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Optimal dosing and duration of linezolid for the treatment of multidrug-resistant and rifampicin-resistant tuberculosis: An individual patient data meta-analysis

Nakwon Kwak[1,*], Joong-Yub Kim[1,*,#], Areum Han[2,3], Catherine Berry[4], Maria Beumont[5], Tweed Conor[6], Angela Crook[6], Keertan Dheda[7,8], Stella Fabiane[6], Muse O Fadeyi[9], Salah Foraida[5], Tinne Gils[10,11], Thi Thanh Thuy Hoang[12], Menal A Jham[13], Richard A Murphy[14], Binh Hoa Nguyen[12], Thi Mai Phuong Nguyen[12], Bern-Thomas Nyang'wa[15,16], Suzette Oelofse[8], Seokyung Hahn[17,18,19], Jae-Joon Yim[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

[2]Interdisciplinary Program of Medical Informatics, Seoul National University College of Medicine, Seoul, Republic of Korea

[3]Integrated Major in Innovative Medical Science, Seoul National University College of Medicine, Seoul, Republic of Korea

[4]Médecins Sans Frontières, London, United Kingdom

[5]TB Alliance, New York, USA

[6]MRC Clinical Trials Unit, University College London, London, United Kingdom

[7]Department of Immunology and Infection, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

[8]Centre for Lung Infection and Immunity, University of Cape Town, Cape Town, South Africa

[9]Damien Foundation Belgium (Nigeria Project), Ibadan, Nigeria

[10]Unit of HIV and Coinfections, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

[11]Global Health Institute, University of Antwerp, Wilrijk, Belgium

[12]National Lung Hospital, Hanoi, Vietnam

[13]UMMA Community Clinic, Los Angeles, USA

[14]Division of Infectious Diseases, Dartmouth Geisel School of Medicine, Hanover, USA

[15]Médecins Sans Frontières, Amsterdam, the Netherlands

[16]Clinical Research Department, London School of Hygiene and Tropical Medicine, London, United Kingdom

[17]Medical Bigdata Research Center, Medical Research Center, Seoul National University, Seoul, Republic of Korea

[18]Institute of Health Policy and Management, Medical Research Center, Seoul National University, South Korea

[19]Department of Human Systems Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

[*]These authors contributed equally

[#]Current address: Department of Microbiology, Harvard Medical School, Boston, USA

Corresponding Author:

Jae-Joon Yim, MD, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-Ro, Jongno-Gu, Seoul, 03080, Republic of Korea. Tel: +82-2-2072-2059, Fax: +82-762-9662, E-mail: yimjj@snu.ac.kr

ABSTRACT

Background: The optimal dosing strategy of linezolid for treating multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) remains unclear. We conducted an individual patient data (IPD) meta-analysis to determine the optimal linezolid dosing strategy.

Methods: We searched PubMed, Embase, and Scopus for randomised controlled trials (RCTs) and prospective cohort studies on short-course, all-oral regimens containing linezolid for treating MDR/RR-TB through 31 August 2023. Patients were grouped according to linezolid dosing patterns. Time to treatment success and adverse events ≥ grade 3 were analysed using the Fine–Gray sub-distribution hazard model.

Results: Of 12 eligible studies, 8 (4 RCTs, 4 prospective) were included. Overall, 945 patients were grouped as follows: group 1 (600 mg linezolid for 8 weeks), group 2 (600 mg for 16 weeks, then 300 mg for 8 weeks), group 3 (600 mg for 39 weeks), and group 4 (1,200 mg for 25 weeks). Proportions of patients achieving treatment success were 59·1%, 90·4%, 91·3%, and 96·0%, respectively. Compared with group 2, groups 1 (adjusted sub-distribution hazard ratio [aSHR], 0·24, 95% confidence interval [CI], 0·08–0·71) and 3 (aSHR, 0·36, 95% CI, 0·16–0·81) had lower success rates. While group 4 showed no significant difference in treatment success versus group 2 (aSHR, 0·57, 95% CI, 0·23–1·43), it had a higher rate of adverse events ≥ grade 3 (aSHR, 2·29, 95% CI, 1·37–3·83).

Conclusion: A dosing strategy of 600 mg linezolid daily for 16 weeks, then 300 mg for 8 weeks, could be optimal for treating MDR/RR-TB when considering effectiveness and safety.

INTRODUCTION

Multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) is a global health threat. In 2023, there were an estimated 400,000 cases of MDR/RR-TB and 150,000 deaths worldwide (1). MDR/RR-TB had conventionally been treated with regimens including injectable drugs for at least 18–24 months because of the limited availability of potent agents (2). However, MDR/RR-TB treatment has been revolutionised over the last decade by new drugs, such as bedaquiline, delamanid, and pretomanid, as well as repurposed drugs, including linezolid and fluoroquinolones, allowing short-course oral regimens without the use of injectable drugs (3-6).

Linezolid, an oxazolidinone derivative that inhibits protein synthesis, has significantly improved treatment outcomes and reduced mortality in MDR/RR-TB patients (7). Although it has become a cornerstone of shorter, fully oral regimens, its use is frequently associated with clinically important adverse events, including optic or peripheral neuropathy and myelosuppression. The reported proportions of patients experiencing peripheral neuropathy and myelosuppression during MDR/RR-TB treatment with linezolid-containing regimens range from 36·1% to 47·1% and from 28·5% to 38·1%, respectively (8, 9). These adverse events, correlated with higher trough linezolid concentrations, lead to frequent interruption, discontinuation, and dose reduction of linezolid (10). Adverse events may necessitate a dose reduction from 600 mg to 300 mg in up to 70% of patients and drug discontinuation in approximately 34% (11).

Given these findings, it is imperative to determine the optimal dosage and duration of linezolid administration to improve treatment outcomes while minimising adverse events. In this study, we ~~aimed to~~ assessed the impact of linezolid dose and duration on outcomes and adverse events

during treatment for MDR/RR-TB using individual patient data (IPD) from randomised controlled trials (RCTs) and prospective cohort studies. Based on these analyses, we aimed to propose an optimal linezolid dosing strategy that maximises the probability of treatment success while minimising adverse events.

METHODS

Study Design and Methods

This IPD meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) of the IPD statement (12). It was conducted after exemption from the need for ethical approval by the Institutional Review Board of Seoul National University Hospital (No. 2308-038-1457). The study protocol was registered in the PROSPERO database (Identifier: CRD42023451843).

Search Strategy and Selection Criteria

We performed a review of the literature about trials on the use of short-course, all-oral regimens containing linezolid to treat MDR/RR-TB across the PubMed, Embase, and Scopus databases. The search query was "[(tuberculosis) AND (linezolid)] AND [(trial) OR (prospective)]" in all fields, with no language restrictions. Two independent investigators (NK and JYK) screened titles and abstracts for eligible studies, defined as RCTs and prospective cohort studies reporting the outcomes of short-course, all-oral regimens containing linezolid for the treatment of MDR/RR-TB or extensively drug-resistant TB (13), published up to 31 August 2023. Papers reporting on drug-susceptible TB, regimens involving injectable drugs, regimens longer than 12 months (14), and regimens without linezolid, as well as those describing preclinical and retrospective studies, were excluded. Conference papers, book chapters, reviews, editorials, guidelines, case reports, and studies focused exclusively on paediatric or pregnant populations were also excluded. At the individual participant level, those with missing outcomes, later addition of linezolid after starting initial treatment, unknown dosage or duration of linezolid, and extrapulmonary TB were excluded.

