents are expensive and toxic, and efficacy is uncertain because data from clinical studies are limited (Chang 2013a). This is especially true for XDR-TB. Treatment for drug-resistant tuberculosis is long: conventional regimens are administered for a total of 20 months for most patients, with an initial intensive phase of around eight months, dependent upon response to therapy (WHO 2016a). This has led to efforts being channeled towards investigation of new and existing drugs and regimens, with a drive to shorten treatment duration, standardize study design and reporting (Mitnick 2015), and focus on low-resource settings that are disproportionately affected by tuberculosis and MDR-TB globally (Sloan 2016).

Description of the intervention

Linezolid was categorized as a 'Group 5' drug in the 2011 WHO drug-resistant tuberculosis guidelines (WHO 2011). Medications assigned to this group were not recommended for use as core drugs, due to insufficient evidence detailing their safety or efficacy. However, the 2016 WHO update re-allocated it as a 'Group C: other core second-line agent', prioritizing its use over some more traditional agents (WHO 2016a). The number of linezolid-treated patients included in reviews of evidence informing both the 2011 and 2016 WHO guidance was insufficient to provide efficacy and safety estimates (WHO 2011, Fox 2017). In 2018, in a rapid communication from the WHO on treatment of MDR-TB and rifampicin-monoresistant-TB, linezolid's position was further upgraded to a 'group A: Medicines to be prioritised' (WHO 2018). A summary of evidence for the 2018 recommendation has been published (Ahmad 2018).

Despite the promoted status of linezolid, concerns about serious adverse effects prompted the 2016 WHO update to caution that where close monitoring for adverse events is unavailable, "linezolid would best be reserved for MDR-TB patients who have additional drug resistance...or who are intolerant to other components of the core regimen" (WHO 2016a). The 2018 WHO rapid communication, which recommends linezolid for all people with MDR-TB unless it cannot be used, still states that, "Optimal duration of use of Lzd [linezolid] is not established. Use for at least 6 months was shown to be highly effective, although toxicity may limit its use" (WHO 2018).

Five meta-analyses have examined the evidence for linezolid in drug-resistant tuberculosis (Cox 2012; Sotgiu 2012; Chang 2013c; Zhang 2015; Ahmad 2018). They include mostly observational data, much of it retrospective. Few randomized studies have been undertaken. There remains much debate surrounding linezolid, due to the lack of high-quality evidence. Many suggest it should be more widely used, hence its upgrade in the recent WHO guidance (Caminero 2015; Ahmad 2018; WHO 2018).

Considerable reliance on retrospective data may have exacerbated the effect of confounders in the meta-analyses of treatment efficacy (Cox 2012; Sotgiu 2012; Chang 2013c; Zhang 2015; Ahmad 2018). These reviews also selected, and focus on, efficacy rather

than safety. As highlighted by the WHO documents, safety is a major area of concern with linezolid (Ramachandran 2015).

How the intervention might work

Linezolid is an oxazolidinone antibiotic that disrupts protein synthesis by binding to the 70S initiation complex of bacterial ribosomes (Sloan 2016). It also binds to human mitochondria and inhibits protein synthesis, which is the mechanism of toxicity in clinical use (De Vriese 2006). It is active against most Gram-positive bacteria, with extensive evidence of in vitro activity against isolates of *M tuberculosis*, including those resistant to first-line drugs (Erturan 2005; Huang 2008).

Linezolid can be taken orally or intravenously. Its excellent oral bioavailability is an advantage, avoiding the need for long-term daily injections (Dryden 2011). Though an adult dose of 600 mg twice daily is commonly used for up to 28 days to treat infections due to Gram-positive bacteria, a variety of dosing strategies have been used in the context of drug-resistant tuberculosis, where treatment duration is much longer. These have ranged from 300 mg to 1200 mg daily, with once- or twice-daily administration. Lower doses have been tried in an attempt to increase tolerability and reduce toxicity (Park 2006; Migliori 2009; Yew 2009; Koh 2012). A thrice-weekly intermittent dosing regimen has also been attempted in limited cohorts to extend the duration of linezolid therapy (Chang 2013b). The optimal dosing and duration of linezolid remains unclear from the perspective of preventing emergence of resistance, as well as efficacy, tolerability, and toxicity.

Adverse effects of linezolid include suppression of the bone marrow causing anaemia and thrombocytopenia, peripheral neuropathy, and optic neuropathy leading to disability and blindness, which is usually irreversible. More commonly, gastrointestinal upset may lead to difficulties with adherence (Ramachandran 2015). Adverse events with courses of linezolid longer than one month appear to be common within antituberculous drug regimens, affecting over 80% of participants in some studies (Lee 2012).

Why it is important to do this review

We set out to perform a systematic review reporting on the efficacy of linezolid for drug-resistant tuberculosis, balanced against an estimate of the risk of linezolid-associated adverse events. Such estimates will assist policy makers who are deciding on the place of linezolid in their national and regional drug-resistant tuberculosis programmes, as well as individual clinicians trying to interpret the wide variety of published data on how effective, safe, and tolerable linezolid is in people being treated for MDR-TB and XDR-TB.

Existing evidence, while of low quality, has concluded that linezolid is efficacious in MDR-TB, leading to its inclusion as a drug to be prioritized in the latest WHO guidance (WHO 2018). However, evidence regarding appropriate dosing and duration is lacking. Importantly, as linezolid is rolled out for wider use, closer interrogation of the adverse events data is desirable.

OBJECTIVES

To assess the efficacy of linezolid when used as part of a second-line regimen for treating people with MDR and XDR pulmonary tuberculosis, and to assess the prevalence and severity of adverse events associated with linezolid use in this patient group.

METHODS

Criteria for considering studies for this review

Types of studies

To assess the efficacy of linezolid we included randomized controlled trials (RCTs) and quasi-RCTs.

To assess the prevalence and severity of adverse events associated with the use of linezolid, we included RCTs and quasi-RCTs, and both prospective and retrospective, non-randomized cohort studies, as defined by the *Cochrane Handbook for Systematic Reviews of Interventions* (Loke 2011), in which some participants received linezolid and others did not.

Types of participants

Adults and children with a diagnosis of MDR (including rifampicin-monoresistant, managed as MDR) or XDR pulmonary tuberculosis.

Types of interventions

Intervention

Antituberculous treatment (ATT) regimens that contained linezolid at any dose and for any duration.

Control

ATT regimens that did not contain linezolid.

Types of outcome measures

These outcome measures are based on those specified by the WHO for tuberculosis programme outcome reporting in MDR- and XDR-TB (WHO 2013).

Primary outcomes

- All-cause death: all deaths that occurred during each included study and until the end of follow-up
- Tuberculosis-associated death: all deaths attributed to tuberculosis by the study investigators that occurred during each study and until the end of follow-up
- Treatment failure: participants who did not show conversion from sputum culture positive to negative by the end of the intensive phase of ATT, or who had reverted from culture-negative to culture-positive, or who had failed to respond clinically to treatment as defined by the study investigators
- Cure: participants who completed ATT as planned without evidence of failure and had at least three consecutive negative sputum cultures in specimens taken at least 30 days apart after the intensive phase of treatment.

Secondary outcomes

- Treatment interrupted: participants who stopped taking ATT for one month or longer at any point in the course of treatment
- Treatment completed: participants who completed ATT as planned but did not have at least three consecutive negative sputum cultures in specimens taken at least 30 days apart after the intensive phase of treatment
- Time to sputum culture conversion: the length of time between starting treatment and conversion from sputum culture positive to sputum culture negative.

Adverse events

- All adverse events
- All serious adverse events
- Adverse events that led to discontinuation of antituberculous drugs or dose reduction
- Adverse events attributed to linezolid, particularly peripheral and optic neuropathy, anaemia, thrombocytopenia, lactic acidosis, and serotonin syndrome

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We searched the following databases for relevant studies using the search terms detailed in Appendix 1:

- the Cochrane Infectious Diseases Specialized Register
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 7) published in the Cochrane Library
- MEDLINE (PubMed)
- Embase (OVID)
- LILACS

We also checked the WHO International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en/), and ClinicalTrials.gov (clinicaltrials.gov/ct2/home), for ongoing studies using the terms: 'linezolid' and 'tuberculosis'.
The latest searches were conducted on 13 July 2018.

Searching other resources

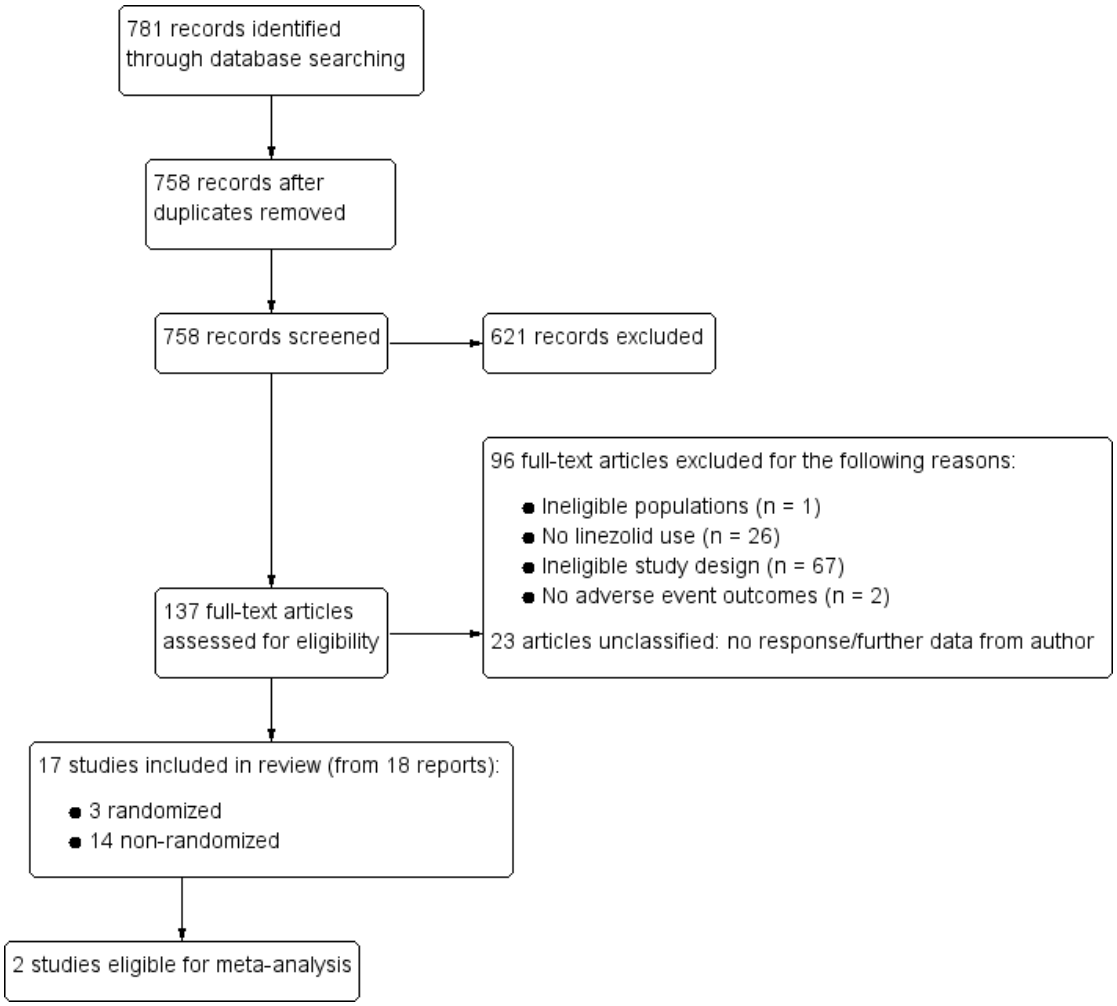
We contacted researchers in the field to identify unpublished or ongoing studies.

Data collection and analysis

Selection of studies

Two review authors (BS and DC) screened the titles and abstracts of the search results independently and coded them as either 'retrieve' (eligible or potentially eligible/unclear), or 'do not retrieve'. We retrieved the full-text study reports of all potentially eligible studies and two review authors (BS and DC) independently screened them for inclusion and recorded the reasons for exclusion of ineligible studies. We resolved any disagreement through discussion or, when required, we consulted a third review author. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We contacted study authors for clarification if a study's eligibility was unclear. We resolved any disagreements through discussion and listed the excluded studies and the reasons for their exclusion in the Characteristics of excluded studies table. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009; Figure 1).

Figure 1. Study flow diagram



Data extraction and management

We designed and piloted a data extraction form, and modified the form based on the results of the pilot. Two review authors (BS and DC) independently extracted data from each included study using the finalized data extraction form. BS and DC compared the extracted data to identify any possible errors, and resolved any discrepancies through discussion and by referring to the original study articles. We extracted the following data from each included study, where available.

- Country and clinical setting, start and end dates of the study, study design, inclusion and exclusion criteria, number of participants eligible for inclusion and number of participants allocated to each group
- Participant characteristics: age, sex, history of previous tuberculosis treatment, known contact with MDR-TB patient, duration of symptoms at presentation, comorbidity (HIV infection, other immunosuppression and other diseases), diagnostic methods used (e.g. culture-based drug susceptibility testing, Xpert MTB/RIF, line probe assay for drug susceptibility), drug susceptibility profile of participants at entry to the study
- Intervention data: description of drugs, dose, route of administration in both the intensive and continuation phase, and duration of all drugs for both phases. Administration of other drugs or therapeutic procedures, including surgery

Primary outcomes

For the primary outcomes we extracted the following data.

All-cause death

- Number of deaths, stratified by drug susceptibility profile, age and HIV status
- Timing of death after start of treatment

Tuberculosis-associated death

- Number of deaths attributed to tuberculosis by the investigators, stratified by drug susceptibility profile, age and HIV status

Treatment failure

- Number of participants who did not show sputum culture conversion by the end of the intensive phase of ATT, stratified by drug susceptibility profile, age and HIV status
- Number of participants who reverted from culture negative to culture positive, stratified by drug susceptibility profile, age and HIV status
- Number of participants who failed to respond clinically to treatment as defined by the investigators, stratified by drug susceptibility profile, age and HIV status
- Method of monitoring treatment and defining treatment failure
- Time between start of treatment and treatment failure
- Outcome following classification as treatment failure

Cure

- Number of participants who completed ATT as planned and had at least three negative sputum cultures in specimens taken at least 30 days apart during the last months of treatment, stratified by drug susceptibility profile, age, and HIV status

Secondary outcomes

For the secondary outcomes we extracted the following data.

Treatment interrupted

- Number of participants who stopped taking ATT for one month or more at any point in the course of treatment, stratified by drug susceptibility profile, age and HIV status
- Method of monitoring treatment adherence
- Reasons for treatment interruption

Treatment completed

- Number of participants who completed ATT as planned but did not have at least three negative sputum cultures in specimens taken at least 30 days apart during the last months of treatment.
- Method of monitoring treatment.

Time to sputum culture conversion

- Time between starting treatment and conversion from sputum culture positive to sputum culture negative
- Method of monitoring treatment, including frequency of sputum sampling

Follow-up

Length of follow-up, follow-up methods, number and characteristics of losses to follow-up.

Adverse events

We extracted information on the total number of the following.

- Adverse events
- Serious adverse events
- Participants experiencing adverse events
- Adverse events that led to discontinuation of antituberculous drugs or linezolid dose reduction
- Adverse events attributed to linezolid, particularly peripheral and optic neuropathy, anaemia, thrombocytopenia, lactic acidosis, and serotonin syndrome

For each outcome, we extracted the number of participants assigned and the number of participants analysed in each treatment group. For dichotomous outcomes, we extracted the number of participants who experienced the event. For count data outcomes, we extracted the number of events in the intervention and control groups.

Assessment of risk of bias in included studies

For RCTs and quasi-RCTs, two review authors independently assessed the methodological quality of each included study using the Cochrane 'Risk of bias' tool and reported the results in a 'Risk of bias' table (Higgins 2011a). We resolved any disagreements through discussion. Regarding generation of allocation sequence and allocation concealment, we classified each as either adequate, inadequate, or unclear in each included study according to Jüni 2001. We reported who was blinded in each included study, and we assessed the risk of bias associated with blinding separately for each primary outcome. If at least 90% of participants were followed up to study completion we classified inclusion of all randomized participants as adequate; otherwise we classified inclusion as inadequate. We attempted to contact the study authors if information was unspecified or unclear.

For non-randomized studies, we used the ROBINS-I risk of bias tool (Sterne 2016), and adapted and piloted it before we used it to assess all included non-randomized studies. The following are areas of confounding that we expected to be relevant to all or most included studies.

- Extent of drug resistance: number of effective drugs available

- Severity of tuberculosis disease at start of treatment
- HIV co-infection
- Timing of addition of linezolid to the regimen
- Duration of linezolid treatment
- Background antituberculous therapy regimen (the other drugs composing the overall regimen)
- Supportive care available in study setting

Measures of treatment effect

We used risk ratio (RR) as the measure of treatment effect for analysis.

Unit of analysis issues

We did not anticipate that any cluster-RCTs would meet the inclusion criteria of the review.

For multi-armed studies, where we wished to include more than one intervention study arm, we planned to split the control group to avoid including the same participants more than once.

Dealing with missing data

The primary analysis was an intention-to-treat analysis where all participants randomized to treatment were included in the denominator. This analysis assumed that all people lost to follow-up did not have the outcome in question. We carried out a sensitivity analysis to explore the impact of missing data on the summary effect estimates for all-cause death, cure and failure.

Assessment of heterogeneity

We planned to assess heterogeneity by visually inspecting the forest plots to determine closeness of point estimates to each other and overlap of confidence intervals (CIs). We planned to use the Chi² test with a P value of 0.10 to indicate statistical significance (Deeks 2017), and the I² statistic (Higgins 2003), to assess heterogeneity with a value of 50% taken to indicate significant statistical heterogeneity.

Assessment of reporting biases

We planned to conduct visual inspection of the funnel plot of the studies for any obvious asymmetry that could be evidence of publication bias if we included at least 10 studies.

