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Epidemiology of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis

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Abstract

Objectives: To estimate the pooled proportion of extensively drug-resistant tuberculosis (XDR-TB) and pre-extensively drug-resistant tuberculosis (pre-XDR-TB) in patients with multidrug-resistant TB (MDR-TB).

Methods: We systematically searched articles from electronic databases: MEDLINE (PubMed), ScienceDirect, and Google Scholar. We also searched gray literature from the different literature sources main outcome of the review was either XDR-TB or pre-XDR-TB in patients with MDR-TB. We used the random-effects model, considering the substantial heterogeneity among studies. Heterogeneity was assessed by subgroup analyses. STATA version 14 was used for analysis.

Results: A total of 64 studies that reported on 12,711 patients with MDR-TB from 22 countries were retrieved. The pooled proportion of pre-XDR-TB was 26% (95% confidence interval [CI]: 22–31%), whereas XDR-TB in MDR-TB cases was 9% (95% CI: 7–11%) in patients treated for

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Author contributions

GD conceptualized, designed, and drafted the manuscript. GD, AA, BY, HHT, HM, DFG, KE, and AK: article searching, data extraction, and quality assessment. GD, AA, DFG, and BY: data analysis of the manuscript. AA, HHT, AK, SM, SA, GT, and MHD: writing, review, and editing of the final manuscript. All authors read, reviewed, and approved the final manuscript.

Declaration of competing interests

The authors have no competing interests to declare.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.04.392.

MDR-TB. The pooled proportion of resistance to fluoroquinolones was 27% (95% CI: 22–33%) and second-line injectable drugs was 11% (95% CI: 9–13%). Whereas the pooled resistance proportions to bedaquiline, clofazimine, delamanid, and linezolid were 5% (95% CI: 1–8%), 4% (95% CI: 0–10%), 5% (95% CI; 2–8%), and 4% (95% CI: 2–10%), respectively.

Conclusion: The burden of pre-XDR-TB and XDR-TB in MDR-TB were considerable. The high burdens of pre-XDR-TB and XDR-TB in patients treated for MDR-TB suggests the need to strengthen TB programs and drug resistance surveillance.

Keywords

Pre-extensively drug-resistant tuberculosis; Extensively drug-resistant tuberculosis; Multidrug-resistant tuberculosis

Introduction

The rise of drug-resistant (DR) bacterial infections is becoming a major public health concern worldwide. It threatens global tuberculosis (TB) control programs and makes TB diagnosis and treatment challenging. In the past 20 years, DR-TB has spread across the world and continued to be a challenge to global TB control efforts [1]. A recent estimate indicated 465,000 incident cases of multidrug resistance/rifampicin (RIF) resistance (MDR/RR-TB) occurred worldwide [2]. In addition, an estimated 3.6% of new TB cases and 18% of previously treated TB cases have developed MDR-TB in 2021 [3]. Moreover, on average, 6.2% of XDR-TB was estimated in 2019 among patients treated for MDR-TB [2]. Prolonged duration required for the treatment, low cure rates, and the cost of drugs and toxicity make DR-TB treatment the most costly challenge [4].

Migration, housing conditions, poverty, and the emergence of other diseases, such as HIV and diabetes, are the factors fueled the burden of MDR/XDR-TB [5,6]. Furthermore, low laboratory diagnosis capabilities that delay DR-TB diagnosis and limited access to second-line MDR-TB treatment are associated with the transmission of resistant strains. Therefore, to stop the emergency of DR-TB strain, the best strategy is evidence-based diagnosis and treatment [7].

Before 2021, XDR-TB was defined as a disease caused by *Mycobacterium tuberculosis* with resistance to at least isoniazid (INH) and RIF (MDR-TB), with further resistance to any fluoroquinolones (FQs) and a second-line injectable drug (SLID) (kanamycin, amikacin, or capreomycin). Pre-XDR-TB is defined as TB with resistance to INH, RIF, and either an FQ or a second-line injectable agent but not both [4]. Based on new experimental and observational data, the World Health Organization (WHO) recently updated its guidelines, in which the late-generation FQs (levofloxacin and moxifloxacin) and WHO group A drugs (linezolid and bedaquiline) are recommended for the treatment of MDR-TB. In this guideline, XDR-TB is defined as an infection with MDR *M. tuberculosis* that is resistant to any FQs and at least one of the group A drugs. The most effective use of group A drugs to improve MDR-TB treatment requires appropriate drug susceptibility testing results [8].