Data Collection and Quality Assessment

We contacted the authors of reports on eligible studies or those with ownership of the data and asked them to participate in this study. If no response was obtained, two additional attempts were made to contact them. If agreement was obtained, anonymised data with the following variables were collected: age, sex, nationality body mass index (BMI), human immunodeficiency virus (HIV) status, acid-fast bacilli (AFB) smear and culture results, presence of cavities, *in vitro* drug susceptibility, site of TB infection, comorbidities including diabetes mellitus, laboratory results, initial linezolid dose, companion drugs used, timing of linezolid adjustment(s) and subsequent dose, treatment duration, treatment outcomes, and adverse events. For adverse events, we focused on grade 3 or higher events commonly associated with linezolid, including optic or peripheral neuropathy and myelosuppression, as assessed by clinicians in each study (15-18). In general, grade 3 refers to severe events that result in hospitalisation or significant impairment of social and functional activities, while grade 4 indicates potentially life-threatening events (15-18). In cases in which data were insufficient or further clarification was required, we communicated with the lead authors or those with ownership of the data. The data from all of the included studies were merged and transformed into a common dataset. The risk of bias in individual studies was assessed using the Cochrane risk-of-bias tool (RoB 2) for RCTs (19) and ROBINS-I for prospective cohort studies (20).

Treatment Outcomes, Grouping, and Statistical Analysis

We adhered to the revised WHO definitions for treatment outcomes (21). Treatment success was determined by summing the cases classified as cured and those that completed treatment. We employed a competing risk analysis method that accounts for patients no longer at risk of

experiencing the primary event (22). Treatment failure and death during treatment were considered competing events that precluded the occurrence of the primary event, namely, treatment success. Patients who were lost to follow-up or who were otherwise unsuccessful were censored. For analysis of the risk of adverse events, death before the occurrence of such events was considered a competing event.

Patients were grouped by clustering using the Partitioning Around Medoids algorithm (23) based on their linezolid usage patterns, incorporating days of use and cumulative dose. The optimal number of clusters was determined using the elbow method (24). Demographic and clinical characteristics, companion drugs, treatment duration, outcomes, and adverse events were summarised as proportions for categorical variables and as medians interquartile ranges for continuous variables. Differences in the proportion and distribution of variables across cluster groups were assessed using ANOVA, the Kruskal–Wallis test, Pearson's chi-square test, or Fisher's exact test, as appropriate.

The sub-distribution hazard ratio (SHR) of the event of interest for each group, which reflects the relative instantaneous rate (probability per unit time) of the event of interest given that the event has not occurred before (25), was estimated using the Fine–Gray sub-distribution hazard model, accounting for the presence of competing risks. The reference group was set by the authors' consensus as the one that best reflects the actual linezolid usage pattern in clinical practice (11, 26, 27). We also accounted for the clustering effect per study in the pooled analysis of random effects and the robust variance (28). In the multivariable model, we adjusted for age, sex, BMI, presence of cavities, and AFB smear positivity. Covariates for which more than 10% of the values were missing were not included in the analysis because of the possibility of bias (29). A two-tailed significance of $P < 0{\cdot}05$ was considered statistically significant. All analyses

were conducted using R software (version 4·4·0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We identified a total of 5,353 records using the predefined keywords. Of these, 1,631 articles were assessed for eligibility, and 12 met the inclusion criteria. The PRISMA IPD flow diagram is depicted in Figure 1. We contacted the corresponding authors of the papers on these studies or those with ownership of the data. Of the 12 studies, anonymised data were provided from 8 studies [4 RCTs (3, 5, 6, 30, 31) and 4 prospective cohort studies (4, 32-34)]. The risk of bias in these studies is provided in Supplementary Figure 1, and all studies had a low risk of bias. In these 8 studies, 965 patients were treated with a short-course all-oral regimen that included linezolid. After excluding 20 patients (11 because of missing outcomes, 6 because linezolid was added to the regimen at a later stage, 2 with unknown linezolid dosage and duration, and 1 with extrapulmonary TB), 945 patients were included in the final analysis. The clinical characteristics of these patients and the design of each study are summarised in Supplementary Table 1.

Based on the clinical contexts and the within-cluster sum of squares (Supplementary Figure 2), the linezolid usage patterns were classified into four groups. The partitioning results are provided in Supplementary Figure 3 as a scatter plot. Group 1 (215 patients) included those who were treated with 600 mg of linezolid daily for 8 weeks. In group 2 (447 patients), patients received 600 mg of linezolid for 16 weeks, followed by 300 mg of linezolid for 8 weeks. In group 3 (183 patients), 600 mg of linezolid was maintained for a median of 39 weeks. Group 4 (100 patients) included those who received 1,200 mg of linezolid for 25 weeks (Table 1). The allocation of patients into groups for each study is presented in Supplementary Table 2.

The median age of the 945 patients was 35 years [interquartile range (IQR), 29–45], with a predominance of males (592 patients, 62.7%). The prevalence rates of HIV infection, the

presence of cavities, and resistance to fluoroquinolones were higher in groups 1 and 4 than in the other two groups (Table 2).

Overall, 873 patients (92·4%) received bedaquiline, most frequently in groups 3 and 4 (100%). Delamanid was used by 92 patients (9·7%), mainly in group 2 (13·4%). Pretomanid was administered to 650 patients (68.8%), with the highest usage in groups 2 (84·7%) and 4 (100%). Fluoroquinolones and clofazimine were used by 412 (43·6%) and 290 (30·7%) patients, respectively, most commonly in group 3 (Table 3).

Among the 945 patients, 794 (84.0%) achieved treatment success. The proportion of such success was lowest in group 1 (59·1%) but exceeded 90% in groups 2–4. Group 1 also had the highest proportions of treatment failure, death, and loss to follow-up. Of the 215 patients in group 1, 34 (15·8%) experienced treatment failure, while only 13 patients across groups 2–4 did so (Table 4).

The impact of each variable on treatment success is presented in Table 5. In the adjusted analysis, age (years; adjusted sub-distribution hazard ratio [aSHR], 0·98; 95% confidence interval [CI], 0·97–0·99) was negatively associated with treatment success, whereas BMI (aSHR, 1·03, 95% CI, 1·01–1·06) was positively associated with it. However, neither the presence of cavities nor a positive AFB smear at enrolment was significantly associated with treatment success.

The relative treatment success rate varied according to linezolid dosing. Compared with group 2 (the reference group), group 1 (adjusted SHR, 0·24; 95% CI, 0·08–0·71) and group 3 (aSHR, 0·36; 95% CI, 0·16–0·81) exhibited significantly lower rates of treatment success. In contrast, the rate of treatment success in group 4 (aSHR, 0·57; 95% CI, 0·23–1·43) did not significantly differ from that in group 2. The cumulative incidence function plot for treatment success is provided in Figure 2.