Data synthesis

Using Review Manager 5 (RevMan 5), we planned to perform a meta-analysis on the data in included studies, but not to combine data from RCTs and non-randomized studies (Review Manager 2014). As we anticipated significant variability in samples from participants across the different studies, we planned to use a random-effects model for meta-analysis, unless there was a very small number of included studies with low heterogeneity, in which case we planned to use a fixed-effect model.

For non-randomized data, we did not plan to perform a meta-analysis. We planned to report these data descriptively in a table that included how the data were collected, and the reported outcomes (unadjusted). If the study authors had adjusted data, we planned to provide this estimate with a short description of the adjustments the study authors made.

We assessed the certainty of the evidence using the GRADE approach. We used GRADEpro GDT software to construct a 'Summary of findings' table (GRADEpro GDT 2015).

Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity through the following subgroup analyses.

- Drug-resistance profile, determined by:
  - % XDR
  - % fluoroquinolone-resistant (resistant to any fluoroquinolone, but susceptible to injectables)
  - % injectable-resistant (resistant to any injectable, but susceptible to fluoroquinolones)
- HIV status (seropositive and seronegative)
- Age (adults and children)
- Daily dose of linezolid (600 mg or less and over 600 mg adult equivalent)
- Duration of linezolid (six months or less and longer than six months)
- Total cumulative dose of linezolid
- Other drugs within the background antituberculous drug regimen

Sensitivity analysis

We performed a worst-case scenario analysis by imputing the missing data as poor outcomes in the linezolid group and good outcomes in the control group, and by comparing this to an available-case analysis to explore the effect of missing data on the primary outcomes all-cause death, cure and failure.

RESULTS

Description of studies

Results of the search

Searches identified 781 records. Of these, we excluded 23 duplicate records. Of the remaining 758, we excluded 621 after assessing titles and abstracts. Following this, we retrieved 137 full-text publications to assess for inclusion. Figure 1 shows the screening process in a flow diagram.

Included studies

We included 17 studies: three randomized studies (138 participants), and 14 non-randomized cohort studies (1678 participants), of which two were prospective and 12 were retrospective (Figure 1). A summary description is provided in Table 1, with more detailed characteristics in the 'Characteristics of included studies' section.

Geographical location and time period

The RCTs were conducted in the Republic of Korea, South Africa and China.

Locations were diverse amongst the non-randomized studies. Three were based in the Republic of Korea; a low tuberculosis burden and low MDR-TB burden country (Jo 2014; Jeong 2015; Kwak 2015), according to WHO definitions of tuberculosis, tuberculosis/HIV and MDR-TB burden (WHO 2015b). Four were conducted in low tuberculosis burden and low MDR-TB burden European countries; Netherlands (Van Altena 2015), Italy (Galli 2016), Norway (Jensenius 2016) and France (Guglielmetti 2017). Two studies recruited from Europe, but also from high MDR-TB burden former Soviet Union states (Migliori 2009; Tiberi 2016). One of these also recruited from centres in South America, with low tuberculosis burden and mixed MDR-TB burden (Tiberi 2016). One study was conducted in China (Zhang 2014), another in India (Udwadia 2010), and two in South Africa (Seddon 2014; Olayanju 2018); these three countries have high tuberculosis, tuberculosis/HIV and MDR-TB burden. Ferlazzo 2018 recruited from Armenia (former Soviet Union country, previously on the high MDR-TB burden list), India and South Africa.

All RCTs and non-randomized studies were conducted in high-income or upper-middle-income countries except for those that recruited in India, a lower-middle-income country.

The RCTs recruited between 2008 and 2011. There was a wide time range amongst the cohort studies: seven of the 14 started recruitment in 2009 or later and three completed recruitment in 2009, with the earliest starting in 1995 and the latest completing in 2017.

Participants

Two studies included children only (Seddon 2014; Galli 2016). Jensenius 2016 recruited participants of all ages. The remainder, including both RCTs, were conducted in adults (four studies not reporting ages (Migliori 2009; Kwak 2015; Van Altena 2015; Guglielmetti 2017), we assumed to have mostly or exclusively included adults).

Most studies included both MDR- and XDR-TB cases. Two RCTs (Lee 2012; Tang 2015), one prospective cohort study (Olayanju 2018), and one retrospective cohort (Zhang 2014), included only XDR-TB cases, and Jo 2014 and Jeong 2015 included MDR cases with at least fluoroquinolone resistance (including XDR). Half (14/28) of the cases in Ferlazzo 2018 were XDR. The remaining studies included a minority of cases with XDR.

Seddon 2014 included 16 (of 149 total) children with rifampicin-monoresistant-tuberculosis, managed as MDR-TB. No other studies reported participants with rifampicin-monoresistant-tuberculosis.

HIV infection status was reported in all but four studies. Eight included participants with HIV infection; two RCTs (Lee 2012; Tang 2015), excluded HIV-positive individuals; and three reported no known HIV-positive participants, but with variable reporting of whether participants had been tested. Studies reporting on antiretroviral therapy (Padayatchi 2012; Seddon 2014), described administration to most participants with HIV infection.

Interventions

Linezolid dose varied widely. Of the RCTs, Lee 2012 investigated the effect of immediate versus delayed (two months after randomization) linezolid 600 mg daily initiation, with a second randomization point after sputum culture conversion to either continue on 600 mg or take a reduced 300 mg daily. Padayatchi 2012 used a dose of 600 mg daily and Tang 2015 used a high initial dose (1200 mg), followed at four to six weeks by a planned reduction to 300 mg or 600 mg daily. Amongst the non-randomized studies, dosing ranged from 300 mg to 1200 mg daily, with inconsistent reporting. Five non-randomized studies did not report a dosing strategy. In several of the remaining studies, the numbers of participants receiving each dose were not clear.

Duration of receipt of linezolid, where known (eight studies), was for a mean or median of over 90 days. Five studies reported average duration of over 180 days, with four of these being over one year. We did not know the duration of four studies; one RCT (Tang 2015), administered linezolid until sputum culture conversion from positive to negative; and Zhang 2014 reported administration for, "at least one month", without further detail.

It was not clear for most non-randomized studies whether linezolid had been used from the commencement of MDR or XDR ATT, or added later. Kwak 2015 reported that linezolid, in addition to all XDR-TB cases, "was added for patients refractory to at least 3-6 months of medical treatment" in those with MDR-TB.

Background regimens were mostly reported to be individualized according to susceptibilities, clinical parameters and WHO guidance, and often not reported in detail. Where reported, most participants received fluoroquinolones, injectable drugs, ethionamide or prothionamide, and para-aminosalicylic acid.

Few studies reported place of treatment. Where reported, ATT was said to be administered on an inpatient basis, at least initially, with some describing continuation of therapy as an outpatient. An exception, Ferlazzo 2018 described some participants receiving outpatient therapy from the outset.

Four studies reported surgical resection being carried out in a minority of participants: Kwak 2015; Van Altena 2015; Jensenius 2016; and Tiberi 2016.

Follow-up

Of the three RCTs, Lee 2012 conducted follow-up until 12 months after completion of ATT, Padayatchi 2012 followed participants until 12 months from commencement of ATT, and Tang 2015 reported follow-up until the end of treatment.

The cohort studies reported follow-up procedures incompletely. Zhang 2014 followed participants until three months after discontinuing linezolid (i.e. not to the end of ATT). Jeong 2015 followed participants until the end of treatment. Guglielmetti 2017 aimed to follow-up until 24 months after ATT completion, Ferlazzo 2018 until six months from commencement, and Olayanju 2018 reported monthly follow-up for the duration of hospital stay. Follow-up duration and frequency were unclear for the remaining studies (Migliori 2009; Udwadia 2010; Jo 2014; Seddon 2014; Kwak 2015; Van Altena 2015; Galli 2016; Jensenius 2016; Tiberi 2016).

Outcome measures

Two RCTs (Padayatchi 2012; Tang 2015), reported the review's primary outcomes of all-cause and tuberculosis-associated death and treatment failure. Padayatchi 2012 did not report cure, due to follow-up not extending beyond 12 months, while Tang 2015 did. These RCTs also reported the review's secondary outcomes of treatment interrupted and treatment completed (the Padayatchi 2012 study did so for treatment of up to 12 months). Lee 2012 did not report these outcomes separately for participants receiving immediate versus delayed linezolid, though apart from death (no-one died in either arm), they would have been less informative because there was only two months' delay in commencement of linezolid.

All three RCTs (Lee 2012; Padayatchi 2012; Tang 2015) reported sputum culture conversion from positive to negative, but not as stipulated in the review protocol (i.e. time to conversion).

Adverse events were reported by all RCTs, although Tang 2015 did not distinguish serious adverse events from the others. Lee 2012 did not separate adverse events between immediate and delayed linezolid groups.

Adverse events reporting in the non-randomized studies was variable. Only six out of 14 studies reported, or provided following our request to the authors, comparative total numbers of adverse events experienced by those who received linezolid versus those who did not (Seddon 2014; Kwak 2015; Galli 2016; Guglielmetti 2017; Ferlazzo 2018; Olayanju 2018). A further three reported or provided a total frequency of adverse events for the linezolid-receiving groups, but not for those who did not receive linezolid (Jo 2014; Zhang 2014; Tiberi 2016). The remaining five studies provided data on frequency of linezolid discontinuation or adverse events, or both, attributed to linezolid only.

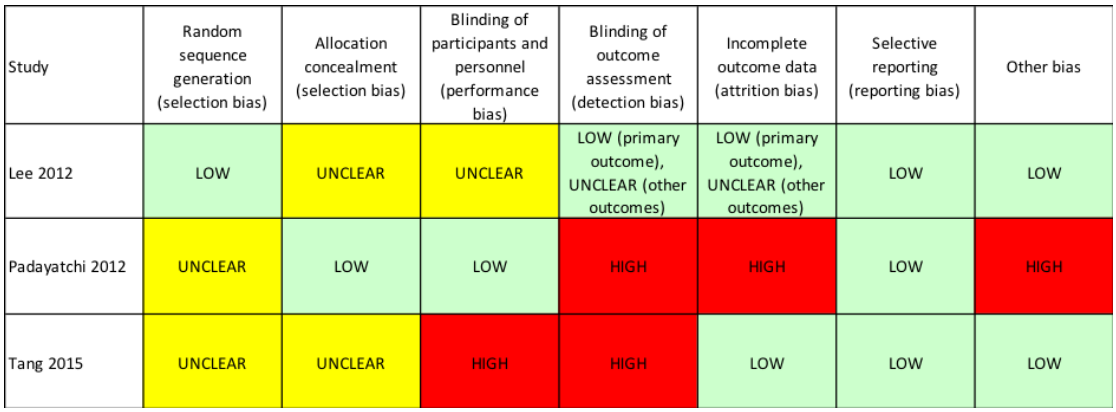
Excluded studies

We excluded 96 studies after review of the full texts (Figure 1). We excluded 67 studies because they were neither a randomized study nor cohort study; 26 did not describe any use of linezolid; and one did not fit the population eligibility criteria of the review. We excluded two studies due to absence of adverse events data. Full details are given in the Characteristics of excluded studies section. A further 23 remained unclassified, due to no response from study authors following our requests for data. See the Studies awaiting classification section for further details.

Risk of bias in included studies

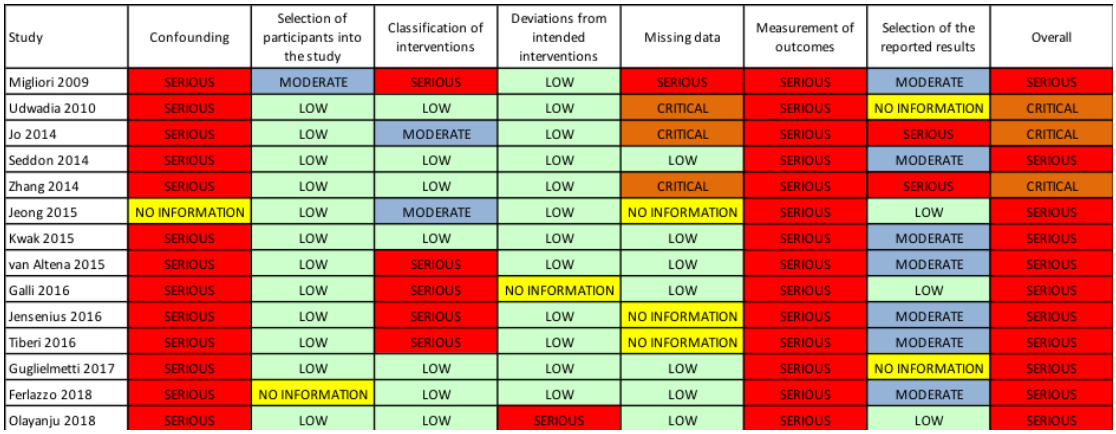
We assessed risk of bias for the included RCTs using the Cochrane 'Risk of bias' assessment tool (Higgins 2011a). We assessed the risk of bias in the cohort studies using ROBINS-I tool (Sterne 2016). See the 'Characteristics of included studies' section, which includes a 'Risk of bias' table for each included study. We summarized the results of the 'Risk of bias' assessments across all included RCTs in Figure 2 and non-randomized studies in Figure 3.

Figure 2. Risk of bias in included RCTs



Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lee 2012	LOW	UNCLEAR	UNCLEAR	LOW (primary outcome), UNCLEAR (other outcomes)	LOW (primary outcome), UNCLEAR (other outcomes)	LOW	LOW
Padayatchi 2012	UNCLEAR	LOW	LOW	HIGH	HIGH	LOW	HIGH
Tang 2015	UNCLEAR	UNCLEAR	HIGH	HIGH	LOW	LOW	LOW

Figure 3. Risk of bias in included non-randomized studies



Study	Confounding	Selection of participants into the study	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported results	Overall
Migliori 2009	SERIOUS	MODERATE	SERIOUS	LOW	SERIOUS	SERIOUS	MODERATE	SERIOUS
Udwadia 2010	SERIOUS	LOW	LOW	LOW	CRITICAL	SERIOUS	NO INFORMATION	CRITICAL
Jo 2014	SERIOUS	LOW	MODERATE	LOW	CRITICAL	SERIOUS	SERIOUS	CRITICAL
Seddon 2014	SERIOUS	LOW	LOW	LOW	LOW	SERIOUS	MODERATE	SERIOUS
Zhang 2014	SERIOUS	LOW	LOW	LOW	CRITICAL	SERIOUS	SERIOUS	CRITICAL
Jeong 2015	NO INFORMATION	LOW	MODERATE	LOW	NO INFORMATION	SERIOUS	LOW	SERIOUS
Kwak 2015	SERIOUS	LOW	LOW	LOW	LOW	SERIOUS	MODERATE	SERIOUS
van Altena 2015	SERIOUS	LOW	SERIOUS	LOW	LOW	SERIOUS	MODERATE	SERIOUS
Galli 2016	SERIOUS	LOW	SERIOUS	NO INFORMATION	LOW	SERIOUS	LOW	SERIOUS
Jensenius 2016	SERIOUS	LOW	SERIOUS	LOW	NO INFORMATION	SERIOUS	MODERATE	SERIOUS
Tiberi 2016	SERIOUS	LOW	SERIOUS	LOW	NO INFORMATION	SERIOUS	MODERATE	SERIOUS
Guglielmetti 2017	SERIOUS	LOW	LOW	LOW	LOW	SERIOUS	NO INFORMATION	SERIOUS
Ferlazzo 2018	SERIOUS	NO INFORMATION	LOW	LOW	LOW	SERIOUS	MODERATE	SERIOUS
Olayanju 2018	SERIOUS	LOW	LOW	SERIOUS	LOW	SERIOUS	LOW	SERIOUS

Most of the subheadings that follow address risk of bias in RCTs; for non-randomized studies, see the subheading Other potential sources of bias.

Allocation

Lee 2012 had low risk of bias for random sequence generation, due to use of permuted block randomization. Padayatchi 2012 and Tang 2015 had unclear risk of bias as procedures were not clearly described.

Padayatchi 2012 described adequate allocation concealment procedures, with resulting low risk of bias, whilst Lee 2012 and Tang 2015 did not report these, so risk of bias was unclear.

Blinding

Lee 2012 described blinding of laboratory personnel only, which allowed outcomes other than the primary outcome of sputum culture conversion to be influenced by knowledge of the intervention. We deemed this to represent an unclear risk of performance bias. For detection bias, we judged the primary outcome to be at low risk, but bias was unclear for other outcomes. Padayatchi 2012 reported appropriate blinding of participants and personnel initially (low risk of performance bias), but at 20 weeks, unblinding occurred, which may have affected measurement of outcomes at 12 months, resulting in high risk of detection bias. Tang 2015 reported no blinding, so there was a high risk of performance and detection bias.

Incomplete outcome data

Lee 2012 had low loss to follow-up at four months (i.e. for the primary outcome), but substantially higher at the end of planned follow-up. We deemed it to be at low risk for the primary outcome of sputum culture conversion but unclear for other outcomes, because of the well-conducted nature of the study. Due to a high proportion of loss to follow-up, without reasons for withdrawal being clear or specified by intervention group, we deemed Padayatchi 2012 to be at high risk of attrition bias. Loss to follow-up was lower in Tang 2015, with specified, balanced reasons for withdrawal, resulting in our judgement of low risk of bias.

Selective reporting

There was no evidence of selective reporting by Lee 2012, with some elements of the original protocol and substantial additional data being provided in a supplement. Padayatchi 2012 reported, within the commentary study and the full study protocol and report, available online, much more than expected from an RCT, with no evidence of selective reporting. Though Tang 2015 did not publish a separate protocol, all outcomes stated in the methods section of the study were reported in the results.

Other potential sources of bias

RCTs

Padayatchi 2012 reported discordance of administration of the study drug (linezolid) and placebo in at least 25% of participants, found incidentally in the pharmacokinetics study nested within the main study. Though not identified with certainty, the study authors concluded, "it appears that the mixing of tablets due to sporadic, human error occurred at the clinical site on more than one occasion over a long time period, rather than in the pharmacy." There was no other source of bias apparent for Lee 2012 or Tang 2015.