During the treatment period, 235 patients (24·9%) experienced adverse events of grade 3 or higher. This proportion was highest in group 4 (43·0%) and lowest in group 3 (13·7%). Peripheral neuropathy occurred most frequently in group 4 (15·0%), and myelosuppression developed most frequently in group 1 (9·8%), followed by group 2 (4·7%). A total of 11 of the 21 patients who experienced myelosuppression in group 1 discontinued linezolid earlier than scheduled. Optic neuropathy was reported in only 2 patients, both of whom were in group 4, in which the highest daily dose of linezolid (1,200 mg) was used (Table 6). Compared with group 2, group 1 had a higher rate of adverse events (aSHR, 1·84; 95% CI, 0·75–4·50), while group 3 showed a lower rate (aSHR, 0·55; 95% CI, 0·18–1·67), although these differences did not reach statistical significance. Group 4, however, had a significantly higher rate of adverse events than group 2 (aSHR, 2·29; 95% CI, 1·37–3·83; Table 7).

DISCUSSION

We conducted an IPD meta-analysis using data from patients who underwent short-course, linezolid-containing oral treatment for MDR/RR-TB to determine the optimal dose and duration of linezolid treatment. Our analyses revealed that a dose-tapering strategy, starting with linezolid at 600 mg daily (for 16 weeks) followed by a reduction to 300 mg daily (for 8 weeks), was potentially the most optimal in terms of effectiveness and safety.

Although linezolid is one of the pivotal drugs for short-course all-oral regimens, its dosage and duration of use varied considerably, even in the clinical trials (3, 4, 6, 30, 31). In our study, a considerable proportion of patients experienced dose reductions, temporary interruptions, or discontinuation of linezolid earlier than scheduled. To account for this variability, we categorised linezolid usage patterns based on the actual dose and duration administered at the individual patient level rather than adhering to the original intent of the protocol. For example, among 109 patients in the Nix-TB study who were scheduled to receive linezolid at 1,200 mg for 26 weeks, 30 were allocated to group 2 and 11 to group 1. This allocation was influenced not only by the original intent of the study but also by adverse events, death, and the patient's response to treatment. For instance, group 1 included patients who were originally intended to receive linezolid for only 8 weeks, as well as those who discontinued linezolid prematurely due to serious adverse events or death. Censoring patients whose linezolid schedules were altered due to treatment failure or death could introduce bias and overestimate the effectiveness of short-term linezolid treatment on treatment success (25). To address this issue, we employed the Fine–Gray sub-distribution hazard model, which accounts for competing events—such as treatment failure or death—that preclude the achievement of treatment success (25).

The proportion of treatment success was comparable between groups 2 and 3. However, when evaluating the probability of treatment success over time using the SHR, group 2 demonstrated

more favourable outcomes than group 3 after adjusting for age, sex, BMI, presence of cavities, and AFB smear positivity. The higher rate of treatment success in group 2 can be explained by two factors. First, the shorter treatment duration in group 2 may have contributed to its higher success rate compared to group 3. Shortening the treatment duration has been shown to improve treatment outcomes in MDR/RR-TB patients by reducing loss to follow-up (35). Second, the relatively higher number of competing events in group 3 likely mitigated the overestimation of its impact on treatment success, as illustrated in Figure 2. This adjustment revealed a clearer distinction between the outcomes of group 2 and group 3.

The high effectiveness of the tapering regimen in group 2 can be explained through a two-stage approach. Initially, a front-loaded 600 mg dose of linezolid enhances bactericidal activity during the early stages of treatment (36, 37). Subsequently, reducing the dose to 300 mg maintains the sterilising effect while minimising the risk of adverse events (38). In the hollow fibre model, a 300 mg dose of linezolid alone was sufficient to achieve a sterilising effect in approximately 90% of the population (38). Our study highlights that a two-stage approach, which balances bactericidal activity, sterilising efficacy, and adverse events, is an effective strategy in clinical settings. This finding is further supported by a recent clinical trial conducted in India, which demonstrated higher treatment success with a dose-tapering strategy of linezolid beginning at 600 mg/day and tapering to 300 mg/day (26).

In this study, adjustments for the effects of companion drugs were not performed because the timing and duration of companion drug use varied widely among patients. Because we focused on the dosing and duration of linezolid administration over time, adjusting for the timing and duration of companion drug administration would have complicated the determination of optimal linezolid dosing and duration. To mitigate these limitations, at the trial level, we adjusted for the effects of individual studies to average the influence of diverse

regimens. At the individual patient level, we also adjusted for age, sex, BMI, and disease severity.

Grade 3 or higher adverse events were more frequent in the group receiving 1,200 mg/day of linezolid. This finding aligns with the characteristics of peripheral neuropathy, a common adverse effect in groups with higher cumulative doses (39). In contrast, myelosuppression was more prevalent in group 1. Unlike peripheral neuropathy, which typically occurs between 3 and 6 months after treatment initiation (40), myelosuppression is known to occur earlier in the treatment course (40). This suggest that some patients in group 1 may have discontinued linezolid earlier than scheduled due to the rapid onset of myelosuppression. Indeed, of the 21 patients in group 1 who experienced myelosuppression, 11 discontinued linezolid immediately after its onset, although it remains unclear whether myelosuppression directly caused the discontinuation.

This study has several limitations. Owing to the lack of availability of such data from most studies, we could not incorporate the minimal inhibitory concentration of linezolid against clinical isolates or patients' pharmacokinetic data, despite these variables potentially impacting treatment outcomes. Second, we were unable to confirm whether tapering linezolid at another timepoint, rather than at 16 weeks, would still yield comparable effects to maintaining the 600 mg dose (26). Third, the unavailability of four studies and the uneven distribution of patients from studies across our groups may have introduced unintended bias. Fourth, no adjustments were made for the use of companion drugs, and factors such as drug resistance pattern, alcohol abuse, diabetes, or HIV infection were not adjusted for due to the high proportion of missing data.

Despite these limitations, this study obtained robust findings by collecting individual patient-level data from RCTs and prospective studies with clearly defined treatment protocols. It

expands on previous IPD meta-analyses (39) by including a larger cohort of patients with diverse background regimens, thereby not only examining adverse events but also proposing an optimal dose and duration for optimal treatment outcomes. The inclusion of nearly 1,000 patients across diverse geographic settings support the generalisability of our findings.

In conclusion, given the high treatment success rate and acceptable risk of adverse events, we propose a dose-tapering strategy for linezolid involving 600 mg daily for the first 16 weeks followed by 300 mg daily for the next 8 weeks as potentially ~~an optimal use~~ optimal approach for the use of linezolid in a short-course, all-oral regimen.