Non-randomized studies

The ROBINS-I assessment process judges risk of bias in seven domains, resulting in an overall judgement of risk of bias corresponding to the highest level of risk displayed in any one domain. For example, if a study is judged to have a serious risk of bias in one study domain, but low risk of bias in all others, the overall risk of bias for the study will be serious.

Risk of bias within the seven domains, and overall, is displayed for all 14 studies in Figure 3. We deemed overall risk of bias to be critical for three studies (Udwadia 2010; Jo 2014; Zhang 2014) and serious for the remaining 11 studies. We deemed all studies to have serious risk of bias in measurement of outcomes, consistent with mostly retrospective design, some with unpublished repurposed data on linezolid. We judged 13 of the 14 studies to have serious risk of bias for confounding, which is again reflective of the largely retrospective studies included. Twelve were at low risk of bias for selection of participants into the study, and 12 were at low risk of bias from deviations from intended interventions.

Effects of interventions

See: **Summary of findings for the main comparison** Linezolid compared to no linezolid for drug-resistant pulmonary tuberculosis

RCTs

Due to the significant discordance of study drug and placebo administration in Padayatchi 2012, we deemed this study unsuitable for any analysis of intervention effect. This left two RCTs, Lee 2012 and Tang 2015. As these did not provide comparable outcome data, we were unable to meta-analyse their results.

Table 2 shows findings from Lee 2012, which reported no deaths prior to or while receiving linezolid. Sputum culture conversion at four months after randomization (the study's primary outcome), was reported to be higher for participants receiving linezolid immediately versus those receiving linezolid after a delay of two months: 15 out of 19 versus 7 out of 20 (RR 2.26, 95% CI 1.19 to 4.28). Cure (27/39 randomized), treatment failure (4/39), and treatment interruption (7/39), were not disaggregated by timing of linezolid introduction (Lee 2012). Permanent linezolid discontinuation was reported in seven out of 39 (17.9%) participants.

Table 3 summarizes findings from Tang 2015. This study reported significantly higher cure (RR 2.36, 95% CI 1.13 to 4.90), and lower failure (RR 0.26, 95% CI 0.10 to 0.70), in participants receiving linezolid, compared to those who did not. No significant difference was reported in the proportions of participants with outcomes of treatment completed, death or treatment interrupted, between linezolid and control groups. Time to sputum culture conversion was not reported in the way that we had planned to analyze this outcome: 26 out of 33 (78.8%) of those receiving linezolid had sputum culture conversion at 24 months; the corresponding figure for those who did not receive linezolid was 12 out of 32 (37.6%; Tang 2015). Treatment interruption, defined in the paper as "default", was reported in four out of 33 of the linezolid-receiving and three out of 32 of the control groups, respectively. Linezolid was discontinued permanently in two out of 33 participants, though an undefined larger number had temporary linezolid interruptions.

With regards to adverse events, Lee 2012 reported 56 adverse events in total, 33 of which they deemed serious (the second report of this study reported another four serious adverse events, but without a corresponding figure for non-serious adverse events). The adverse events included 21 out of 39 instances of peripheral neuropathy, 7 out of 39 optic neuropathy and 7 out of 39 with myelosuppression (bone marrow suppression). Tang 2015 reported a significantly higher incidence of anaemia (17/33 versus

2/32), nausea and vomiting (16/33 versus 3/32), peripheral neuropathy (8/33 versus 1/32), and optic neuropathy (6/33 versus 0/32), amongst participants in receipt of linezolid, compared with controls. Confidence intervals were not provided for these results; significance was reported on the basis of P values.

We undertook a sensitivity analysis of the death, cure and failure outcomes for Tang 2015. Imputing worst-case and best-case outcomes by linezolid administration for participants with incomplete data did not change the similar proportion of death in the two groups. Cure remained higher and failure remained lower for participants who received linezolid, albeit with a loss of statistical significance when worst-case scenario outcomes were imputed (lower CI = 0.89 for cure, and upper CI 1.05 for failure). The worst-case analysis assumes that all the missing participants in the linezolid group did not achieve cure and failed therapy, and all the missing participants not receiving linezolid achieved cure and did not fail therapy (Table 4).

Non-randomized studies

Table 5 contains a summary of findings from the included non-randomized studies, and Table 6 shows more detailed adverse event data from these studies. We did not plan primary and secondary outcome data extraction and meta-analysis for non-randomized cohorts.

Disaggregated data were available from 12 studies (639 participants), on total number of 'any' or 'serious' adverse events or linezolid discontinuation, amongst participants receiving linezolid (Migliori 2009; Jo 2014; Seddon 2014; Zhang 2014; Kwak 2015; Van Altena 2015; Galli 2016; Jensenius 2016; Tiberi 2016; Guglielmetti 2017; Ferlazzo 2018; Olayanju 2018). Six studies (487 participants), provided data for total number of 'any' or 'serious' adverse events amongst participants who did not receive linezolid (Seddon 2014; Kwak 2015; Galli 2016; Guglielmetti 2017; Ferlazzo 2018; Olayanju 2018).

A total of 602 adverse events were reported from 426 participants (from 8 studies), receiving linezolid. Among 478 participants (5 studies), who did not receive linezolid, there were 813 adverse events. Fifty-seven serious adverse events occurred amongst 164 participants (7 studies), who received linezolid, and 47 serious adverse events occurred in 270 participants (5 studies), who did not receive linezolid.

Linezolid-attributed adverse events were reported in a total of 529 participants from 10 studies (Migliori 2009; Udwadia 2010; Jo 2014; Seddon 2014; Zhang 2014; Kwak 2015; Galli 2016; Tiberi 2016; Guglielmetti 2017; Olayanju 2018). These included 108 bone marrow-related (e.g. anaemia, thrombocytopaenia, leukopenia), and 110 neuropathic (peripheral or optic) events.

Clear information on the numbers of participants experiencing adverse events was not available due to incomplete reporting, so we could not ascertain proportions. Follow-up duration was also not available for all participants, so we could not describe event rates.

Linezolid was discontinued in 141 of 624 participants (22.6%; 11 cohorts).

DISCUSSION

Summary of main results

Table 2 and Table 3 summarize findings from the two RCTs for which we were able to assess intervention effect (104 participants), Lee 2012 and Tang 2015, respectively. Table 5 and Table 6 include a summary of adverse events findings from the 14 non-randomized studies (1678 participants; 2 prospective, 12 retrospective). We were unable to generate pooled effect estimates using meta-analysis due to heterogeneity of outcomes studied and reported. Summary of findings for the main comparison provides a GRADE assessment of outcomes from Tang 2015.

Settings varied: the RCTs were based in the Republic of Korea (Lee 2012), and China (Tang 2015); three cohort studies recruited in the Republic of Korea, five in Europe (one included a centre in a former Soviet Union country), two from South Africa, one each in China and India, and two from multiple heterogeneous centres. Tang 2015, and seven of the 14 non-randomized studies, commenced recruitment in 2009 or later.

Dosing and duration of linezolid in studies were variable, but also reported incompletely. Five studies did not report dosing at all. In the majority of the remainder it was not clear how many participants received each reported dose. Lee 2012 used 600 mg daily until a second planned randomization to continuing 600 mg or reducing to 300 mg daily. Tang 2015 used 1200 mg daily, then at four to six weeks, all were reduced to 300 mg or 600 mg, until sputum culture conversion. Only eight of the 14 non-randomized cohorts stated a mean or median duration, all of which were reported to be longer than 90 days. Incompleteness of these data precluded comment on the effect of dose and duration of linezolid on outcomes. Follow-up duration was variable, when reported; nine of the 14 non-randomized studies did not report follow-up duration.

Lee 2012 did not report data in a manner that permitted reporting of the primary outcomes of this review. However, their reporting of sputum culture conversion did permit comparison between those receiving linezolid immediately versus those starting it two months after randomization. Tang 2015 reported all of the review's primary and secondary outcomes, but reported sputum culture conversion in a way that made it difficult to compare directly with the data for that outcome reported by Lee 2012. In both studies, the group randomized to receive linezolid from the outset achieved a significantly higher proportion of sputum culture conversion from positive to negative at the time points specified by

the study authors than the comparator group, who either started linezolid late or were not given it at all.

Tang 2015 reported significantly higher cure and lower failure amongst the linezolid-treated group than controls, with no other significant differences in death, treatment completed and treatment interruption. The differences in cure and failure became insignificant when we performed worst-case sensitivity analysis, though this method produces extreme effect estimates. Our level of certainty in the evidence was very low for cure and failure, following downgrading for risk of bias, indirectness and imprecision, as presented in Summary of findings for the main comparison.

Tang 2015 reported more anaemia, nausea, and vomiting, and neuropathy events amongst participants in the linezolid group compared with controls. Lee 2012 did not provide comparative adverse event data for those receiving linezolid versus those who did not. Linezolid was discontinued in seven out of 39 (17.9%) participants in Lee 2012 and two out of 33 (6.1%) participants in Tang 2015.

Where reported within the cohort studies, 141 out of 624 (22.6%; 11 cohorts), discontinued linezolid. We could not reliably compare total adverse events, serious adverse events, and overall and specific linezolid-attributed adverse events, but we have shown these outcomes descriptively in Table 6. This is due to a lack of data on follow-up duration and numbers of participants experiencing events.

Overall completeness and applicability of evidence

Settings of the studies, in terms of tuberculosis incidence and drug-resistant tuberculosis prevalence, were diverse. India was the only lower-middle-income country (Udwadia 2010; Ferlazzo 2018), with the remainder being upper-middle- or high-income countries. Children were included in three studies, two of which exclusively recruited children (Seddon 2014; Galli 2016). Four non-randomized studies did not report ages of their participants.

Reporting of linezolid dose and duration, and follow-up was variable, as described in the Summary of main results and Table 1. Seven cohort studies included participants with HIV, of which two reported that most were taking antiretroviral therapy. Four did not report HIV status, and three reported that no participants were known to have HIV. The RCTs excluded people with known HIV (Lee 2012; Tang 2015).

All participants in the Lee 2012 and Tang 2015 RCTs had XDR-TB. Amongst the 12 cohorts contributing adverse events outcome data disaggregated for linezolid receipt, 38.7% had XDR-TB. Background regimens, where reported, were individualized to drug susceptibility results, as per WHO guidance, in all of the non-randomized studies, but one RCT, Tang 2015, used a specified universal regimen, whilst Lee 2012 reported a variety of background regimens. Thoracic surgical interventions were undertaken in a minority (< 25%) of participants, and proportions appeared balanced between those who received linezolid and those who did not, where reported.

This review highlights the lack of RCT evidence, with only one, with no placebo or blinding, being suitable for analysis for primary and secondary outcomes (Tang 2015), and the Lee 2012 RCT providing limited comparative data for participants according to receipt of linezolid. Outcome reporting was poor overall in the non-randomized studies, which were included for adverse events outcomes only. This means the evidence is neither complete, nor widely applicable.

Certainty of the evidence

We were unable to find directly comparable RCT data, and had planned, due to anticipated clinical and methodological heterogeneity, not to perform a meta-analysis on the data from non-randomized studies. We did not therefore perform a meta-analysis, but we have provided a GRADE assessment in Summary of findings for the main comparison. This found very low certainty in the evidence for all outcomes.

As we have described, we found significant problems with risk of bias. We classified 11 of the non-randomized cohort studies as having serious overall risk of bias, and three as having critical overall risk of bias, using the ROBINS-I tool (Characteristics of included studies; Sterne 2016).

Potential biases in the review process

We took measures to limit bias in the review process, by following procedures outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). The Cochrane Infectious Diseases Group (CIDG) Information Specialist conducted the literature search. It is unlikely that the search missed major studies, but some small unpublished studies may have been missed. We did not make a funnel plot, as included studies did not provide data suitable for meta-analysis. Two of the review authors examined the search results, determined study selection, and extracted data independently, to minimize bias in study selection and data extraction.

Agreements and disagreements with other studies or reviews

We found five, previously published systematic reviews. These reviews are summarized in Table 7. All of these reviews conclude that linezolid is efficacious in the treatment of drug-resistant tuberculosis, although authors comment on the high likelihood of adverse effects (Cox 2012; Sotgiu 2012; Chang 2013c; Zhang 2015; Ahmad 2018). Three reviews used studies as the unit of analysis, while two were individual patient data analyses. One review, Ahmad 2018, reported a risk of bias assessment. Only one of the

reviews included a RCT (Ahmad 2018), and only two included a comparator group of people who did not receive linezolid (Chang 2013c; Ahmad 2018).

Cox 2012, Sotgiu 2012, and Zhang 2015 assessed treatment outcomes and adverse events in 11 (148 participants), 12 (121 participants), and 15 (367 participants) studies, respectively. Most of these studies were case series in which all participants received linezolid. Risk ratios could not be calculated due to the lack of comparative adverse events data on participants who did not receive linezolid. Cox 2012 and Sotgiu 2012 concluded that linezolid was efficacious for drug-resistant tuberculosis, though both advised caution in its use due to high incidence of adverse events. Zhang 2015 suggested that linezolid was a "promising option as treatment of MDR/XDR TB", but advised randomized studies to define dosing.

Chang 2013c assembled a cohort from 20 studies reporting on the then-named "group 5" anti-tuberculous drugs, including 194 participants, of whom 162 received linezolid. They used a composite "favorable outcome" as the primary outcome, defined as "sputum culture conversion, cure, or treatment completion in the absence of death, treatment interruption, treatment failure, or relapse." Random-effects meta-analysis of "favorable outcome" according to linezolid use resulted in a pooled RR of 1.55 (95% CI 1.10 to 2.21), favouring linezolid. The outcomes in our review were not reported separately by Chang 2013c; in particular, there was no summary or meta-analysis of adverse events outcomes.

Ahmad and colleagues conducted an individual patient data meta-analysis of 50 studies reporting treatment outcomes in drug-resistant tuberculosis, including 39 studies reporting use of linezolid (Ahmad 2018), of which one was a RCT included in our review (Lee 2012). Their primary outcomes were treatment success and death, with no summary of adverse events outcomes due to heterogeneity in measuring and reporting. The data were in favour of treatment success with linezolid use (722/799) versus without (5066/5864), with a crude odds ratio of 1.5 (95% CI 1.2 to 1.9), adjusted odds ratio 3.4 (95% CI 2.6 to 4.5), and adjusted risk difference 0.15 (0.11 to 0.18). Mortality was lower with linezolid use (84/883) versus without (1456/7320), with a crude odds ratio of 0.4 (95% CI 0.3 to 0.5), adjusted odds ratio 0.3 (95% CI 0.2 to 0.3), and adjusted risk difference −0.20 (95% CI −0.23 to −0.16). However, they found high heterogeneity (> 50%) in the studies overall. When XDR-TB patients' outcomes were meta-analysed separately, the effect estimates remained in favour of linezolid use, with low heterogeneity amongst these studies (< 10%). Similar to our review, the authors highlighted a lack of data from RCTs, prospective studies, and low- and middle-income settings (Ahmad 2018).

Our proportion of linezolid discontinuation (22.6%) was lower than the 36% pooled discontinuation found by Cox 2012, and 35% reported by Zhang 2015. The other three previous systematic reviews did not report discontinuation specifically.

When evidence for the use of linezolid was reviewed for the 2016 WHO guidelines (Annex 4 of WHO 2016a), the GRADE assessment for Tang 2015 concluded moderate certainty in the evidence for their comparison of treatment success versus a composite outcome of failure/relapse/death in patients with XDR-TB. They downgraded for serious risk of bias and imprecision, but upgraded for a strong association. This is methodologically incorrect: upgrading for strong association is only for observational studies where GRADE starts as very low, and is not applicable to RCTs, where GRADE starts as high (Guyatt 2011). The WHO 2016a assessments for treatment success versus failure/relapse/death, and death versus all other outcomes in patients with both MDR- and XDR-TB, when Tang 2015 and six non-randomized studies were combined, resulted in very low certainty. Our GRADE assessment, with a population of MDR- and XDR-TB in mind, was very low for all outcomes. This was in part due to downgrading by one level for indirectness (the population in Tang 2015 was limited to adults, with XDR-TB, without HIV co-infection, in one country), and two levels each for risk of bias (no blinding, no placebo, unclear randomization and allocation methods), and imprecision (small sample size, and for most outcomes, low number of events and wide CIs). We did not upgrade for a large effect size (Summary of findings for the main comparison).

AUTHORS' CONCLUSIONS

Implications for practice

Two small randomized controlled trials (RCTs) in people with extensively drug-resistant tuberculosis (XDR-TB), reported better efficacy outcomes with linezolid use. The first reported higher cure (very low-certainty evidence), lower failure (very low-certainty evidence), and higher sputum culture conversion at 24 months (very low-certainty evidence), in participants who received linezolid compared with those who did not receive linezolid. The second RCT reported higher sputum culture conversion rates at four months for participants receiving linezolid immediately versus those who delayed initiation by two months. A lack of high-quality, comparative evidence resulted in our inability to calculate pooled effect estimates of efficacy and safety of linezolid, so we cannot conclude implications for its use in all patients with drug-resistant tuberculosis.

Implications for research

Whilst our review presents very low-certainty evidence for efficacy of linezolid for XDR-TB, a lack of comparative design and reporting limits our certainty in the evidence for the use of linezolid in all patients with drug-resistant pulmonary tuberculosis.

The safety of linezolid, in comparison with alternative or background regimens for drug-resistant pulmonary tuberculosis remains unclear, even when previous reviews are consulted. In addi-

tion, the questions of optimal dosing, duration and combination therapy all remain unanswered, with the majority of existing comparative datasets coming from retrospective studies carried out in high- and upper-middle-income countries.