Table 1. Clustering of linezolid use patterns by days of linezolid use and cumulative dose

	Total (N = 945)	Group 1 (N = 215)	Group 2 (N = 447)	Group 3 (N = 183)	Group 4 (N = 100)	P-value*
Total treatment duration, days, median (IQR)	181 (167–236)	181 (108–270)	167 (167–175)	272 (184–281)	181 (181–186)	< 0.001
Duration of linezolid use, days, median (IQR)						
Total	166 (126–181)	63 (57–63)	166 (166–167)	272 (182–276)	181 (148–181)	< 0.001
1,200 mg/day	0	0 (0–18)	0	0	178 (116–181)	< 0.001
600 mg/day	111 (55–112)	57 (7–63)	111 (109–111)	272 (181–276)	0 (0–9)	< 0.001
300 mg/day	0 (0–55)	0	55 (55–56)	0	0	< 0.001
Cumulative dose of linezolid, mg, median (IQR)	83,100 (75,600–127,200)	37,800 (36,000–63,000)	83,100 (83,100–83,700)	163,200 (111,000–166,200)	181,000 (161,700–200,100)	< 0.001

IQR, interquartile range

* The P-value indicates the overall difference among the four groups.

Table 2. Demographic and clinical characteristics of the patients

	Total (N = 945)	Group 1 (N = 215)	Group 2 (N = 447)	Group 3 (N = 183)	Group 4 (N = 100)	P-value*
Age, years, median (IQR)	35 (29–45)	35 (29–43)	36 (28–46)	38 (30–50)	35 (29–44)	0.108
Male sex, N (%)	592 (62.7)	141 (65.6)	268 (60.0)	124 (67.8)	59 (59.0)	0.188
Weight, kg, median (IQR)	57 (50–66)	57 (51–66)	57 (50–66)	55 (50–64)	61 (51–67)	0.465
BMI, kg/m^2, median (IQR)	19.7 (17.9–22.4)	20.0 (17.9–22.8)	19.8 (18.0–22.3)	19.1 (17.7–21.6)	20.3 (17.9–23.2)	0.085
HIV-positive, N (%)	218/741 (29.4)	54/122 (44.3)	114/435 (26.2)	19/121 (15.7)	31/63 (49.2)	< 0.001
Diabetes, N (%)	45/769 (5.9)	8/154 (5.2)	29/445 (6.5)	1/70 (1.4)	7/100 (7.0)	0.349
Acid-fast bacilli smear positivity, N (%)	524/900 (58.2)	114/211 (54.0)	266/437 (60.9)	96/179 (53.6)	48/73 (65.8)	0.111
Presence of cavity on chest radiography, N (%)	579/929 (62.3)	135/209 (64.6)	269/444 (60.6)	99/176 (56.3)	76/100 (76.0)	0.007
Resistance to fluoroquinolone, N (%)	256/788 (32.5)	99/169 (58.6)	82/379 (21.6)	37/169 (21.9)	38/71 (53.5)	< 0.001

BMI, body mass index; IQR, interquartile range

* The P-value indicates the overall difference among the four groups.

Table 3. Antituberculous drugs used among the patients

	Total (N = 945)	Group 1 (N = 215)	Group 2 (N = 447)	Group 3 (N = 183)	Group 4 (N = 100)	P-value*
Bedaquiline	873 (92.4)	203 (94.4)	387 (86.6)	183 (100.0)	100 (100.0)	< 0.001
Delamanid	92 (9.7)	18 (8.4)	60 (13.4)	14 (7.7)	0	< 0.001
Pretomanid	650 (68.8)	130 (60.5)	374 (84.7)	46 (25.1)	100 (100.0)	< 0.001
Later-generation fluoroquinolone	412 (43.6)	89 (41.4)	200 (44.7)	123 (67.2)	0	< 0.001
Levofloxacin	275 (29.1)	79 (36.7)	73 (16.3)	123 (67.2)	0	< 0.001
Moxifloxacin	137 (14.5)	10 (4.7)	127 (28.4)	0	0	< 0.001
Clofazimine	290 (30.7)	70 (32.6)	107 (23.9)	113 (61.8)	0	< 0.001
High-dose isoniazid	84 (8.9)	60 (27.9)	6 (1.3)	18 (9.8)	0	< 0.001

* The P-value indicates the overall difference among the four groups.

Table 4. Treatment outcomes according to group

N (%, 95% confidence interval)	Total (N = 945)	Group 1 (N = 215)	Group 2 (N = 447)	Group 3 (N = 183)	Group 4 (N = 100)	P-value*
Cured or treatment completed	794 (84.0, 81.7–86.4)	127 (59.1, 52.5–65.6)	404 (90.4, 87.6–93.1)	167 (91.3, 87.2–95.3)	96 (96.0, 92.2–99.8)	
Treatment failed	47 (5.0, 3.6–6.4)	34 (15.8, 10.9–20.7)	5 (1.1, 0.1–2.1)	6 (3.3, 0.7–5.9)	2 (2.0, 0–4.7)	
Died	21 (2.2, 1.3–3.2)	17 (7.9, 4.3–11.5)	1 (0.2, 0–0.7)	3 (1.6, 0–3.5)	0	< 0.001
Lost to follow-up	26 (2.8, 1.7–3.8)	15 (7.0, 3.6–10.4)	6 (1.3, 0.3–2.4)	5 (2.7, 0.4–5.1)	0	
Unevaluated or unassigned outcome	57 (6.0, 4.5–7.5)	22 (10.2, 6.2–14.3)	31 (7.0, 4.6–9.3)	2 (1.1, 0–2.6)	2 (2.0, 0–4.7)	

* The P-value indicates the overall difference among the four groups.

Table 5. Sub-distribution hazard ratios (SHRs) for treatment success

	Crude SHR (95% CI)	Adjusted SHR (95% CI)
Age, years	0.99 (0.98–0.10)	0.98 (0.97–0.99)
Sex, male	0.86 (0.82–0.90)	0.89 (0.79–1.01)
BMI, kg/m^2	1.03 (1.00–1.06)	1.03 (1.01–1.06)
Cavity	1.03 (0.86–1.24)	1.08 (0.98–1.19)
Acid-fast bacilli smear positivity	1.06 (0.90–1.25)	1.14 (0.92–1.42)
Linezolid use pattern		
Group 1	0.28 (0.08–0.96)	0.24 (0.08–0.71)
Group 2	Reference	Reference
Group 3	0.36 (0.13–0.96)	0.36 (0.16–0.81)
Group 4	0.70 (0.22–2.20)	0.57 (0.23–1.43)

BMI, body mass index; CI, confidence interval; SHR, sub-distribution hazard ratio

Table 6. Adverse events of grade 3 or higher by group

N (%, 95% CI)	Total (N = 945)	Group 1 (N = 215)	Group 2 (N = 447)	Group 3 (N = 183)	Group 4 (N = 100)	P-value*
Total	235 (24.9, 22.1–27.6)	66 (30.7, 24.5–36.9)	101 (22.6, 18.7–26.5)	25 (13.7, 8.7–18.6)	43 (43.0, 33.3–52.7)	< 0.001
Peripheral neuropathy	33 (3.5, 2.3–4.7)	4 (1.9, 0.1–3.7)	8 (1.8, 0.5–3.0)	6 (3.3, 0.7–5.9)	15 (15.0, 8.0–22.0)	< 0.001
Myelosuppression	47 (5.0, 3.6–6.4)	21 (9.8, 5.8–13.7)	21 (4.7, 2.7–6.7)	2 (1.1, 0–2.6)	3 (3.0, 0–6.3)	< 0.001
Optic neuropathy	2 (2.1, 0–0.5)	0	0	0	2 (2.0, 0–4.7)	0.011

CI, confidence interval

* The P-value indicates the overall difference among the four groups.

Table 7. Sub-distribution hazard ratios for adverse events of grade 3 or higher

	Crude SHR (95% CI)	Adjusted SHR (95% CI)
Age, years	1.01 (0.99–1.03)	1.02 (1.00–1.04)
Sex, male	0.87 (0.73–1.04)	0.84 (0.73–0.97)
BMI, kg/m^2	1.00 (0.97–1.03)	0.96 (0.94–0.99)
Cavity	0.91 (0.51–1.63)	0.69 (0.49–0.98)
Acid-fast bacilli smear positivity	0.82 (0.53–1.28)	0.91 (0.57–1.45)
Linezolid use pattern		
Group 1	1.60 (0.61–4.21)	1.84 (0.75–4.50)
Group 2	Reference	Reference
Group 3	0.51 (0.16–1.65)	0.55 (0.18–1.67)
Group 4	2.48 (1.28–4.82)	2.29 (1.37–3.83)

BMI, body mass index; CI, confidence interval; SHR, sub-distribution hazard ratio

Figure legends

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) individual patient data (IPD) flow diagram

Figure 2. Cumulative incidence function plot for treatment success

Supplementary Figure 1. Risk of bias for the included studies

Supplementary Figure 2. Within-cluster sum of squares according to the number of clusters

Supplementary Figure 3. Scatter plot of data points coloured by each cluster based on the Partitioning Around Medoids algorithm

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None

Conflict of interests

R. A. M. received payment for expert testimony in a medical malpractice case that involved an infected prosthesis. R. A. M received support for speaking at the Pacific AIDS Education and Training Center-Nevada HIV conference in November, 2024, hosted by the University of Nevada. These do not relate to this manuscript in any way. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest to the Journal.

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Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) individual patient data (IPD) flow diagram

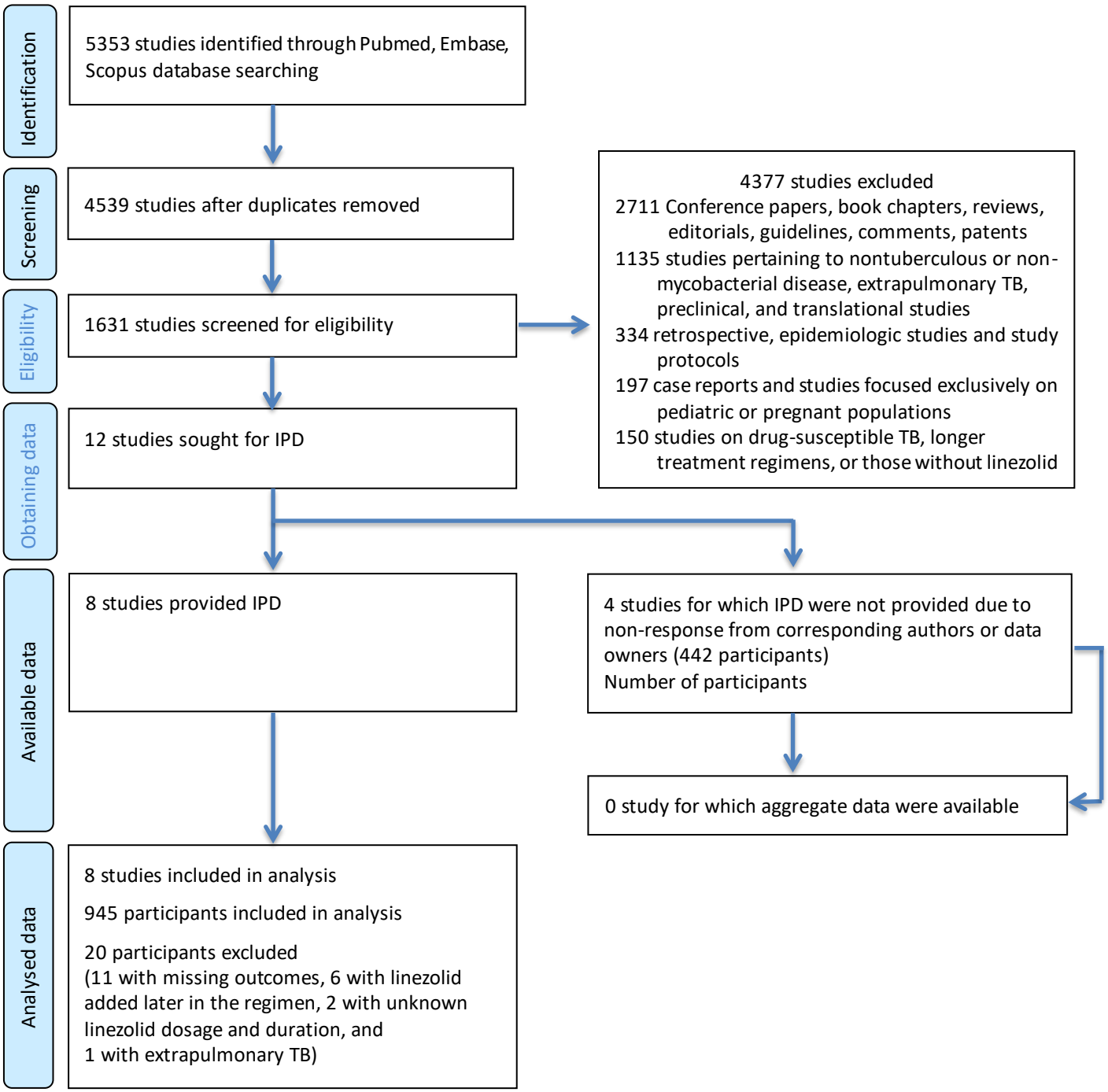
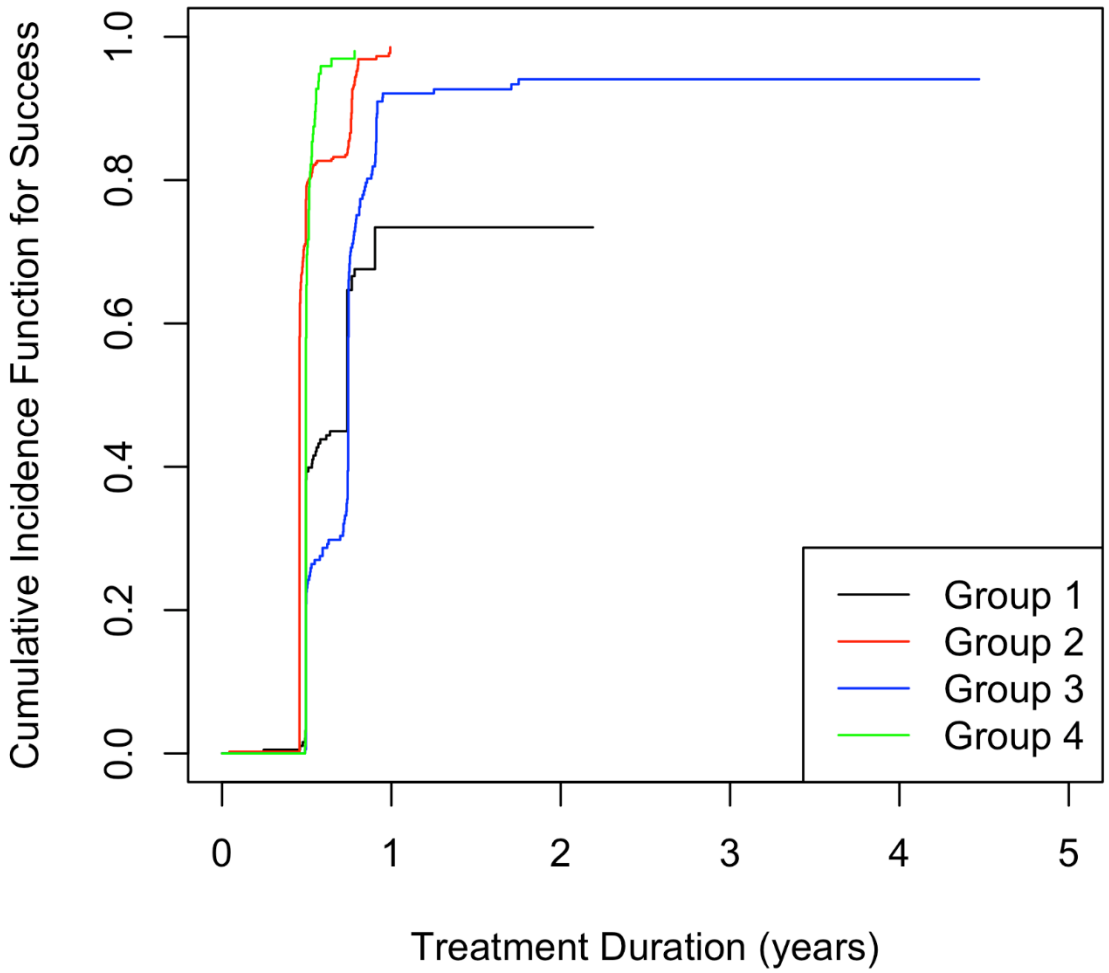