RCTs in low- and lower-middle-income countries comparing linezolid-containing regimens with alternative regimens not containing linezolid would be desirable to inform guidance on its place in management of drug-resistant pulmonary tuberculosis. Ongoing studies may help, though they have not been designed to examine linezolid's efficacy and safety specifically, and are unlikely to report before the next WHO guidelines are produced. In particular, we would welcome improved, comparable safety reporting in drug studies and observational studies, in order to answer difficult and important questions relating to toxicity and tolerability of drug-resistant tuberculosis treatments.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[author-defined order]*

Lee 2012

Methods	RCT of immediate and delayed (2 months from randomization) addition of linezolid to an XDR-TB regimen. Laboratory assessors blinded to intervention status, but not participants nor clinicians. No placebo used Follow-up: weekly to 16 weeks, then monthly to 7 months, then 2-monthly to end of treatment, then 6 months and 12 months after end of treatment Loss to follow-up: at 12 months after end of treatment, 3 lost to follow-up, 8 withdrew (including 4 failing therapy on linezolid)
Participants	Setting: tertiary referral hospitals in South Korea: National Masan Hospital in Changwon and the National Medical Center in Seoul Number of participants: 41 initially, of whom 21 randomized to receive immediate and 20 delayed linezolid. 2 did not receive linezolid in the immediate arm, so 19 reported on in immediate group **Inclusion criteria** • Aged ≥ 20 years • Pulmonary tuberculosis • Radiographic evidence of lung tuberculosis • Smear and culture positive • Confirmed genotypic or phenotypic XDR-TB (definition below), or failure of treatment despite susceptibility • Failure to respond to 6 months of anti-tuberculosis regimen including active agents • Willingness to be inpatient until 2 consecutive negative smears, then weekly follow-up tests/visits **Exclusion criteria** • Previous linezolid use • Women who were pregnant, breastfeeding, or of childbearing potential and unable to use contraception • Men unwilling to use contraception • Pre-existing low blood cell counts/renal failure/liver failure (see cut-offs in protocol) • History/presence of neuropathy, HIV infection or connective tissue disease • Allergy or serious adverse reaction to linezolid • Anticipated surgical intervention • Use of antidepressants listed in protocol HIV status: excluded people with HIV co-infection Baseline drug susceptibilities: all had XDR-TB. The immediate group were resistant to a mean 11.6 (range 8-15) anti-tuberculosis drugs tested. The delayed linezolid group were resistant to mean 10.4 (range 6 to 14) anti-tuberculosis drugs tested
Interventions	Planned linezolid regimen: started immediately or 2 months after randomization on 600 mg/day After confirmed sputum-smear conversion or 4 months (whichever came first), participants underwent a 2nd randomization to continued linezolid therapy at a dose of 600

	mg/day or 300 mg/day for additional ≥ 18 months Median duration overall 781 days 33 in total underwent second randomization: 17 continued 600 mg/day, 16 switched to 300 mg/day Background regimen: see Lee 2012 Supplemental Table 1 in the Supplementary Appendix for the article available at: www.nejm.org/doi/suppl/10.1056/NEJMoa1201964/suppl_file/nejmoa1201964_appendix.pdf. Unable to summarize due to heterogeneity of timing of regimens and not stratified by immediate/delayed linezolid Other interventions: not reported. Surgical candidates were excluded systematically
Outcomes	**Primary outcome** • Sputum culture conversion at 4 months from randomization. Culture on solid medium used as primary outcome, but liquid medium also tested and reported **Secondary outcomes** • Pharmacokinetic analysis of linezolid on blood samples • AEs
Notes	Date: Recruitment December 2008 to May 2011 Authors: collaboration between authors based at recruiting centres, centrally in South Korea, and international collaborators from Singapore and the USA Study sponsors: supported by the Intramural Research Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health, and by the Ministry of Health and Welfare, South Korea

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Appropriate method of sequence generation: permuted-block randomization
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Laboratory staff were unaware of allocation, but there was a risk of amending co-interventions and dictating sputum collection by clinicians, though the effects may be indirect
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Unclear risk for all but primary outcome** As laboratory staff were blinded from intervention status, low risk for that outcome assessment, but for others there might be a higher risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Unclear risk for all but primary outcome** For primary outcome, low loss to follow-up Further outcomes not reported separately

Lee 2012 (*Continued*)

		for each group, and overall loss to follow-up was much higher
Selective reporting (reporting bias)	Low risk	There is no evidence of selective reporting
Other bias	Low risk	No other source of risk of bias identified

Padayatchi 2012

Methods	RCT, double-blind, placebo-controlled Follow-up for 12 months: every 2 weeks until 16 weeks, then months 5, 6 and 12 Loss to follow-up of 31% (11/35), at median 15 days from start of study
Participants	Setting: King George V Hospital, Durban, South Africa - public sector tertiary referral hospital Number of participants: 36; linezolid, 18 (16 analysed); no linezolid, 18 **Inclusion criteria** • Pulmonary tuberculosis with/without extrapulmonary tuberculosis with a *M tuberculosis* isolate confirmed resistant to at least rifampin and isoniazid (without regard to prior treatment for tuberculosis) • Documented positive sputum culture result for *M tuberculosis* from a sputum obtained in the 4 months prior to enrolment • Willingness to have HIV testing performed, if HIV serostatus unknown or if last documented negative HIV test was > 6 months prior to enrolment • Age > 18 years • Karnofsky score > 40 • Willingness to attend scheduled follow-up visits and undergo study assessments • Willingness of women with child-bearing potential to practice an adequate method of birth control or to abstain from heterosexual intercourse during study therapy. (Standard birth control measures provided free of charge by public health institutions) • Laboratory parameters within 14 days prior to screening: ○ serum creatinine level < 2 times ULN ○ haemoglobin level of > 9.0 g/dL ○ platelet count > 80,000/mm^3 ○ ANC > 1000/mm^3 ○ negative pregnancy test (for women of childbearing potential) • Able to provide informed consent or legally authorized representative able to do so if decisionally impaired **Exclusion criteria** • Currently breast-feeding or pregnant • Known allergy or intolerance to linezolid • Planned therapy during the intensive phase of tuberculosis treatment using drugs with unacceptable interactions with linezolid, including dopamine, selective serotonin uptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), amitriptyline, bupropion, mirtazepine, levodopa, carbidopa, sinemet, or herbal medications. • Significant peripheral neuropathy as evidenced by < 5 seconds of vibratory sense

	to a 128 Hz tuning fork on either big toe when tested bilaterally • Pain, aching or burning of the feet that interfere with walking or sleep • Life expectancy < 4 weeks (in the judgment of the physician) • Anticipated surgical intervention for the treatment of pulmonary tuberculosis • Visual acuity of ≤ 20/200 (6/60 meters) best corrected vision • Poor colour vision as evidenced by incorrect answers on > 4/12 screening Ishihara plates • Participation in another drug study • Taken second-line tuberculosis drugs for > 14 days immediately prior to enrolment (note: use of first-line drugs such as INH, Rifampin, PZA, or ethambutol for > 7 days immediately prior to enrolment is allowed) HIV status: linezolid: 9/18, 4 on antiretroviral therapy; no linezolid: 11/18, 8 on antiretroviral therapy Baseline drug susceptibilities: all MDR - no further details available
Interventions	Planned linezolid regimen: 600 mg once daily for 16 weeks, from outset of MDR therapy; control arm received placebo once daily for 16 weeks Background regimen: individual regimens not stated, though some degree of individualization took place. The standard initial treatment regimen for MDR-TB consisted of: 18-24 months ethionamide, kanamycin, pyrazinamide, ethambutol or cycloserine/terizidone, and ofloxacin The standard empirical XDR-TB regimen was: capreomycin, para-aminosalicylic acid, ethambutol and/or cycloserine, and pyrazinamide Therapy was administered for the initial 4 months as an inpatient, and then at home with direct observation Other interventions: pyridoxine was given to all participants
Outcomes	**Primary** • Tolerability: proportion of participants in each arm who take at least 80% of the 112 directly observed doses of study drug (i.e. at least 90 doses) within 18 weeks of study treatment initiation • Safety: cumulative rate of SAEs (number of SAEs per person days) during the period of study drug therapy and the 4 weeks of post-study drug therapy follow-up. **Secondary** • Microbiological outcomes: including the proportion of culture-conversions at 2-week intervals, time-to-conversion of cultures, and Mycobacterial Growth Indicator Tube (MGIT) "time to detection," during the first 16 weeks in the 2 study arms • Microbiologic outcomes and survival rates in those treated with linezolid and OBT vs those treated with OBT at 16 weeks and 5 months of therapy • Determine the ability to identify and recruit eligible patients with MDR-TB and XDR-TB treatment study, and to retain and follow them for up to 5 months
Notes	Date: 14 April 2009 to 16 April 2010 Authors: TB Trials Consortium Study sponsors: "The study was supported by funding by the US Centers for Disease Control and Prevention (CDC) through the Division of Tuberculosis Elimination. Linezolid was kindly donated by Pfizer Pharmaceuticals along with funding for the creation of a placebo study drug and for conducting the pharmacokinetic analysis of linezolid." Discordance in blood linezolid detection in two participants in each arm - thought due

	to pill allocation (linezolid/placebo). Prompted investigation, finding around 25% of participants had received incorrect pills Full protocol available at: tbtrialsnetwork.org/wp-content/uploads/2014/09/Protocol-TBTC-Study-30-Linezolid-MDR-XDR-TB.pdf Full report available at: tbtrialsnetwork.org/wp-content/uploads/2014/09/Final-Report-TBTC-Study-30-Linezolid-MDR-TB.pdf

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The study will use unrestricted randomization. The statistician will prepare the randomization procedure and provide it to the research pharmacist." Comment: method of randomization not described clearly
Allocation concealment (selection bias)	Low risk	Quote: "The pharmacist will execute the randomization procedure when a patient is enrolled and will assign the study ID and provide blinded medication to study personnel."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Drugs provided during the initial phase of therapy will be mechanically packaged by the study pharmacist and labeled similarly with patient name and ward number by the site pharmacy using a label printer."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding maintained for 20 weeks after randomization but outcomes assessed at 12 months
Incomplete outcome data (attrition bias) All outcomes	High risk	5/16 participants in linezolid arm and 4/18 in the placebo group lost to follow-up. Reasons for study withdrawal not clear, but study authors present a table of presumed reasons for withdrawal, although this is not disaggregated by intervention group
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	High risk	Study authors report that a nested pharmacokinetics study demonstrated that significant numbers of participants in the placebo group actually received linezolid, and significant numbers of people in the linezolid

Padayatchi 2012 (*Continued*)

		group actually received placebo. Discordance of study drug was found for 9/36 (25%) of participants overall

Tang 2015

Methods	Multi-centre RCT; no blinding or placebo Follow-up: "Patients underwent baseline and serial safety evaluations on a weekly basis until the linezolid was reduced at 4-6 weeks, after which it was undertaken every 2 weeks until the linezolid was stopped and then it was once a month." Loss to follow-up: linezolid 4/33; no linezolid 3/32; actually defined later as "default"
Participants	Setting: "Five large-scale TB specialised hospitals in China" Number of participants: 65; linezolid 33; no linezolid 32 **Inclusion criteria** • Aged 18 to 64 years • Positive sputum cultures with an XDR strain • Continuously smear-positive after using available chemotherapeutic options during the previous ≥ 12 months **Exclusion criteria** • Allergic to linezolid • Severe cardiovascular, liver, kidney or blood system disease or other serious illnesses • Mentally ill • Pregnant or lactating women • Positive HIV test result • Unable to purchase linezolid for economic reasons HIV status: no HIV-positive participants (positive HIV test was an exclusion criterion) Baseline drug susceptibilities: all XDR
Interventions	Planned linezolid regimen (added to background regimen in intervention arm; not in control arm): "Start dose of 1200 mg linezolid per day for 4-6 weeks, after which they continued taking linezolid at a dose of 300-600 mg per day in accordance with body weight and tolerability. This continued until the patients provided two consecutive negative sputum cultures during a 2-month period (taken at least 30 days apart)" Background regimen: all received prothionamide, pyrazinamide, moxifloxacin or gatifloxacin or levofloxacin, and para-aminosalicylic acid. Capreomycin or amikacin were given to 55% in the linezolid arm and 53% in the control arm. Clofazamine was used by 67% in the linezolid arm and 59% in the control arm. 55% in the linezolid arm and 52% in the control arm received clarithromycin Other interventions: none reported
Outcomes	Treatment outcomes, as defined by the WHO, were recorded "Additionally, cured and completed treatment categories were combined as 'treatment success', whereas others were combined as 'poor treatment outcome'." AEs: including leukopenia, anaemia, peripheral neuropathy and optic neuropathy

Tang 2015 (*Continued*)

Notes	Date: October 2009 to August 2011 Authors: based at 6 specialist hospitals, and Shanghai Minhang Center for Disease Control and Prevention, Shanghai, China Study sponsors: "Key Project of Chinese National Programs (grant No. 2009ZX10003-017)" Linezolid was not provided to participants free of charge, so those who could not afford it were excluded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the linezolid arm 4/33 participants were lost to follow-up, and 3/32 in the control arm. Of these, 2 in each arm were due to "economic problems", and the other 3 (2 in the linezolid arm, and 1 in the control arm) were due to AEs. All participants were included in the analysis
Selective reporting (reporting bias)	Low risk	The study protocol was not available for review. All outcomes stated in introduction and methods section were reported
Other bias	Low risk	No other source of bias identified

Migliori 2009

Methods	Retrospective cohort study Follow-up: specific details of follow-up methods not reported Loss to follow-up: linezolid, 40/85 had no treatment outcome, 1 had interrupted treatment and 1 was transferred out; no linezolid, not reported
Participants	Setting: 21 hospitals in Belarus, Germany, Italy and Switzerland Number of participants: total 195; linezolid, 85 (45 included in efficacy analysis, 85 included in safety and tolerability analysis); no linezolid, 110 **Inclusion criteria** • MDR/XDR culture confirmed • Definitive treatment end-points recorded (cured, completed, died or failed) **Exclusion criteria** • Still on treatment at the time of the data collection (for efficacy analysis; not for safety and tolerability) HIV status: not recorded Baseline drug susceptibilities: linezolid, 75/85 MDR; 41/45 in the efficacy analysis; 10/85 XDR; 4/45 in efficacy analysis. They had resistance to a mean of 1.5 second-line drugs. No linezolid, 102/110 MDR; 8/110 XDR; mean resistance to 0.9 second-line drugs
Interventions	Planned linezolid regimen: of 85, 28 received 600 mg once daily, and 57 received 600 mg twice daily. Mean (+/- SD) duration was 222 +/- 249 days; median 93 days The intended duration was 3 months in Belarus due to limited availability; other countries did not report an intended duration Background regimen: "In all countries, regimens to treat MDR/XDR-TB cases were tailored to DST results according to WHO recommendations, using fluoroquinolones, injectable agents and other second-line oral agents." Specific regimens were not reported Other interventions: none reported
Outcomes	Safety and tolerability end-points included SAEs and AEs. SAE defined as any adverse reaction that resulted in temporary or permanent discontinuation of linezolid, whereas AE required only dose adjustment and/or addition of concomitant treatment Efficacy end-points included time to and proportion of sputum smear and culture conversions, and treatment outcome
Notes	Date: 2001-2007 Authors: TBNET Study Group Study sponsors: "This study was supported by the current research funds of the participating institutions. The data collection system was initiated in 1996 with funding obtained by the Italian Association of Hospital Pulmonologists (AIPO) through a Ministry of Health/Superior Institute of Health grant (National TB Project, Grant No. 1, 641/96). The study is partially funded by the European Respiratory Society as a Clinical Research Collaboration."