Figure 2. Cumulative incidence function plot for treatment success



Impact of linezolid dosing and duration on treatment outcomes of multidrug-resistant and rifampicin-resistant tuberculosis: An individual patient data meta-analysis

<Supplementary Material>

Nakwon Kwak[1,*], Joong-Yub Kim[1,*,#], Areum Han[2,3], Catherine Berry[4], Maria Beumont[5], Tweed Conor[6], Angela Crook[6], Keertan Dheda[7,8], Stella Fabiane[6], Muse O Fadeyi[9], Salah Foraida[5], Tinne Gils[10,11], Thi Thanh Thuy Hoang[12], Menal A Jham[13], Richard A Murphy[14], Binh Hoa Nguyen[12], Thi Mai Phuong Nguyen[12], Bern-Thomas Nyang'wa[15,16], Suzette Oelofse[8], Seokyung Hahn[17,18,19], Jae-Joon Yim[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

[2]Interdisciplinary Program of Medical Informatics, Seoul National University College of Medicine, Seoul, Republic of Korea

[3]Integrated Major in Innovative Medical Science, Seoul National University College of Medicine, Seoul, Republic of Korea

[4]Médecins Sans Frontières, London, United Kingdom

[5]TB Alliance, New York, USA

[6]MRC Clinical Trials Unit, University College London, London, United Kingdom

[7]Department of Immunology and Infection, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

[8]Centre for Lung Infection and Immunity, University of Cape Town, Cape Town, South Africa

[9]Damien Foundation Belgium (Nigeria Project), Ibadan, Nigeria

[10]Unit of HIV and Coinfections, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

[11]Global Health Institute, University of Antwerp, Wilrijk, Belgium

[12]National Lung Hospital, Hanoi, Vietnam

[13]UMMA Community Clinic, Los Angeles, USA

[14]Division of Infectious Diseases, Dartmouth Geisel School of Medicine, Hanover, USA

[15]Médecins Sans Frontières, Amsterdam, the Netherlands

[16]Clinical Research Department, London School of Hygiene and Tropical Medicine, London, United Kingdom

[17]Medical Bigdata Research Center, Medical Research Center, Seoul National University, Seoul, Republic of Korea

[18]Institute of Health Policy and Management, Medical Research Center, Seoul National University, South Korea

[19]Department of Human Systems Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

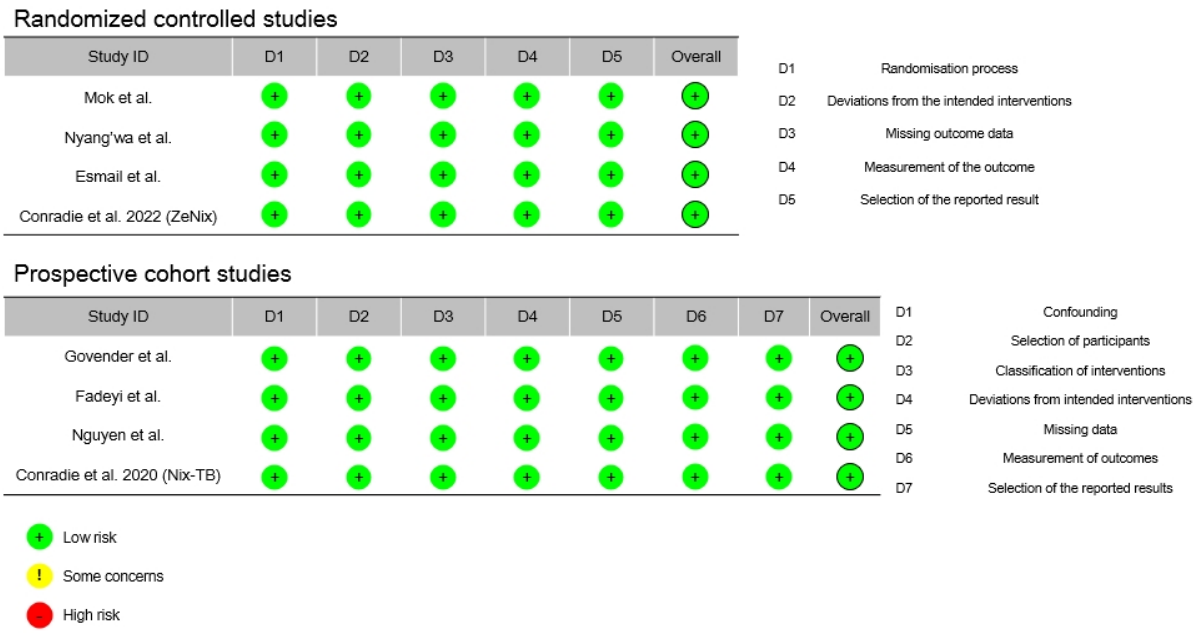
[*]These authors contributed equally

[#]Current address: Department of Microbiology, Harvard Medical School, Boston, USA