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious Incomplete control of confounding variables **2. Selection of participants into the study:** moderate Possible influence of intervention and outcome on selection into the study

Migliori 2009 (*Continued*)

		3. Classification of interventions: serious Some concerns about intervention status definition **4. Deviations from intended interventions:** low Unlikely deviation from usual practice **5. Missing data:** serious Lack of AE outcomes in those not receiving linezolid **6. Measurement of outcomes:** serious Multi-centre retrospective study with outcome assessment by treating physicians **7. Selection of the reported results:** moderate No selection evident, however no detailed protocol **Overall:** serious One or more domain judged to be serious

Udwadia 2010

Methods	Prospective cohort study Follow-up: specific follow-up methods not reported Loss to follow-up: linezolid, 3/18; no linezolid, not reported
Participants	Setting: tertiary private hospital Mumbai, India Number of participants: total 78; linezolid, 18; no linezolid, 60 Inclusion criteria: consecutive participants with MDR- and XDR-TB Exclusion criteria: none reported HIV status: not reported Baseline drug susceptibilities: linezolid, 11/18 had MDR, 7/18 had XDR
Interventions	Planned linezolid regimen: 600 mg twice daily was given for a mean 20.6 months Background regimen: this was individualized, but specific details were not reported Other interventions: none reported
Outcomes	Treatment outcomes and AEs were reported for those receiving linezolid
Notes	Date: 2000 to 2007 Authors: based in the department of pulmonary medicine at the hospital in which the participants were treated Study sponsors: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious No control for confounding **2. Selection of participants into the study:** low Unlikely to be selected with knowledge of the outcome **3. Classification of interventions:** low Intervention is well defined, and likely defined based on

Udwadia 2010 (*Continued*)

		”information collected at the time of intervention“ **4. Deviations from intended interventions:** low Likely to be similar to usual practice **5. Missing data:** critical Critical differences between groups in amount of data provided **6. Measurement of outcomes:** serious ”The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants); and the outcome was assessed by assessors aware of the intervention received by study participants“ **7. Selection of the reported results:** no information Not enough information **Overall:** critical One or more domain judged to be critical

Jo 2014

Methods	Retrospective cohort study Follow-up: no specific follow-up methods reported Loss to follow-up: 4/70 participants were lost to follow-up; this was not stratified according to whether or not they received linezolid
Participants	Setting: Asian Medical Centre, Seoul, Korea - tertiary referral centre Number of participants: 70 total; linezolid, 26; no linezolid, 44 **Inclusion criteria** • Diagnosed with MDR-TB January 2006-December 2012, at Asan Medical Center • Identified using MDR-TB register **Exclusion criteria** • Ofloxacin-sensitive isolate • “treated with later-generation FQs [fluoroquinolones] that were added to an initial failed regimen due to the unavailability of other effective drugs” • “Another seven patients were excluded at the request of a pharmaceutical company sponsoring a clinical study for a novel MDR-TB drug, in which these patients were enrolled” HIV status: only 9/70 tested - all negative Baseline drug susceptibilities: linezolid, 13/26 had XDR-TB; no linezolid, 13/44 had XDR-TB
Interventions	Planned linezolid regimen: 16/26 received 300 mg/day; 10/26 received 600 mg/day. Duration ranged from 14-752 days; median was 258.5 (interquartile range 154.5-548) days Background regimen: this was individualized according to drug susceptibility testing, and comprised a median 5 drugs. 54/70 received a later generation fluoroquinolone, and 2/70 received delamanid Other interventions: surgical resection was performed in 16/70 participants
Outcomes	Treatment outcomes, as defined by WHO: “cured, treatment completed, treatment failed, died, lost to follow-up and not evaluated” AEs, including discontinuation of linezolid, were also reported

Jo 2014 (*Continued*)

Notes	Date: January 2006 to December 2012 Authors: based in the Department of Pulmonary and Critical Care Medicine, in Asan Medical Center, where the participants were treated Study sponsors: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious "At least one known important domain was not appropriately measured, or not controlled for" **2. Selection of participants into the study:** low Probably selected without bias, and follow-up started when intervention started **3. Classification of interventions:** moderate Intervention groups were not defined well enough **4. Deviations from intended interventions:** low Likely to reflect usual practice **5. Missing data:** critical Critical differences in reporting of outcomes for those receiving and not receiving linezolid, with no analysis to correct for this **6. Measurement of outcomes:** serious Subject outcome measure, determined by treating clinicians **7. Selection of the reported results:** serious Lack of data for those not receiving linezolid **Overall:** critical One or more domain judged to be critical

Seddon 2014

Methods	Retrospective review of register of children treated for MDR-TB Follow-up: methods for follow-up not reported specifically Loss to follow-up: 8/149 participants were lost to follow-up
Participants	Setting: Tygerberg Hospital, Western Cape, South Africa - regional tertiary referral paediatric hospital Number of participants: 149 in total; linezolid, 3; no linezolid, 146 **Inclusion criteria** • Children < 15 years treated for MDR-TB (includes rifampicin monoresistant tuberculosis as per guidelines). • "Children with confirmed and presumed MDR-TB were included. A presumed diagnosis was typically made by the attending clinical team if the child had clinical symptoms, signs and radiology of TB with documented close MDR-TB exposure, or whose condition was failing to respond to a first-line TB regimen with documented good adherence." **Exclusion criteria:** • "Children initially started on MDR-TB treatment due to MDR-TB exposure but those who were

	subsequently confirmed to have drug-susceptible TB were excluded from analysis." HIV status: 146 participants had known HIV status; linezolid, 1/3 had HIV co-infection; no linezolid, 31/143 participants had HIV co-infection Baseline drug susceptibilities: linezolid, 1 had MDR, and 2 had XDR; no linezolid, 142/146 had MDR, and 4/146 XDR
Interventions	Planned linezolid regimen: the 3 participants were treated for 4 months, 16 months and 21 months. The dose was not reported Background regimen: participants received individualized regimens. Most received isoniazid and ofloxacin. An injectable agent was given in 94/149. 103/149 were admitted to hospital for 5 months; the rest treated at home Other interventions: none reported
Outcomes	"The most severe grade of adverse event experienced over the course of treatment, for each category, was determined. MDR-TB treatment outcome was classified as cure, probable cure, treatment completed, failure, death, lost to follow-up and transferred out."
Notes	Date: 2009 to 2012 Authors: included those based at Tygerberg Hospital, but also collaborators in London, UK Study sponsors: "This research was supported by a United States Agency for International Development (USAID) Cooperative Agreement (TREAT TB Agreement No. GHN-A-00-08-00004-00) (JAS and HSS), the Sir Halley Stewart Trust (JAS) and the National Research Foundation of South Africa (HSS)." All participants were children

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious No evidence of controlling for confounding **2. Selection of participants into the study:** low Probably selected without bias, and follow-up started when intervention started **3. Classification of interventions:** low Intervention well defined, based on contemporaneous information **4. Deviations from intended interventions:** low Likely to reflect usual practice **5. Missing data:** low Data reasonably complete **6. Measurement of outcomes:** serious Subject outcome measure, determined by treating clinicians **7. Selection of the reported results:** moderate No evidence of selected reporting, but no detailed protocol **Overall:** serious One or more domain judged to be serious

Zhang 2014

Methods	Retrospective record review Follow-up: this occurred "at least monthly"; "patients enrolled in this study only received less than 6 months LZD [linezolid] treatment rather than ≥18-24 months. And the follow-up period for those patients was completed only for 3 months after discontinuing LZD." Loss to follow-up: not reported
Participants	Setting: Beijing Chest Hospital, Beijing, China (tuberculosis specialized hospital) Number of participants: 43 in total; linezolid, 15; no linezolid 28 **Inclusion criteria** • XDR-TB confirmed by culture and drug susceptibility testing **Exclusion criteria** • None reported HIV status: "All… negative" Baseline drug susceptibilities: all XDR; 81% resistant to para-aminosalicylic acid; 72% resistant to prothionamide; 77% resistant to ethambutol. "No statistical difference between LZD group and control group without LZD regarding the proportions of drug-resistant cases was detected (P>0.05)."
Interventions	Planned linezolid regimen: 600 mg once daily, for ≥ 1 month Background regimen: participants received unspecified "individualized treatment regimens" Other interventions: none reported
Outcomes	Sputum culture conversion: time; "favourable outcome" = 2 consecutive negative cultures; "adverse outcome" = positive culture at the endpoint of treatment AEs Linezolid minimum inhibitory concentration (MIC) and genotypic resistance mutation determination
Notes	Date: March 2012 to February 2013 Authors: some were based at the treating centre; others were at the National Center for Tuberculosis Control and Prevention, Beijing, China Study sponsors: "Supported by National Key Project (2013003ZX003)" Not all could afford linezolid - not provided free of charge by the Chinese Government

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious No evidence of controlling for confounding **2. Selection of participants into the study:** low Probably selected without bias, and follow-up started when intervention started **3. Classification of interventions:** low Intervention well defined, based on contemporaneous information **4. Deviations from intended interventions:** low Similar to usual practice **5. Missing data:** critical No AE outcome data for those not receiving linezolid

Zhang 2014 (*Continued*)

		6. Measurement of outcomes: serious Subject outcome measure, determined by treating clinicians **7. Selection of the reported results:** serious Lack of methods on AE outcome measurement **Overall:** critical One or more domain judged to be critical

Jeong 2015

Methods	Retrospective cohort study Follow-up: "Sputum smear examinations and cultures were performed monthly for the first 6 months and then at 2 to 3 month intervals until the end of treatment." Loss to follow-up: 23/337 were lost to follow-up; no further details were provided on time of loss to follow-up or breakdown by receipt of linezolid
Participants	Setting: "Samsung Medical Center, a 1961 bed referral hospital in Seoul, Korea" Number of participants: initially 337, but then analysis provided for the 144 who had fluoroquinolone resistance: linezolid, 58; no linezolid, 86 **Inclusion criteria** • Pulmonary MDR-TB • also with fluoroquinolone resistance **Exclusion criteria** • "(i)…Transferred to our hospital after negative conversion of sputum culture with >3 months of treatment with second-line drugs; (ii) … transferred to a national TB hospital after <3 months of treatment in our hospital; and (iii) … treated for extra-pulmonary MDR-TB" HIV status: "None of the patients was positive for HIV infection" Baseline drug susceptibilities: all had fluoroquinolone-resistant MDR; linezolid, 30/58 (51.7%) had XDR-TB; no linezolid 18/86 (20.9%) had XDR-TB

Interventions	Planned linezolid regimen: 53/62 (note inconsistent denominator) received 300 mg once daily; 7/62 received 600 mg once daily; 2/62 had 600 mg initially followed by 300 mg once daily
	Background regimen: individualized according to WHO guidelines. Drugs used within regimens:
	• linezolid:
	  ○ injectable drug: 50/58 (86.2%)
	  ○ fluoroquinolone: 57/58 (98.3%)
	  ○ prothionamide: 19/58 (32.8%)
	  ○ cycloserine: 42/58 (72.4%)
	  ○ para-aminosalicylic acid: 23/58 (39.7%)
	• no linezolid:
	  ○ injectable drug: 78/86 (90.7%)
	  ○ fluoroquinolone: 82/86 (95.3%)
	  ○ prothionamide: 64/86 (74.4%)
	  ○ cycloserine: 80/86 (93%)
	  ○ para-aminosalicylic acid: 51/86 (59.3%)
	Other interventions: surgical resection; linezolid, 22/58; no linezolid 24/86

Outcomes	Treatment outcomes according to 2013 WHO definitions

Jeong 2015 (*Continued*)

Notes	Date: January 2005 to December 2011 Authors: based at the institution treating the participants, without external collaborators Study sponsors: grant of the Korean Health technology R&D Project, Ministry for Health & Welfare, Republic of Korea (HI13C0871)

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** no information No comparative AE data, so no confounding or control for this would be relevant **2. Selection of participants into the study:** low Probably selected without bias, and follow-up started when intervention started **3. Classification of interventions:** moderate "The addition of linezolid to the treatment regimen was decided by the attending physician" **4. Deviations from intended interventions:** low Similar to usual practice **5. Missing data:** no information Reasons for missing data not provided **6. Measurement of outcomes:** serious Subject outcome measure, determined by treating clinicians **7. Selection of the reported results:** low Only 1 AE outcome reported, with no effect estimate possible **Overall:** serious One or more domain judged to be serious

Kwak 2015

Methods	Retrospective cohort study Follow-up: no details of follow-up were reported Loss to follow-up: 6 (4.8%) were lost to follow-up, including those not evaluated in the final analysis; no further details were provided
Participants	Setting: Seoul National University College of Medicine, a tertiary referral centre in Seoul, Korea Number of participants: 123; linezolid 12; no linezolid, 111 **Inclusion criteria** • MDR-TB **Exclusion criteria** • None reported HIV status: not reported Baseline drug susceptibilities: 123 MDR; 26 XDR, 13 quinolone-resistant (but not resistant to injectable drugs), 33 injectable-resistant (but not resistant to fluoroquinolones)

Kwak 2015 (*Continued*)

Interventions	Planned linezolid regimen: dose not reported, but "Linezolid was added for patients refractory to at least 3-6 months of medical treatment and those who proved to have extensively drug-resistant [TB]" Background regimen: "Although treatment for MDR-TB was individualised, the basic principles were based on World Health Organization (WHO) recommendations." "MDR-TB patients were treated with a median of five drugs (IQR 5.0-6.0) for a median of 24.4 months (IQR 18.4-27.3)." 113/123 (91.9%) received fluoroquinolones 90/123 (73.2%) received injectable drugs Other interventions: "Surgical resection was considered for patients with localised lesions refractory to 3-6 months of medical treatment." This was carried out in 18 (14.6%) participants
Outcomes	Treatment outcomes according to WHO criteria A combined "unfavourable outcome" was determined: "Failed, died, defaulted and relapse patients comprised the 'unfavourable outcomes' group."
Notes	Date: 2006-2010 Authors: based at the institution managing participants, collaborating with authors from "Department of Internal Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Science, Seoul" Study sponsors: Seoul National University College of Medicine Research Fund, Seoul, Republic of Korea (grant number 30-2013-0180). "The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. Statistical analysis was supported by the Medical Research Collaborating Center (MRCC), Seoul National University College of Medicine."

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious No control for confounders for AE outcomes **2. Selection of participants into the study:** low Probably selected without bias, and follow-up started when intervention started **3. Classification of interventions:** low Intervention well defined, based on contemporaneous information **4. Deviations from intended interventions:** low Similar to usual practice **5. Missing data:** low Data reasonably complete **6. Measurement of outcomes:** serious Subject outcome measure, determined by treating clinicians **7. Selection of the reported results:** moderate No evidence of selected reporting, but no detailed protocol **Overall:** serious One or more domain judged to be serious

Van Altena 2015

Methods	Retrospective cohort study Follow-up: not stated specifically, but some inpatient stay and then outpatient nurse supervision Loss to follow-up: "Only 28/98 patients were consistently followed up for at least 24 months; 28 patients had zero follow-up days after treatment discontinuation or completion, mainly because they left the country." In addition, "2 defaulted/stopped treatment"
Participants	Setting: 2 dedicated tuberculosis centres in the Netherlands - all MDR cases in the Netherlands are admitted there Number of participants: 113 were enrolled; 104 started therapy, linezolid, 53; no linezolid 51 **Inclusion criteria** • "All patients diagnosed with MDR-TB between January 2000 and December 2009. Patients diagnosed earlier who started treatment during the study period were also included." • All participants had culture-confirmed tuberculosis **Exclusion criteria** • "Patients diagnosed in 2009 but who started treatment in 2010 were excluded" HIV status: 14/113 were reported to have HIV infection; no breakdown by linezolid receipt status was reported Baseline drug susceptibilities: 4/112 had XDR; remaining MDR. 10/112 were aminoglycoside-resistant, and 7/110 were resistant to a fluoroquinolone
Interventions	Planned linezolid regimen: 300 mg twice daily; sometimes reduced based on therapeutic drug monitoring results There was no stated timing in relation to commencement of tuberculosis therapy Linezolid was given for a mean duration of 99 days (range 12-706), median 56 days [IQR 26-91] Background regimen: individualized, with a wide variety of regimens being used ≥ 18 months in total, and ≥ 12 months after sputum culture conversion from positive to negative Median 6 active drugs were used (IQR 5-6, range 3-10) Other interventions: 8 had thoracic surgery
Outcomes	• Treatment outcomes • Drug discontinuation and related AEs
Notes	Date: 2000 to 2009 Authors: from various institutions within the Netherlands Study sponsors: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious Inadequate controlling **2. Selection of participants into the study:** low Probably selected without bias, and follow-up started when intervention started **3. Classification of interventions:** serious Intervention status was not well defined **4. Deviations from intended interventions:** low Similar to usual practice **5. Missing data:** low Paucity of outcomes data, but similar regardless of inter-

		vention group **6. Measurement of outcomes:** serious Subject outcome measure, determined by treating clinicians **7. Selection of the reported results:** moderate Paucity of outcomes data, but no clear active selection **Overall:** serious One or more domain judged to be serious

Galli 2016

Methods	Retrospective cohort study Follow-up: not reported Loss to follow-up: not reported
Participants	Setting: recruitment from national tuberculosis register - i.e. various settings within Italy Number of participants: 11 had MDR-TB, linezolid, 5; no linezolid 6 **Inclusion criteria** • Children (< 18 years) treated for active or latent tuberculosis • Case recorded in Italian national tuberculosis register **Exclusion criteria:** • None reported HIV status: not reported Baseline drug susceptibilities: 1 participant receiving linezolid had XDR; the remainder were MDR
Interventions	Planned linezolid regimen: not reported Background regimen: not reported Other interventions: none reported
Outcomes	Descriptive study, collecting a wide range of demographic, treatment, AE and treatment outcome data
Notes	Date: January 2010 to December 2012 Authors: various authors within Italy - no international collaborators Study sponsors: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious Inadequate controlling **2. Selection of participants into the study:** low Probably selected without bias, and follow-up started when intervention started **3. Classification of interventions:** serious Intervention status was not well defined **4. Deviations from intended interventions:** no infor-

		mation Not enough information on interventions to judge this **5. Missing data:** low Data reasonably complete once authors provided additional data **6. Measurement of outcomes:** serious Participant outcome measure, determined by treating clinicians **7. Selection of the reported results:** moderate No evidence of selected reporting, but no detailed protocol **Overall:** serious One or more domain judged to be serious

Jensenius 2016

Methods	Retrospective cohort study Follow-up: not reported Loss to follow-up: 12/68 participants were lost to follow-up. Age 16-25 and illicit drug use were identified as independent risk factors for loss to follow-up in a multivariate analysis
Participants	Setting: "The university hospitals at Bergen, Oslo, Tromsø and Trondheim." (Norway) Number of participants: 89 participants were enrolled, 68 started treatment; linezolid, 52; no linezolid, 16. Note denominators for proportions of participants vary between 89 and 68 **Inclusion criteria** • Notified as having MDR-TB between 1999 and 2014 **Exclusion criteria** • None reported HIV status: 3/89 reported to have HIV infection Baseline drug susceptibilities: 6/89 participants had XDR-TB; the remainder had MDR
Interventions	Planned linezolid regimen: "Usually 600mg twice a day"; no planned duration or timing in relation to commencement of drug-resistant tuberculosis therapy Background regimen: 65/68 received an injectable; 63/68 received a fluoroquinolone; 59/64 had direct observation of therapy at home on discharge from hospital Other interventions: 2 participants had lung resection surgery (both XDR)
Outcomes	• Treatment outcomes • Drug discontinuation (serious adverse drug effect recorded if prompted this)
Notes	Date: 1995 to 2014 Authors: collaborators within Norway Study sponsors: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Jensenius 2016 (*Continued*)

Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious Inadequate controlling **2. Selection of participants into the study:** low Probably selected without bias, and follow-up started when intervention started **3. Classification of interventions:** serious Intervention status was not well defined **4. Deviations from intended interventions:** low Similar to usual practice **5. Missing data:** no information Not enough outcomes data to judge this **6. Measurement of outcomes:** serious Subject outcome measure, determined by treating clinicians **7. Selection of the reported results:** moderate No evidence of selected reporting, but no detailed protocol **Overall:** serious One or more domain judged to be serious

Tiberi 2016

Methods	Retrospective cohort study Follow-up: details of follow-up not reported Loss to follow-up: in the 2 studies feeding into this cohort, treatment interruption was reported as 21/264 (8%) and 11/140 (7.9%)
Participants	Setting: hospital inpatients in multiple centres in Belarus, Belgium, Brazil, Ecuador, Greece, Holland, Italy, Peru, Slovakia, and UK Number of participants: linezolid, 267; no linezolid, 81 **Inclusion criteria:** • "Only adults with a culture-confirmed diagnosis of MDR-TB (i.e. tuberculosis caused by *M tuberculosis* isolates resistant to at least isoniazid and rifampicin) were enrolled" **Exclusion criteria** • "Individuals aged <15 years were excluded." HIV status: in the 2 studies, 13/251 (5.2%) and 10/173 (5.8%) were reported to have HIV infection Baseline drug susceptibilities: in the first study, 57/264 (21.6%) were XDR, 73/255 (28.6%) fluoroquinolone-resistant, and 25%-33% resistant to the injectables amikacin, capreomycin or kanamycin. In the second study, 104/180 (57.8%) were XDR, 110/175 (62.9%) fluoroquinolone-resistant, and 49%-61% resistant to injectables
Interventions	Planned linezolid regimen: this was variable, ranging from 300 mg once daily to 600 mg twice daily Background regimen: the majority received a fluoroquinolone (mostly moxifloxacin), and only < 10% received bedaquiline or delamanid Other interventions: in the first study, surgery took place in 21/257 (8.2%) and antiretrovirals were used in 11/13 (84.6%) of those with HIV infection. In the second study, 32/176 (18.2%) had surgery and 8/10 (80%) received antiretrovirals

Tiberi 2016 (*Continued*)

Outcomes	Treatment outcomes and AEs
Notes	Date: 2003 to 2015 Authors: multinational collaboration, including clinicians looking after participants in treating centres Study sponsors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious Inadequate controlling **2. Selection of participants into the study:** low Probably selected without bias, and follow-up started when intervention started **3. Classification of interventions:** serious Intervention status was not well defined **4. Deviations from intended interventions:** low Similar to usual practice **5. Missing data:** no information Not enough outcomes data to judge this **6. Measurement of outcomes:** serious Subject outcome measure, determined by treating clinicians **7. Selection of the reported results:** moderate No evidence of selected reporting, but no detailed protocol **Overall:** serious One or more domain judged to be serious

Guglielmetti 2017

Methods	Retrospective cohort study Follow-up: during treatment then 24 months after if possible. Frequency not reported Loss to follow-up: at end of treatment, 5/45; at 12 months after treatment, 9/36; at 24 months after treatment, 2/23
Participants	Setting: multiple referral centres in France - hospitalized and treated for free Number of participants: linezolid, 43; no linezolid, 2 **Inclusion criteria** • "All MDR-TB patients treated with bedaquiline from January 1, 2011 to December 31, 2013 and hospitalised at three French referral TB centres (Bligny, Pitié Salpêtrière and Bichat Hospitals)." **Exclusion criteria:** • None reported HIV status: 2/45 reported to have HIV infection Baseline drug susceptibilities: 24/45 (53%) had XDR-TB, 11/45 (24%) had fluoroquinolone-resistant MDR-TB, and 6/45 (13%) had MDR-TB with additional resistance to injectable drugs. Only 4/45 had MDR-TB without resistance to fluoroquinolones or injectables

Guglielmetti 2017 (*Continued*)

Interventions	Planned linezolid regimen: 600 mg daily Background regimen: all 45 received bedaquiline, 35/45 (78%) an injectable, 32/45 (71%) a fluoroquinolone, 40/45 (89%) para-aminosalicyclic acid, 11/45 (24%) ethionamide, 32/45 (71%) cycloserine, 20/45 (44%) clofazimine, and 28/45 (62%) imipenem/clavulanate Other interventions: "Lung surgery, mostly lobectomy, was performed in 12 (26.7%) patients after a median (IQR) of 170 (75-269) days from treatment start and after sputum culture conversion in 75% of cases."
Outcomes	"At the end of treatment, favourable outcomes were defined as the sum of cured and treatment completed; all other outcomes were defined as unfavourable." AEs
Notes	Date: 2011 to 2013 Authors: multicentre collaborators from various centres in France, including those based at sites recruiting participants Study sponsors: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious Inadequate controlling **2. Selection of participants into the study:** low Probably selected without bias, though information on start of follow-up and start of intervention not clear **3. Classification of interventions:** low Intervention status well defined, though post-hoc **4. Deviations from intended interventions:** low Similar to usual practice (retrospective) **5. Missing data:** low Outcomes data available for nearly all participants **6. Measurement of outcomes:** serious Potential subjectivity of outcome measures, determined by treating clinicians **7. Selection of the reported results:** no information Not enough information reported on outcome measurement or analysis **Overall:** serious One or more domain judged to be serious

Ferlazzo 2018

Methods	Multicentre retrospective cohort study of patients receiving bedaquiline and delamanid in combination Follow-up: lab tests "at least monthly". ECG every 2 weeks for first 3 months, then monthly. Follow-up results reported up to 6 months Loss to follow-up: at 6 months, 1/28 (participant had been culture-positive at 5 months)
Participants	Setting: "Primary" and hospital care, various sites in Armenia (25% participants), India (25%), South Africa (50%) Number of participants: 28; linezolid, 23; no linezolid, 5 **Inclusion criteria** • MDR-TB • Started on bedaquiline and delamanid for at least 1 week • "Patients were eligible to receive the combination if a regimen with at least four other effective drugs could not be constructed because of confirmed drug resistance, suspected resistance in the setting of previous drug exposure, drug intolerance, or a combination of these three factors." **Exclusion criteria** • Not reported HIV status: 10/23 and 1/5 had HIV co-infection Baseline drug susceptibilities: overall: 14/28 had XDR, 2/28 MDR with additional injectable resistance, 10/28 MDR with additional fluoroquinolone resistance, 2/28 MDR
Interventions	Planned linezolid regimen: not reported Background regimen: all received bedaquiline and delamanid, 19/28 had clofazimine, 6/28 moxifloxacin and 15/28 carbapenems Other interventions: not reported
Outcomes	**Efficacy** • sputum culture conversion at 6 months • culture positivity/negativity at 6 months, regardless of baseline status **Safety** • SAE occurring within 6 months, • Prolonged QTc **Tolerability** • Retention in care at 6 months
Notes	Date: January to August 2016 Authors: members of South African, French, Armenian and Indian Médecins Sans Frontières units, and researchers in South Africa and the USA Study sponsors: Médecins Sans Frontières

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious Lack of controlling for confounding **2. Selection of participants into the study:** low Probably selected without bias, though information on start of follow-up and start of intervention not clear **3. Classification of interventions:** low

Ferlazzo 2018 (*Continued*)

		Intervention status well defined and collected programmatically, though post-hoc data received **4. Deviations from intended interventions:** low Similar to usual practice (retrospective) with robust follow-up plans **5. Missing data:** low Outcomes data available for nearly all participants **6. Measurement of outcomes:** serious Assessors of AEs likely to be aware of linezolid use and may have been influenced in judging outcomes **7. Selection of the reported results:** moderate Relatively well defined outcome measurements, with post-hoc linezolid-specific analysis **Overall:** serious One or more domain judged to be serious

Olayanju 2018

Methods	Prospective cohort study Follow-up: monthly sputum smear and culture during hospital stay, less frequently thereafter; treated for 24 months Loss to follow-up: 30/272 (11%)
Participants	Setting: Brooklyn Chest Hospital - Western Cape referral centre, Cape Town, South Africa Number of participants: linezolid, 55; no linezolid, 217 **Inclusion criteria** • Initiated treatment for culture confirmed XDR-TB **Exclusion criteria** • None reported HIV status: 22/55 (40%) receiving linezolid and 101/217 (47%) who did not receive linezolid had HIV co-infection Baseline drug susceptibilities: all had XDR-TB
Interventions	Planned linezolid regimen: not reported Background regimen: • linezolid; all received bedaquiline, 1/55 an injectable, 54/55 a fluoroquinolone, 52/55 para-aminosalicylic acid, 51/55 terizidone, 53/55 pyrazinamide, 15/55 ethambutol and 54/55 clofazimine • no linezolid; 13/217 received bedaquiline, 209/217 an injectable, 205/217 a fluoroquinolone, 206/217 para-aminosalicylic acid, 211/217 terizidone, 214/217 pyrazinamide, 200/217 ethambutol and 78/217 clofazimine Other interventions: not reported
Outcomes	Treatment outcomes: "…cure/treatment completion, deceased, treatment failure, treatment default and lost to follow-up. Patients who achieved cure/completion were said to have had a favourable outcome while the deceased, defaulted and those who failed treatment were said to have had unfavourable outcomes." AEs
Notes	Date: Jan 2008-June 2017 Authors: based at the centre and affiliated university in Cape Town Study sponsors: European Union (European and Developing Countries Clinical Trials Partnership: TESA, Oppenheimer Foundation, South African Medical Research Council and South African National Research Foundation)

Olayanju 2018 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Other bias	Unclear risk	ROBINS-I assessment: **1. Confounding:** serious Inadequate controlling of confounding **2. Selection of participants into the study:** low Prospective recruitment should avoid selection bias **3. Classification of interventions:** low Intervention status well defined **4. Deviations from intended interventions:** serious Background regimen differed significantly between the groups **5. Missing data:** low Outcomes data available for nearly all participants **6. Measurement of outcomes:** serious Potential subjectivity of outcome measures, determined by treating clinicians, though exact procedures not reported **7. Selection of the reported results:** low No evidence of multiple outcome measurements or analyses **Overall:** serious One or more domain judged to be serious

Abbreviations: AE: adverse event; ANC: absolute neutrophil count; DST: drug susceptibility testing; ECG: electrocardiogram; INH: isoniazid; *M tuberculosis*: *Mycobacterium tuberculosis*; MDR: multi-drug resistant; OBT: optimized background therapy; PZA: pyrazinamide; QTc: corrected Q-T interval on electrocardiography; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; TB: tuberculosis; ULN: upper limit of normal; WHO: World Health Organization; XDR: extensively drug resistant.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbate 2007	Not a trial/cohort study
Abbate 2010	Not a trial/cohort study
Aggarwal 2009	Not a trial/cohort study
Altet 2013	Not a trial/cohort study

(*Continued*)

Anger 2010	Not a trial/cohort study
Bang 2010	Not a trial/cohort study
Berry 2016	Not a trial/cohort study
Bolhuis 2012	Not a trial/cohort study
Bolhuis 2015	Not a trial/cohort study
Cadena 2009	Not a trial/cohort study
Carroll 2011	Ineligible population
Chan 2013	Not a trial/cohort study
Chang 2012	Not a trial/cohort study
Chang 2013	Not a trial/cohort study
Cherenko 2013	Not a trial/cohort study
Coban 2009	Not a trial/cohort study
Coleman 2014	Not a trial/cohort study
Conradie 2014	No linezolid use
Corpe 1964	Not a trial/cohort study
Cox 2013	Not a trial/cohort study
Dauby 2011	Not a trial/cohort study
De Lorenzo 2012	Not a trial/cohort study
De Lorenzo 2013	Not a trial/cohort study
Dheda 2017	No linezolid use
Dhingra 2008	No linezolid use
Diacon 2012	No linezolid use
Farshidpour 2013	Not a trial/cohort study
Fattorini 2012	No linezolid use

(*Continued*)

Fortun 2005	Not a trial/cohort study
Griffith 2004	Not a trial/cohort study
Gunther 2015	No linezolid use
Henry 2016	Not a trial/cohort study
Heyckendorf 2018	Lack of adverse event outcomes
Huang 2012	Not a trial/cohort study
Hughes 2015	Not a trial/cohort study
Jaramillo 2013	Not a trial/cohort study
Jaspard 2017	Not a trial/cohort study
Jiang 2013	No linezolid use
Joseph 2011	No linezolid use
Kjollerstrom 2011	Not a trial/cohort study
Koh 2009	Not a trial/cohort study
Koh 2012	Not a trial/cohort study
Lai 2008	No linezolid use
Laniado-Laborin 2012	Not a trial/cohort study
Maartens 2015	Not a trial/cohort study
Macedo 2012	Not a trial/cohort study
Maimakov 2013	No linezolid use
Manfredi 2009	Not a trial/cohort study
Milanov 2015	No AE outcomes reported
Mirsaeidi 2005	No linezolid use
Moyo 2015	No linezolid use
Nam 2009	Not a trial/cohort study

(*Continued*)

Nie 2013	Not a trial/cohort study
O'Donnell 2013	No linezolid use
Palmero 2004	No linezolid use
Palmero 2010	Ineligible population
Palmero 2015	Not a trial/cohort study
Park 2004	No linezolid use
Park 2006	Not a trial/cohort study
Park 2010	Not a trial/cohort study
Pasticci 2012	No linezolid use
Pawar 2009	Not a trial/cohort study
Pietersen 2014	No linezolid use
Prajapati 2017	Not a trial/cohort study
Ralli 2011	Not a trial/cohort study
Roongruangpitayakul 2013	Not a trial/cohort study
Rose 2012	Not a trial/cohort study
Schecter 2010	Not a trial/cohort study
Seddon 2012	No linezolid use
Shah 2011	Not a trial/cohort study
Singla 2012	Not a trial/cohort study
Slebos 2004	Not a trial/cohort study
Sokolova 2008	No linezolid use
Sotgiu 2015	Not a trial/cohort study
Stoltz 2017	Not a trial/cohort study
Tabarsi 2010	No linezolid use

(*Continued*)

Tang 2011	Not a trial/cohort study
Tang 2012	Not a trial/cohort study
Tangg 2011	Not a trial/cohort study
Tiberi 2016b	No linezolid use
Tortoli 2010	No linezolid use
Tse-Chang 2013	Not a trial/cohort study
Udwadia 2017	Not a trial/cohort study
Van der Walt 2013	No linezolid use
Van Heurck 2013	Not a trial/cohort study
Velasquez 2014	No linezolid use
von der Lippe 2006	Not a trial/cohort study
Ward 2005	No linezolid use
Wirth 2017	Not a trial/cohort study
Xu 2012a	Not a trial/cohort study
Xu 2012b	No linezolid use
Yao 2011	Not a trial/cohort study
Yew 2008	Not a trial/cohort study
Yew 2009	Not a trial/cohort study
Yew 2014	Not a trial/cohort study
Yi 2017	Not a trial/cohort study

AE: adverse effects

Characteristics of studies awaiting assessment *[ordered by study ID]*

Agarwal 2005

Methods	Comparative study; unclear if retrospective or prospective
Participants	81 patients with MDR-TB
Interventions	"Study group treated with linezolid, clarithromycin, capreomycin, pyrazinamide, ethambutol and ethionamide. Control group, treated with streptomycin, pyrazinamide, ethambutol and ethionamide. The course of treatment was 18 months. Linezolid was given for 6 months and aminoglycosides (capreomycin/streptomycin) for 10 weeks."
Outcomes	Sputum conversion (not stated if smear or culture), radiological improvement, closure of lung cavities, AEs
Notes	Only the abstract was available for assessment, which lacked key elements required for classification. When contacted for further data, there was no response from the study authors

Agarwal 2007

Methods	Comparative study; unclear if retrospective or prospective
Participants	92 patients aged 18-50 years with MDR-TB; "HIV negative, smear-positive, non-pregnant and had been receiving anti-TB drugs for an average of 76 weeks (32 to 132 weeks)."
Interventions	Study group treated with "linezolid, azithromycin along with kanamycin, pyrazinamide, ethionamide and ethambutol under direct supervision." Control group "were given kanamycin, pyrazinamide, ethionamide and ethambutol." "Linezolid was given in the dose of 600mg once a day for 6 months. Kanamycin was given in the dose of 25 mg/kg body weight on alternate days for 24 weeks. Pyrazinamide was given for full course of therapy."
Outcomes	Sputum conversion (not stated if smear or culture), radiological improvement, closure of lung cavities, AEs
Notes	Only the abstract was available for assessment, which lacked key elements required for classification. When contacted for further data, there was no response from the study authors

Anderson 2013

Methods	"Retrospective-prospective cohort study"
Participants	People with MDR-TB
Interventions	Individualized ATT; some of the cohort received linezolid
Outcomes	Treatment outcomes, and risk factors associated with these
Notes	8 of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. Contact with the corresponding author was not possible, despite multiple attempts

Arnold 2017

Methods	Retrospective cohort study
Participants	100 consecutive cases of MDR-TB
Interventions	Individualized ATT; some of the cohort received linezolid
Outcomes	Treatment outcomes; treatment modalities; hospital admission
Notes	35 of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. The study authors, when contacted, were unable to provide sufficient data to enable classification

Bionghi 2017

Methods	Retrospective cohort study
Participants	153 rifampicin-monoresistant-, MDR- and XDR-TB cases
Interventions	"24 patients were initiated on Bedaquiline and 129 on Bedaquiline and Linezolid containing regimens."
Outcomes	Treatment outcomes, sputum culture conversion
Notes	129/153 participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. When contacted for further data, there was no response from the study authors

Borisov 2017

Methods	Retrospective cohort study
Participants	"428 culture-confirmed MDR-TB cases"
Interventions	Individualized ATT: "Treatment regimens included, among others, linezolid, moxifloxacin, clofazimine and carbapenems (82.0%, 58.4%, 52.6% and 15.3% of cases, respectively)."
Outcomes	Sputum smear and culture conversion; treatment outcomes; AEs
Notes	82% of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. When contacted for further data, there was no response from the study authors

Catho 2015

Methods	Retrospective cohort study
Participants	"Twenty-three consecutive adult MDR TB patients"
Interventions	Individualized ATT; most received amikacin, a fluoroquinolone, para-aminosalicylic acid and linezolid

Catho 2015 (*Continued*)

Outcomes	Treatment outcomes; AEs
Notes	18 of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. When contacted for further data, there was no response from the study authors