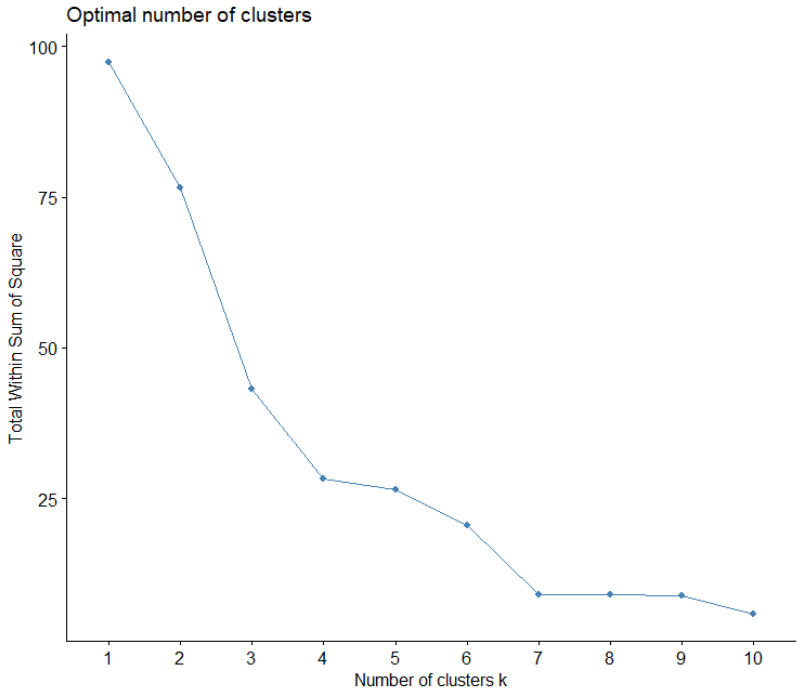
Corresponding Author:

Jae-Joon Yim, MD, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-Ro, Jongno-Gu, Seoul, 03080, Republic of Korea. Tel: +82-2-2072-2059, Fax: +82-762-9662, E-mail: yimjj@snu.ac.kr

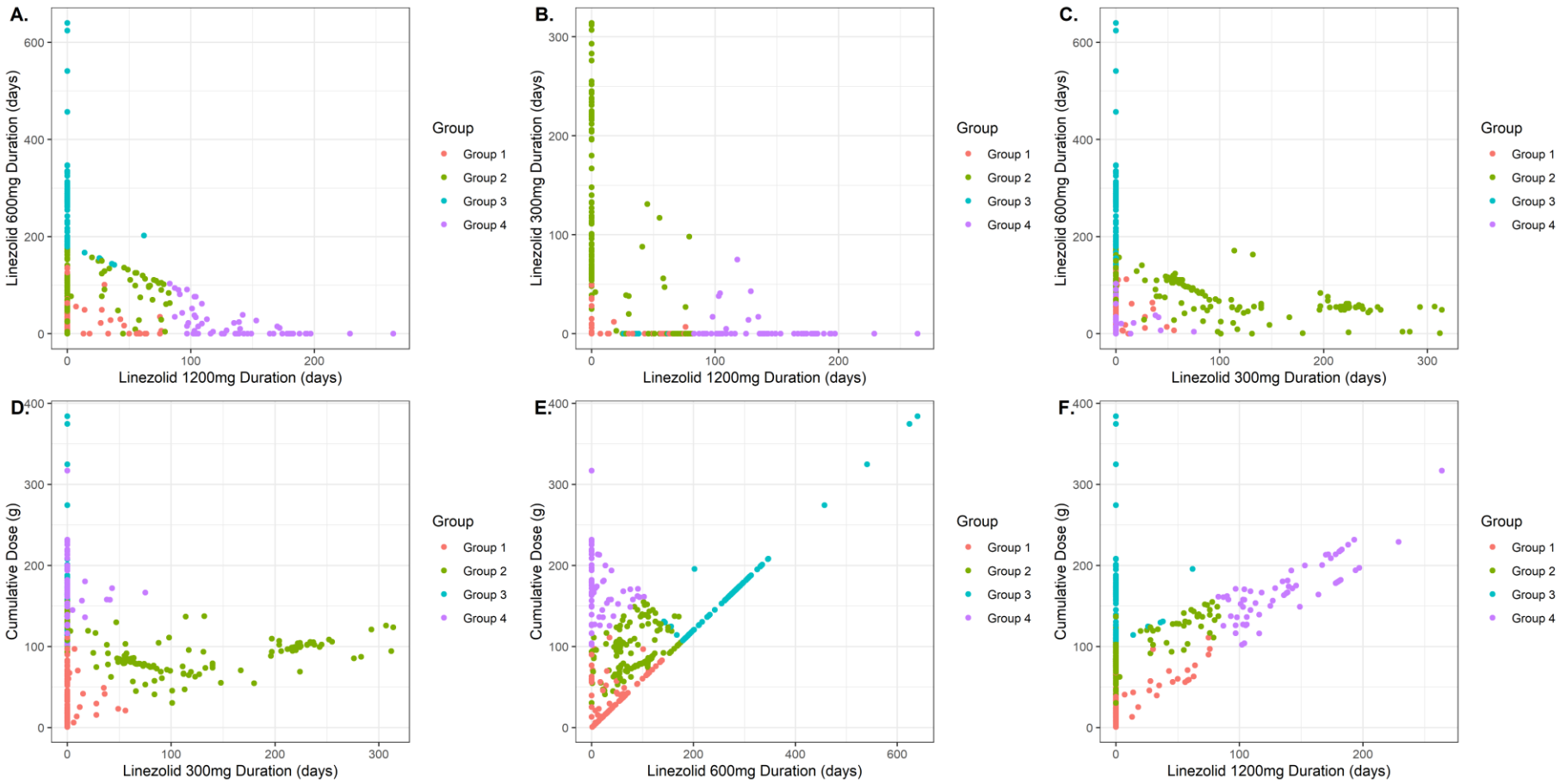
Supplementary Figure 1. Risk of bias for the included studies



Supplementary Figure 2. Within-cluster sum of squares according to the number of clusters



Supplementary Figure 3. Scatter plot of data points coloured by each cluster based on the Partitioning Around Medoids algorithm



Supplementary Table 1. Baseline characteristics, administered drugs, treatment outcomes, and adverse events by study