Dey 2015

Methods	Retrospective cohort study
Participants	Children with drug-resistant tuberculosis
Interventions	ATT, but the abstract does not include much further detail on interventions
Outcomes	AEs
Notes	Only the abstract was available for assessment, which lacked key elements required for classification. The study author, when contacted, was unable to provide sufficient data to enable classification

Ganatra 2017

Methods	Retrospective cohort study
Participants	20 clinical profiles of 45 linezolid-resistant cases, of whom 14 "had prior exposure to linezolid"
Interventions	ATT, but the abstract does not include much further detail on interventions
Outcomes	Risk factors for resistance AEs
Notes	Only the abstract was available for assessment, which lacked key elements required for classification. When contacted for further data, there was no response from the study authors

Grard 2015

Methods	Retrospective cohort study
Participants	30 people with MDR-TB; 23 received linezolid
Interventions	Individualized ATT; most received a fluoroquinolone, amikacin or streptomycin, cycloserine or para-aminosalicylic acid
Outcomes	Time to sputum culture conversion; treatment outcomes; AEs; pharmacokinetic data
Notes	23 of the participants received linezolid, but outcomes were only reported for those receiving linezolid within the publication. When contacted for further data, there was no response from the study authors

Jeon 2009

Methods	Retrospective cohort study
Participants	176 people with XDR-TB
Interventions	Individualized ATT
Outcomes	Treatment outcomes, with composite ”favorable“ and ”unfavorable“ outcomes; mortality
Notes	7 of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. When contacted for further data, there was no response from the study authors

Kim 2007

Methods	Retrospective cohort study
Participants	211 people with MDR-TB (20% XDR)
Interventions	Individualized ATT; most received a fluoroquinolone, and injectable, para-aminosalicylic acid, cycloserine and prothionamide
Outcomes	Treatment outcomes; AEs
Notes	3 of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. When contacted for further data, there was no response from the study authors

Kim 2018

Methods	Retrospective cohort study
Participants	61 people with pulmonary MDR-TB
Interventions	All received delamanid and/or bedaquiline in a regimen with median 5 drugs; the following drugs were each present in > 50% of regimens: an injectable, a fluoroquinolone and linezolid
Outcomes	Treatment outcomes, AEs
Notes	33 of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. When contacted for further data, there was no response from the authors

Kuksa 2017

Methods	Retrospective cohort study
Participants	19 patients with MDR- or XDR-TB
Interventions	All received delamanid within a programmatic optimized background regimen

Kuksa 2017 (*Continued*)

Outcomes	Treatment outcomes
Notes	14 of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. When contacted for further data, there was no response from the study authors

Lee 2017

Methods	Retrospective cohort study
Participants	76 participants with rifabutin-sensitive MDR-TB
Interventions	Individualized ATT; most received a fluoroquinolone, an injectable and cycloserine
Outcomes	Treatment outcomes
Notes	17 of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. The study authors, when contacted, were unable to provide sufficient data to enable classification

Mehta 2016

Methods	Retrospective cohort study
Participants	136 people initiating drug-resistant tuberculosis treatment
Interventions	ATT, but the publication does not include much further detail on interventions
Outcomes	Optic neuropathy in those receiving linezolid
Notes	AE outcome data were limited to those concerning ocular symptoms and signs, and only reported for those participants receiving linezolid. The study authors, when contacted, were unable to provide sufficient data to enable classification

Meressa 2015

Methods	Prospective cohort study
Participants	"All patients with MDR-TB...Additionally, patients with rifampicin-monoresistance or those with clinically presumed MDR TB, based on multiple treatment failures despite directly observed therapy (DOT), or those who were close contacts of patients with MDR TB, were also eligible for treatment."
Interventions	ATT: "(1) at least three oral agents to which the patient was presumed to have susceptibility (eg, levofloxacin, ethionamide, cycloserine or para-aminosalicylic acid (PAS)), (2) pyrazinamide and (3) an aminoglycoside (amikacin or kanamycin) or polypeptide (capreomycin) injectable agent. Injectables were maintained for a minimum of 8 months based on clinical, microbiological and radiographic evolution, and ultimate treatment duration was a minimum of 18 months after bacteriological conversion."
Outcomes	Treatment outcomes; AEs

Meressa 2015 (*Continued*)

Notes	Some (< 6) of the participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. When contacted for further data, there was no response from the study authors

Pang 2017

Methods	Retrospective cohort study
Participants	29 people with "XDR-TB-Plus", i.e. XDR plus additional resistance
Interventions	Individualized ATT, average 4.4 drugs; > 50% received each of moxifloxacin, protionamide, clofazimine and pyrazinamide
Outcomes	Risk and treatment outcomes of XDR-TB-Plus
Notes	10 received linezolid, but outcomes were not reported in enough detail to include the study. When contacted for further data, there was no response from the study authors

Ramirez-Lapausa 2016

Methods	Retrospective cohort study
Participants	55 people aged > 17 years, with MDR- or XDR-TB, admitted to hospital
Interventions	Individualized ATT regimen of 4-6 drugs
Outcomes	Treatment outcomes; AEs
Notes	Comparative data were not reported for those receiving versus those not receiving linezolid. When contacted for further data, there was no response from the study authors

Soman 2014

Methods	Retrospective cohort study
Participants	52 consecutive patients with tuberculosis with drug resistance between MDR and XDR: "We defined MDR+ as resistance to rifampin (RMP), isoniazid (INH) and at least one more drug other than fluoroquinolone (FQ) and second-line injectable agent (IA); and Pre-XDR as MDR with additional resistance to either FQ or IA."
Interventions	"Treatment regimen was devised as per DST [drug susceptibility testing] and predominantly consisted of a second-line injectable agent (IA), para-aminosalicylic acid (PAS) and clofazimine. Additionally, cycloserine, linezolid, co-amoxiclav and clarithromycin were used to complete a regimen of four to five drugs."
Outcomes	Clinical and radiological improvement; AEs

Soman 2014 (*Continued*)

Notes	14 participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. When contacted for further data, there was no response from the study authors

Tornheim 2017

Methods	Prospective cohort study
Participants	286 people with MDR-TB
Interventions	Not reported in detail in available publication
Outcomes	Treatment outcomes, sputum culture conversion, adverse events
Notes	147 participants received linezolid, but outcomes were not reported comparatively for those who did and did not receive linezolid. The study authors, when contacted, were unable to provide sufficient data to enable classification

Udwadia 2014

Methods	Prospective cohort study
Participants	78 "consecutive patients having a microbiological diagnosis of MDR-TB"; 7% had XDR-TB; 50% had fluoroquinolone resistance. "Surgical resection of the infected lobe or lung was carried out in eight (10.2%) patients."
Interventions	Individualized ATT: "empirical drug regimen containing at least four drugs they had not previously received while awaiting their sensitivity report."
Outcomes	Treatment outcomes; AEs
Notes	18 participants received linezolid, but outcomes were not stratified by receipt of linezolid within the publication. The study authors, when contacted, were unable to provide sufficient data to enable classification

Abbreviations: ATT: antituberculous treatment; AE: adverse event; MDR: multi-drug resistant; TB: tuberculosis; XDR: extensively drug resistant

Characteristics of ongoing studies *[ordered by study ID]*

NCT02333799

Trial name or title	A phase 3 study assessing the safety and efficacy of bedaquiline plus pa-824 plus linezolid in subjects with drug resistant pulmonary tuberculosis
Methods	Intervention model: single group assignment Masking: none (open-label)

NCT02333799 (*Continued*)

Participants	Estimated recruitment: 200 Aged ≥ 14 years Culture-positive pulmonary tuberculosis: MDR-TB with failure of or intolerance to standard second-line treatment; or XDR-TB Includes HIV-infected individuals with CD4 cell count > 50 cells/microlitre
Interventions	Experimental arm (no control arm): bedaquiline + PA-824 (pretomanid) + linezolid
Outcomes	"Incidence of bacteriologic failure or relapse or clinical failure through follow-up until 24 months after the end of treatment."
Starting date	March 2015
Contact information	Joanna Moreira; Joanna.Moreira@tballiance.org Dan Everitt; Dan.Everitt@tballiance.org
Notes	Estimated completion: October 2021 Countries: South Africa Linezolid daily dose: 1200 mg

NCT02454205

Trial name or title	An open-label RCT to evaluate a new treatment regimen for patients with multi-drug resistant tuberculosis (NEXT)
Methods	Allocation: randomized Intervention model: parallel assignment Masking: none (open-label)
Participants	Estimated recruitment: 300 Aged ≥ 18 years "Newly-diagnosed culture and/or GeneXpert positive pulmonary TB", with rifampicin resistance Excluded if known to have fluoroquinolone, injectable, XDR or if on MDR-TB treatment for > 2 weeks; or if known to have rifampicin monoresistance Includes HIV-infected individuals
Interventions	Experimental arm: 6-9 months of oral linezolid; bedaquiline; levofloxacin; pyrazinamide; ethionamide or high-dose isoniazid or terizidone Control arm: 21-24 months total therapy; 6-8 month intensive phase of kanamycin; moxifloxacin; pyrazinamide; ethionamide and terizidone; continuation phase of moxifloxacin; pyrazinamide; ethionamide and terizidone
Outcomes	**Primary outcome:** treatment success 24 months after initiation of treatment **Secondary outcomes** • "Favourable outcome rate • Time specific rate of treatment failure • Time specific culture conversion proportions and rates • Time specific relapse rate

NCT02454205 (*Continued*)

	• Rate of re-infection • All-cause mortality • Composite measure of QT interval on ECG, grade 3 and 4 adverse events, stopping drugs (safety and tolerability end-points) • Default rate • Rate of loss of follow-up“
Starting date	October 2015
Contact information	Aliasgar Esmail; a.esmail@uct.ac.za Melissa Pascoe; mellissa.pascoe@uct.ac.za
Notes	Estimated completion: January 2019 Countries: South Africa Linezolid daily dose: 600 mg (reduced to 300 mg if toxicity occurs)

NCT02589782

Trial name or title	Pragmatic clinical trial for a more effective concise and less toxic MDR-TB treatment regimen(s) (TB-PRACTECAL)
Methods	Allocation: randomized Intervention model: parallel assignment Masking: none (open-label)
Participants	Estimated recruitment: 630 Aged ≥ 18 years Culture-confirmed tuberculosis with resistance to at least rifampicin; includes extrapulmonary tuberculosis, except meningoencephalitis, brain abscesses, osteomyelitis or arthritis Excluded if known resistance to or prior use of bedaquiline or pretomanid; or prior use of linezolid Includes HIV-infected individuals
Interventions	Experimental regimen 1: 24 weeks of bedaquiline, pretomanid, moxifloxacin and linezolid Experimental regimen 2: 24 weeks of bedaquiline, pretomanid, linezolid, and clofazimine Experimental regimen 3: 24 weeks of bedaquiline, pretomanid, and linezolid Control regimen: ”Locally accepted standard of care which is consistent with the WHO recommendations for the treatment of M/XDR-TB.“
Outcomes	**Primary** • Culture conversion at 8 weeks post-randomization • Treatment discontinuation or death at 8 weeks post-randomization, • Unfavourable outcome (failure, death, recurrence, loss to follow-up) at 72 weeks post-randomization. **Secondary outcomes** • ≥ grade 3 QT prolongation within 8 weeks post-randomization • Experiencing ≥ 1 serious or new ≥ grade 3 AE at 8, 72, and 108 weeks post-randomization • Culture conversion at 12 weeks post-randomization • Unfavourable outcome (i.e. failure, treatment discontinuation, death, loss to follow-up) at 24 and 108 weeks post-randomization, and at end of treatment

NCT02589782 (*Continued*)

	• Time to culture conversion • Change in corrected QT at 24 weeks post-randomization • Recurrence at week 48 post-randomization
Starting date	January 2017
Contact information	Kristen LeBeau; kristen.lebeau@london.msf.org
Notes	Estimated completion: June 2020 Countries: Belarus, South Africa, Uzbekistan Linezolid daily dose: "600mg for 16 weeks then 300mg (or 600mg x3/week) for the remaining 8 weeks or earlier when moderately tolerated."

NCT02619994

Trial name or title	Treatment shortening of MDR-TB using existing and new drugs (MDR-END)
Methods	Allocation: randomized Intervention model: parallel assignment Masking: none (open-label)
Participants	Estimated recruitment: 238 Aged 19 to 85 years Known rifampicin-resistant tuberculosis within 14 days of starting tuberculosis therapy; excludes people with fluoroquinolone-resistant MDR-TB and XDR-TB No information on testing for of recruitment of people with HIV infection
Interventions	Experimental arm: "Regimen consists of only oral medication using delamanid, linezolid, levofloxacin, and pyrazinamide, for nine or twelve months depending on the time of sputum culture conversion to negative." Control arm: "locally-used WHO-approved MDR-TB regimen in Korea"; at least 20 months; "Intensive phase regimen consists of four effective second-line anti-TB drugs (including injectables) and pyrazinamide. "
Outcomes	**Primary outcome:** treatment success rate 24 months after treatment start **Secondary outcomes** • Time to sputum culture conversion to negative • Sputum culture conversion proportion at 2 months of treatment • Sputum culture conversion proportion at 6 months of treatment • Number of participants with treatment-related AEs
Starting date	January 2016
Contact information	Jae-Joon Yim; yimjj@snu.ac.kr
Notes	Estimated completion: December 2019 Countries: Republic of Korea Linezolid daily dose: 600 mg for 2 months, then 300 mg until the end of treatment

NCT02754765

Trial name or title	Evaluating newly approved drugs for multidrug-resistant tuberculosis (endTB)
Methods	Allocation: randomized Intervention model: parallel assignment Masking: none (open-label)
Participants	Estimated recruitment: 750 **Inclusion criteria** • ≥ 15 years • Pulmonary tuberculosis with documented resistance to rifampicin and susceptibility to fluoroquinolones, determined by rapid molecular test. • Willing to use contraception, if pre-menopausal woman who has not had sterilization procedure. • "Lives in a dwelling that can be located by study staff and expects to remain in the area for the duration of the study." **Exclusion criteria** • Known allergies or hypersensitivity to any of the investigational drugs • Pregnant or unwilling/unable to stop breast-feeding an infant • Unable to comply with treatment or follow-up schedule • Any social or medical condition which, in the opinion of the site principal investigator, would make study participant unsafe • Has had exposure in the past 5 years, or resistance to, bedaquiline, delamanid, linezolid, or clofazimine; exposure to other anti-tuberculosis drugs is not a reason for exclusion • Has one or more of the following: • Abnormal blood test results as defined by the study investigators. • Has cardiac risk factors as defined by the study investigators. • Is currently taking part in another study of a medicinal product • Is taking any medication that is contraindicated with the medicines in the study regimen which cannot be stopped (with or without replacement) or requires a wash-out period > 2 weeks HIV status: not reported
Interventions	6 arms: 1. Intervention regimen 1: bedaquiline, moxifloxacin, linezolid and pyrazinamide 2. Intervention regimen 2: bedaquiline, clofazimine, levofloxacin, linezolid and pyrazinamide 3. Intervention regimen 3: bedaquiline, delamanid, levofloxacin, linezolid and pyrazinamide 4. Intervention regimen 4: delamanid, clofazimine, levofloxacin, linezolid and pyrazinamide 5. Intervention regimen 5: delamanid, clofazimine, moxifloxacin and pyrazinamide 6. Control regimen: standard of care according to local and WHO guidelines
Outcomes	**Primary outcome** • Efficacy at week 73 from randomization. • "Favorable" outcome defined as having negative cultures between week 65 and 73, or lack of positive cultures with most recent cultures negative and "bacteriological, radiological and clinical evolution is favorable." **Secondary outcomes** • Efficacy at week 104 (as for week 73) • Early (8-week) treatment response, i.e. culture conversion • Efficacy at week 39 (as for week 73) • Survival at week 73 • Survival at week 104

NCT02754765 (*Continued*)

	• Safety at week 73 (proportion of participants with ≥ grade 3 AEs and SAEs) • Safety at week 104 (as for week 73) • QTc interval prolongation of ≥ 60 ms from baseline or QTc interval of > 500 ms at week 73
Starting date	December 2016
Contact information	Celine Delifer; endtb.clinicaltrial@paris.msf.org
Notes	Estimated completion: April 2021 Countries: Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru, South Africa Linezolid daily dose: "600 mg QD [per day] for 4 months (followed by 300 mg QD or intermittent dose for 5 months)"

NCT03237182

Trial name or title	The individualized M(X) drug-resistant TB treatment strategy study (InDEX)
Methods	Allocation: randomized Intervention model: "Patients randomized to the intervention receive a individualized tuberculosis treatment based on whole genome sequencing and the patients randomized to the control receive the standard of care tuberculosis treatment" Masking: none (open-label)
Participants	Estimated recruitment: 300 ≥ 18 years Microbiological (molecular) confirmation of rifampicin-resistant, MDR- or XDR- pulmonary tuberculosis Includes HIV-infected individuals Excludes: • "Persons suffering from any serious acute condition." • "Any other chronic or clinically significant medical condition that in the opinion of the attending clinician would render the patient unsuitable for participation in the study."
Interventions	"Patients with drug resistance will have whole genome sequencing performed on the respective positive MGIT sample. An individualized TB treatment regimen will be provided to patients based on the whole genome sequencing results." Individuals in the control arm will have South African standard drug-resistant tuberculosis treatment regimen
Outcomes	**Primary outcome** Time to culture conversion from positive to negative; on 2 consecutive samples 30 days apart for MDR-TB and 3 consecutive samples 30 days apart each for people with XDR-TB **Secondary outcomes** • Tuberculosis treatment outcomes: treatment success, mortality, retention in care • AEs compared between each arm • Characterization of the strains: "The minimum inhibitory concentrations of Mtb isolates will be correlated with the genotypic mutations detected and the evolution of drug resistance will be monitored by comparing serial isolates from patients"
Starting date	June 2017

NCT03237182 (*Continued*)