Characteristics	Mok et al. 2022 (MDR-END)	Govender et al. 2023	Fadeyi et al. 2023	Nguyen et al. 2023	Nyang'wa et al. 2022/ Nyang'wa et al. 2024 (TB-PRACTECAL)	Esmail et al. 2022 (NExT Study)	Conradie et al. 2020 (Nix-TB)	Conradie et al. 2022 (ZeNix)	P-value*
	(N=72)	(N=50)	(N=20)	(N=106)	(N=360)	(N=47)	(N=109)	(N=181)	
Study design	RCT	Prospective cohort	Prospective cohort	Prospective cohort	RCT	RCT	Prospective cohort	RCT	N/A
Age, years, median (IQR)	49.0 (40.0-57.0)	35.0 (30.9-45.9)	34.0 (28.5-41.0)	40.5 (29.0-57.0)	34.0 (27.0-43.0)	35.0 (28.5-40.0)	35.0 (28.0-43.0)	35.0 (30.0-40.0)	<0.001
Male sex, N (%)	48 (66.7)	36 (72.0)	12 (60.0)	75 (70.8)	209 (58.1)	33 (70.2)	57 (52.3)	122 (67.4)	0.021
Weight, kg, median (IQR)	57.0 (51.0-66.0)	55.5 (50.8-60.0)	46.5 (43.0-54.5)	NA	56.9 (50.0-65.3)	54.8 (50.1-61.5)	53.0 (47.0-64.0)	61.0 (53.8-67.3)	<0.001
BMI, kg/m^2, median (IQR)	20.6 (18.9-22.6)	19.4 (16.8-22.1)	17.8 (17.0-19.2)	18.7 (17.0-20.4)	19.7 (17.8-22.2)	19.4 (17.7-22.9)	19.3 (17.1-22.5)	20.8 (18.8-23.2)	<0.001
HIV positive, N (%)	0 (0)	35 (70.0)	1 (5.0)	1/84 (1.2)	99/359 (27.6)	26 (55.3)	56 (51.4)	NA	<0.001
Diabetes, N (%)	14 (19.4)	NA	NA	NA	13 (3.6)	1 (2.1)	9 (8.3)	8 (4.4)	<0.001
Acid-fast bacilli smear positivity, N (%)	21 (29.2)	21 (42.0)	15/19 (78.9)	53/103 (51.5)	236 (65.6)	29/46 (63.0)	58/69 (84.1)	91 (50.3)	<0.001
Presence of cavity on chest radiography, N (%)	33 (45.8)	42/45 (93.3)	18/18 (100)	42 (39.6)	216 (60.0)	24/38 (63.2)	92 (84.4)	112 (61.9)	<0.001
Resistance to fluoroquinolone, N (%)	41/63 (65.1)	25/36 (69.4)	13/19 (68.4)	0/105 (0)	37/315 (11.7)	4/44 (9.1)	31/63 (49.2)	105/143 (73.4)	<0.001
Initial dose of linezolid, N (%)									<0.001
1,200 mg/day	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	109 (100)	91 (50.3)	
600 mg/day	72 (100)	50 (100)	20 (100)	106 (100)	360 (100)	47 (100)	0 (0)	90 (49.7)	
Drugs administered, N (%)									
Bedaquiline	0 (0)	50 (100)	20 (100)	106 (100)	360 (100)	47 (100)	109 (100)	181 (100)	<0.001
Delamanid	72 (100)	0 (0)	20 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<0.001
Pretomanid	0 (0)	0 (0)	0 (0)	0 (0)	360 (100)	0 (0)	109 (100)	181 (100)	<0.001
Later-generation fluoroquinolone	72 (100)	50 (100)	0 (0)	106 (100)	137 (38.1)	47 (100)	0 (0)	0 (0)	<0.001
Levofloxacin	72 (100)	50 (100)	0 (0)	106 (100)	0 (0)	47 (100)	0 (0)	0 (0)	<0.001
Moxifloxacin	0 (0)	0 (0)	0 (0)	0 (0)	137 (38.1)	0 (0)	0 (0)	0 (0)	<0.001

Clofazimine	0 (0)	50 (100)	20 (100)	105 (99.1)	114 (31.7)	1 (2.1)	0 (0)	0 (0)	<0.001
High-dose isoniazid	0 (0)	50 (100)	0 (0)	0 (0)	0 (0)	34 (72.3)	0 (0)	0 (0)	<0.001
Ethambutol	0 (0)	50 (100)	0 (0)	0 (0)	0 (0)	13 (27.7)	0 (0)	0 (0)	<0.001
Pyrazinamide	72 (100)	50 (100)	0 (0)	106 (100)	0 (0)	47 (100)	0 (0)	0 (0)	<0.001
Duration of total treatment, days, median (IQR)	279 (271-286)	270 (270-270)	279 (123-323)	272 (272-289)	167 (167-167)	184 (155-263)	181 (181-187)	181 (181-181)	<0.001
Duration of linezolid administration, days, median (IQR)	268 (132-283)	60 (60-60)	279 (123-323)	272 (272-283)	166 (166-166)	181 (136-209)	171 (138-181)	63 (63-181)	<0.001
Duration of ≥ 600mg of linezolid administration, days, median (IQR)	55 (49-57)	60 (60-60)	279 (123-323)	272 (272-280)	111 (111-111)	179 (130-198)	162 (125-181)	63 (63-181)	<0.001
Cumulative dose of linezolid, $x10^3$ mg, median (IQR)	94.3 (57.2-101.8)	36.0 (36.0-36.0)	167.1 (73.8-193.5)	163.2 (163.2-168.0)	83.1 (83.1-83.1)	107.4 (80.4-118.8)	151.2 (124.8-181.2)	63.0 (37.8-109.2)	<0.001
Treatment outcome									
Favorable outcome	55 (76.4)	41 (82.0)	14 (70.0)	96 (90.6)	305 (84.7)	24 (51.1)	100 (91.7)	159 (87.8)	<0.001
Adverse events ≥ grade 3, N (%)									<0.001
Total	24 (33.3)	11 (22.0)	2 (10.0)	10 (9.4)	65 (18.1)	16 (34.0)	62 (56.9)	45 (24.9)	<0.001
Peripheral neuropathy	0 (0)	1 (2.0)	0 (0)	3 (2.8)	0 (0)	5 (10.6)	24 (22.0)	0 (0)	<0.001
Myelosuppression	7 (9.7)	4 (8.0)	0 (0)	0 (0)	12 (3.3)	6 (12.8)	12 (11.0)	6 (3.3)	<0.001
Optic neuropathy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)	1 (0.6)	0.665

* The P-value indicates the overall difference among the studies.

Supplementary Table 2. The number of patients allocated to each group within each study

	Total (N=945)	Group 1 (N=215)	Group 2 (N=447)	Group 3 (N=183)	Group 4 (N=100)
Mok et al. 2022 (MDR-END)	72	12	60	0	0
Govender et al. 2023	50	50	0	0	0
Fadeyi et al. 2023	20	6	0	14	0
Nguyen et al. 2023	106	5	2	99	0
Nyang'wa et al. 2022/ Nyang'wa et al. 2024 (TB-PRACTECAL)	360	27	333	0	0
Esmail et al. 2022 (NExT Study)	47	12	11	24	0
Conradie et al. 2020 (Nix-TB)	109	11	30	5	63
Conradie et al. 2022 (ZeNix)	181	92	11	41	37