Contact information	Natasha Gounden; natasha.gounden@caprisa.org Resha Boodhram; resha.boodhram@caprisa.org
Notes	Estimated completion: December 2021 Countries: South Africa Linezolid daily dose: not reported Other: linezolid is listed as a possible drug in both arms, but it is likely in the review authors' opinion that some will receive and others will not receive linezolid

Abbreviations: ATT: antituberculous treatment; AE: adverse event; ECT: electrocardiogram; MDR: multi-drug resistant; SAE: serious adverse event; TB: tuberculosis; WHO: World Health Organization; XDR: extensively drug resistant

ADDITIONAL TABLES

Table 1. Summary of characteristics of included studies

Study	Study design	Country	Recruitment dates	Age	Drug resistance	HIV status reported	Linezolid daily dose	Linezolid duration	Number of participants		
									Linezolid	No linezolid	Total
Lee 2012	RCT, no placebo, partial blinding	Republic of Korea	2008 to 2011	Adults > 20 years	All XDR	Yes, excluded	600 mg, then randomized to 300 mg or 600 mg	Median 781 days	19 immediate	20 delayed	39
Padayatchi 2012	RCT, placebo, blinding	South Africa	2009 to 2010	Adults > 18 years	All MDR	Yes, included, mostly on antiretrovirals	600 mg	112 days	16	18	34
Tang 2015	RCT, no placebo/ blinding	China	2009 to 2011	Adults 18 to 64 years	All XDR	Yes, excluded	1200 mg 4 to 6 weeks, then 300 to 600 mg	Until sputum culture negative	33	32	65

Table 1. Summary of characteristics of included studies (*Continued*)

Migliori 2009	Retrospective cohort	Belarus, Germany, Italy, Switzerland	2001 to 2007	Not reported	18/195 XDR, rest MDR	No	600 to 1200 mg	Median 93 days	85	110	195
Udwadia 2010	Prospective cohort	India	2000 to 2007	Adults > 18 years	7/18 XDR, rest MDR (linezolid group)	No	1200 mg	Mean 247 days	18	60	78
Jo 2014	Retrospective cohort	Republic of Korea	2006 to 2012	Adults >18 years	26/70 XDR, rest MDR; all ofloxacin-resistant	Yes, 9/70 tested - all negative	300 to 600 mg	Median 259 days	26	44	70
Seddon 2014	Retrospective cohort	South Africa	2009 to 2012	Children < 15 years	6/149 (2/3 receiving linezolid) XDR, 16/149 rifampicin-monoresistant, rest MDR	Yes, included, mostly on antiretrovirals	Unknown	Median 480 days	3	146	149
Zhang 2014	Retrospective cohort	China	2012 to 2013	Adults > 18 years	All XDR	Yes, all negative	600 mg	Unknown (”at least one month“)	15	28	43
Jeong 2015	Retrospective cohort	Republic of Korea	2005 to 2011	Adults > 18 years	All fluoroquinolone resistant MDR, or XDR	Yes, no HIV-positive participants	300 to 600 mg	Median 426 days	58	86	144

Table 1. Summary of characteristics of included studies (*Continued*)

Kwak 2015	Retrospective cohort	Republic of Korea	2006 to 2010	Not reported	26/123 XDR, rest MDR	No	Unknown	Unknown	12	111	123
Van Altena 2015	Retrospective cohort	Netherlands	2000 to 2009	Not reported	4/112 XDR, rest MDR	Yes, included	600 mg	Mean 99 days, median 56 days	53	51	104
Galli 2016	Retrospective cohort	Italy	2010 to 2012	Children < 18 years	1/11 XDR, rest MDR	No	Unknown	Unknown	5	6	11
Jensenius 2016	Retrospective cohort	Norway	1995 to 2014	All, range 2 to 57 years	6/89 XDR, rest MDR	Yes, included	"Usually" 1200 mg	Unknown	52	16	68
Tiberi 2016	Retrospective cohort	Belarus, Belgium, Brazil, Ecuador, Greece, Holland, Italy, Peru, Slovakia, UK	2003 to 2015	Adults > 15 years	XDR and MDR	Yes, included, mostly on antiretrovirals	300 to 1200 mg	Unknown	267	81	348
Guglielmetti 2017	Retrospective cohort	France	2011 to 2013	Not reported	24/45 XDR	Yes, included	600 mg	Unknown	43	2	45
Ferlazzo 2018	Retrospective cohort	Armenia, India, South Africa	2016	> 18 years and one 14-year old	14/28 XDR, rest MDR (10 fluoroquinolone resistant)	Yes, included	Unknown	Unknown	23	5	28

Table 1. Summary of characteristics of included studies (*Continued*)

Olayanju 2018	Prospective cohort	South Africa	2008 to 2017	Adults > 18 years	All XDR	Yes, included	Unknown	Unknown	55	217	272

Abbreviations: MDR: multi-drug resistant; RCT: randomized controlled trial; XDR: extensively drug resistant.

Table 2. Findings from the Lee 2012 randomized trial

Factor	Participants who received linezolid immediately	Participants who received delayed linezolid	Relative effect RR (95% CI)
Study characteristics	Korea, all XDR, HIV co-infection excluded, adults		-
Participants	19	20	-
Death	0/19	0/20	Unable to calculate
Sputum culture conversion at 4 months	15/19 (78.9%)	7/20 (35.0%)	2.26 (1.19 to 4.28)
Total adverse events	56[a]		N/A
Serious adverse events	37[a]		N/A
Linezolid discontinuation	7/39 (17.9%)		N/A

[a]Adverse events reported without disaggregation for linezolid receipt being immediate or delayed; total adverse events reported in Lee 2012 but not updated in 2015 article; serious adverse events updated in 2015 article (in 2012 article, 33 were reported)
Abbreviations: CI: confidence interval; N/A: not applicable; RR: risk ratio; XDR: extensively drug-resistant

Table 3. Findings from the Tang 2015 randomized trial

Factor	Participants who received linezolid	Participants who did not receive linezolid	Relative effect RR (95% CI)
Study characteristics	China, all XDR, HIV co-infection excluded, adults		
Participants	33	32	-
Death	2/33 (6.1%)	3/32 (9.4%)	0.65 (0.12 to 3.62)
Failure	4/33 (12.1%)	15/32 (46.9%)	0.26 (0.10 to 0.70)
Cure	17/33 (51.5%)	7/32 (21.9%)	2.36 (1.13 to 4.90)
Treatment completed	6/33 (18.2%)	4/32 (12.5%)	1.45 (0.45 to 4.68)

Table 3. Findings from the Tang 2015 randomized trial (*Continued*)

Treatment interruption ("default")	4/33 (12.1%)	3/32 (9.4%)	1.29 (0.31 to 5.33)
Sputum culture conversion at 24 months	26/33 (78.8%)	12/32 (37.6%)	2.10 (1.30 to 3.40)
Total adverse events	74	28	Unable to calculate
Serious adverse events	NR	NR	Unable to calculate
Linezolid discontinuation	2/33 (6.1%)	N/A	N/A

Abbreviations: CI: confidence interval; N/A: not applicable; NR: not reported; RR: risk ratio; XDR: extensively drug-resistant

Table 4. Sensitivity analysis for Tang 2015

Sensitivity analysis	Participants who received linezolid	Participants who did not receive linezolid	Relative effect RR (95% CI)
Death			
ITT analysis (as in review protocol)	2/33	3/32	0.65 (0.12 to 3.62)
Worst-case analysis	6/33	3/32	1.94 (0.53 to 7.10)
Best-case analysis	2/33	6/32	0.32 (0.07 to 1.48)
Cure			
ITT analysis (as in review protocol)	17/33	7/32	2.36 (1.13 to 4.90)
Worst-case analysis	17/33	10/32	1.65 (0.89 to 3.04)
Best-case analysis	21/33	7/32	2.91 (1.44 to 5.88)
Failure			
ITT analysis (as in review protocol)	4/33	15/32	0.26 (0.10 to 0.70)
Worst-case analysis	8/33	15/32	0.52 (0.26 to 1.05)
Best-case analysis	4/33	18/32	0.22 (0.08 to 0.57)

Abbreviations: CI: confidence interval; ITT: intention to treat; RR: risk ratio.

Table 5. Summary of findings in non-randomized studies

Baseline characteristics	Participants who received linezolid		Participants who did not receive linezolid	
Number of studies reporting outcomes	12		6	
Participants	639 participants, including 8 children		487 participants, including 160 children	
Proportion with XDR-TB[a]	440/1137 (38.7%)		343/628 (54.6%)	
Included participants with HIV	8/12		4/6	
Outcomes	**Number of events**	**Number of participants (studies)**	**Number of events**	**Number of participants (studies)**
Total adverse events	602	426 (8)	813	478 (5)
Serious adverse events	57	164 (7)	47	270 (5)
Linezolid discontinuation	141	624 (11)	N/A	N/A

[a]Where reported; not disaggregated for participants receiving linezolid
Abbreviation: XDR: extensively drug-resistant

Table 6. Adverse events outcomes data in non-randomized studies

Study	Total adverse events		Serious adverse events		Linezolid discontinuation	Linezolid-attributed adverse events			Our observations
	Linezolid	No linezolid	Linezolid	No linezolid		Total	Neuropathy	Bone marrow	
Migliori 2009	NR	NR	NR	NR	19/85	52/85	3/85	30/85	No comparative data
Udwadia 2010	NR	NR	NR	NR	NR	9/18	8/18	1/18	No comparative data
Jo 2014	20/26	NR	6/26	NR	8/26	22/26	16/26	2/26	No comparative data

Table 6. Adverse events outcomes data in non-randomized studies (*Continued*)

Seddon 2014	0/3	245/142	0/3	11/146	0/3	0/3	0/3	0/3	No RR/ P-value reported; small group received linezolid
Zhang 2014	11/15	NR	NR	NR	NR	11/15	1/15	4/15	No comparative data
Kwak 2015	8/12	36/111	8/12	32/111	2/12	3/12	2/12	0/12	No RR/ P-value reported; linezolid added if failing therapy, or XDR
Jeong 2015	-	-	-	-	-	-	-	-	Jeong 2015 reported no adverse event data other than linezolid dose reduction
Van Altena 2015	NR	NR	NR	NR	5/53	NR	NR	NR	No comparative data
Galli 2016	2/5	0/6	0/5	0/6	0/5	2/5	0/5	1/5	No RR/ P-value reported; small sample size
Jensenius 2016	NR	NR	23/52	NR	23/52	NR	NR	NR	No comparative data
Tiberi 2016	253/267	NR	NR	NR	61/267	97/267	47/267	50/267	No comparative data

Table 6. Adverse events outcomes data in non-randomized studies (*Continued*)

Guglielmetti 2017	127/43	7/2	8/43	0/2	5/43	31/43	22/43	9/43	No RR/P-value reported; small control group; post-hoc analysis
Ferlazzo 2018	NR	NR	12/23	4/5	0/23	NR	NR	NR	No RR/P-value reported; post-hoc analysis
Olayanju 2018	181/55	525/217	NR	NR	18/55	NR	12/55	11/55	No RR/P-value reported; post-hoc analysis

Abbreviations: NR: not reported; RR: risk ratio; XDR: extensively drug-resistant.

Table 7. Previous systematic reviews of linezolid for drug-resistant tuberculosis

Study	Unit of analysis	Risk of bias assessment	Type and number of included studies	Number of participants who received linezolid	Number of participants who did not receive linezolid	Studies in countries with high tuberculosisburden[a]	Efficacy outcomes assessed	Adverse events outcomes assessed	Main results	Authors' conclusions
Cox 2012	Study	Not performed	11 case series	148	0	1/11	Yes	Yes	Treatment success: 68% Adverse events incidence: 61% Linezolid discontinuation: 36%	"…Linezolid appears…a useful drug…with significant adverse events, and should be considered

Table 7. Previous systematic reviews of linezolid for drug-resistant tuberculosis (*Continued*)

										in the treatment of complicated DR-TB."
Sotgiu 2012	Study	Not performed	12 non-randomized studies	121	0	2/12	Yes	Yes	Treatment success: 82%. Adverse events incidence: 59%	"… excellent efficacy but also the necessity of caution in the prescription of linezolid."
Chang 2013c	Individual participant data	Not performed	20 non-randomized studies	162	32	3/12 (countries)	Yes	No	RR for favourable outcome with linezolid use vs without: 1.55 (95% CI 1.10 to 2.21)	"Our findings substantiated the use of linezolid in the treatment of XDR-TB or fluoroquinolone-resistant MDR-TB"
Zhang 2015	Study	Not performed	One RCT and 14 non-randomized studies	367	0	3/15	Yes	Yes	Treatment success: 83% (95% CI 75 to 90) Pooled mortality lower (P < 0.001) and nervous system adverse	"…Linezolid could be considered as a promising option as treatment of MDR/XDR TB."

Table 7. Previous systematic reviews of linezolid for drug-resistant tuberculosis (*Continued*)

									events higher (P < 0.01) if receiving < 600 mg/day	
Ahmad 2018	Individual participant data	Yes	50 non-randomized cohort studies and case series	1011	11019	22/50 (recruiting from ≥1 high-burden country)	Yes	No	For treatment success with linezolid use vs without: crude OR 1.5 (95% CI 1.2 to 1.9), adjusted OR 3.4 (2.6 to 4.5), adjusted RD 0.15 (0.11 to 0.18) For death with linezolid use vs without: crude OR 0.4 (95% CI 0.3 to 0.5), adjusted OR 0.3 (95% CI 0.2 to 0.3), adjusted RD −0.20 (95% CI −0.23 to −0.16)	"Although inferences are limited by the observational nature of these data, treatment outcomes were significantly better with use of linezolid…for treatment of multidrug-resistant tuberculosis."

Table 7. Previous systematic reviews of linezolid for drug-resistant tuberculosis (*Continued*)

									For people with XDR-TB, adjusted ORs (success 6.6 (95% CI 4.1 to 10.6), death 0.2 (95% CI 0.1 to 0.3)) and RDs (success 0.31 (95% CI 0.24 to 0.38), death −0.29 (95% CI −0.36 to −0.23)) remained significantly in favour of linezolid use	

Abbreviations: CI: confidence interval; DR: drug resistant; MDR: multi-drug resistant; N/A: not applicable; OR: odds ratio; RD: risk difference; RR: risk ratio; XDR: extensively drug-resistant.

[a] High-tuberculosis-burden countries as defined in WHO 2015b.

APPENDICES

Appendix 1. Search strategy

Search set	CIDG SR	CENTRAL	MEDLINE	Embase	LILACS
1	Tuberculosis OR TB	Tuberculosis OR TB ti, ab	Tuberculosis OR TB ti, ab	Tuberculosis OR TB ti, ab	Tuberculosis OR TB
2	Multi-drug resistant	drug resist* OR MDR OR DR OR XDR ti, ab	drug resist* OR MDR OR DR OR XDR ti, ab	drug resist* OR MDR OR DR OR XDR ti, ab	Multi-drug resistant
3	MDR-TB	1 and 2	1 and 2	1 and 2	MDR-TB
4	Drug-resistant	DR-TB OR MDR-TB OR XDR-TB ti, ab	DR-TB OR MDR-TB OR XDR-TB ti, ab	DR-TB OR MDR-TB OR XDR-TB ti, ab	Drug-resistant
5	XDR-TB	Tuberculosis, Multidrug-Resistant"[Mesh] OR "Extensively Drug-Resistant Tuberculosis"[Mesh]	Tuberculosis, Multidrug-Resistant"[Mesh] OR "Extensively Drug-Resistant Tuberculosis"[Mesh]	Multidrug resistant tuberculosis [Emtree] OR "extensively drug resistant tuberculosis" [Emtree] OR "drug resistant tuberculosis" [Emtree]	XDR-TB
6	2 or 3 or 4 or 5	3 or 4 or 5	3 or 4 or 5	3 or 4 or 5	2 or 3 or 4 or 5
7	1 and 6	"Oxazolidinones"[Mesh]	"Oxazolidinones"[Mesh]	Linezolid ti, ab OR "Linezolid" [Emtree]	1 and 6
8	linezolid	"linezolid" [Supplementary Concept]	"linezolid" [Supplementary Concept]	LZD OR Zyvox ti, ab	linezolid
9	7 and 8	Linezolid OR LZD OR Zyvox ti, ab	Linezolid OR LZD OR Zyvox ti, ab	"oxazolidinone derivative" [Emtree]	7 and 8
10	-	7 or 8 or 9	7 or 8 or 9	7 or 8 or 9	-
11	-	6 and 10	6 and 10	6 and 10	-
12	-	-	Limit 11 to Humans	Limit 11 to Human	-

CONTRIBUTIONS OF AUTHORS

BS and DC assessed the eligibility of the studies and extracted the data. BS, DC and HR assessed risk of bias of the included studies. BS drafted the text. DC, HR and DS gave input to the final draft. All review authors read and approved the final version of the review. BS is the guarantor of the review.

DECLARATIONS OF INTEREST

BS is a Clinical Research Fellow for the NIHR Global Health Research Group on Brain Infections at the University of Liverpool, and also works at the Royal Liverpool University Hospital, UK, and has no known conflicts of interest.

HR works at the Royal Liverpool University Hospital, UK, and has no known conflicts of interest.

DC is a PhD candidate supported by a Wellcome Trust Clinical Training Fellowship, based at the Liverpool School of Tropical Medicine, UK, and has no known conflicts of interest.

DS is a Senior Clinical Lecturer at the University of St Andrews, UK, and is a principal or co-investigator on projects funded through grants from the Cunningham Trust, the Wellcome Trust, MRC-Newton Fund, and EDCTP, and has no known conflicts of interest.

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Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Following peer review, we amended the Dealing with missing data and Assessment of reporting biases sections. We clarified that we would assume missing participants to have not experienced the outcome being assessed, and a minimum of 10 studies would be required for construction of a funnel plot, respectively.

Editorial review prompted consideration of performing a sensitivity analysis on the third primary outcome, failure. We included this, which is reflected in amendments within the relevant tables (Table 4 and Summary of findings for the main comparison), and sections of the text (Dealing with missing data, Sensitivity analysis, Effects of interventions, and Summary of main results).