The DR-TB treatment method has been updated in 2022. This document includes two new recommendations. The first regimen is the use of bedaquiline, pretomanid, linezolid, and moxifloxacin regimen for 6 months. This regimen is composed of bedaquiline, pretomanid, linezolid, and moxifloxacin and given to patients with MDR/RR-TB. However, patients with MDR/RR-TB with FQs additional resistance (pre-XDR-TB) should be treated for 9 months with all oral regimens. The consolidated guidelines includes the existing recommendations in the treatment regimens for INH-resistant TB with longer all oral regimens, monitoring of treatment response, timing of antiretroviral therapy in MDR/RR-TB for the patients infected with HIV, and the use of surgery for patients receiving MDR-TB treatment [8].

Several review studies have attempted to pool the proportion of MDR-TB cases. However, there are few review studies that attempted to estimate the pooled proportion of pre-XDR-TB and XDR-TB. Thus, we aimed to determine the pooled proportion of pre-XDR-TB and XDR-TB among patients diagnosed with MDR-TB from published primary studies.

Methods

Protocol registration

To prevent duplicates, the review study databases were searched for similar systematic reviews before this review commenced. The protocol of this systematic review and meta-analysis was registered in International Prospective Register of Systematic Reviews at the University of York database and obtained registration number PROSPERO ID: CRD42022343112.

Databases and search strategy

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines for reporting systematic reviews and meta-analyses [9,10]. We estimated the pooled proportion of pre-XDR-TB and XDR-TB in patients with MDR-TB for global occurrence. We conducted systematic searches of the following electronic databases: MEDLINE (PubMed), ScienceDirect, and Google Scholar, until July 20, 2022 for articles published in English, without limiting the year of publication. Studies that reported pre-XDR-TB and XDR-TB globally were included in the analysis. We used search terms: “(extensively drug-resistant tuberculosis OR XDR-TB) AND (pre-extensively drug-resistant tuberculosis OR Pre-XDR-TB) AND (drug-resistant tuberculosis OR DR-TB) AND (second-line drug resistance)” for the PubMed database search in both free text and medical subject heading.

Inclusion and exclusion criteria

We included cross-sectional studies that reported the proportion of either pre-XDR or XDR-TB among patients diagnosed with MDR-TB. However, we excluded studies that compared or validated the diagnostic methods for the detection of DR-TB and treatment outcomes. In addition, we excluded case studies, editorials, author comments, commentaries, general evaluations, and professional opinions to avoid duplicates.

Study selection

To identify potential studies, two authors (GD and BY) independently searched the electronic databases. Two reviewers (GD and DFG) independently screened the full-text papers to choose relevant articles based on the inclusion criteria. Differences between the two reviewers were resolved through discussion between the two authors (GD and DFG).

PICOS criteria

- Participants: patients with MDR-TB with pre-XDR-TB and XDR-TB.
- Intervention: not applicable.
- Comparator: not applicable.
- Outcome: pre-XDR-TB and XDR-TB among patients with MDR-TB.
- Study design: observational studies.
- Study setting: any setting in any country worldwide.

Definition of terms

Based on a previous 2021 definition, pre-XDR-TB and XDR-TB were defined as:

- Pre-XDR-TB was defined as TB with resistance to INH and RIF and either an FQ or a second-line injectables.
- XDR-TB referred to MDR-TB that is resistant to INH and rifampin plus any fluoroquinolone and at least one of the three SLIDs.
- New TB case is defined as a newly registered episode of TB in a patient who has never been treated for TB or has taken anti-TB drugs for less than a month.
- Previously treated TB case refers to a patient who has received anti-TB drugs in the past for a month or longer.

Data extraction

We extracted the data in a standard prepared Microsoft Excel sheet. Two authors (GD and BY) independently extracted the data from the selected primary studies. Data were extracted on the variables: first author name; year of publication; study period; study area (country); study design; a number of MDR-TB; a number of XDR-TB; a number of pre-XDR-TB; FLQ resistance; SLIDs resistance, new drugs resistance Bedaquiline (BDQ), Clofazimine (CFZ), Delamanid (DLM), and Linezolid (LZD), and previous treatment history. Discrepancies between the two authors' on data records were resolved by consensus.

Risk of bias assessment and quality assessment

Two authors (GD and AA) evaluated the quality of the selected studies independently and in cases of inconsistencies a third reviewer (BY) was involved. We used Newcastle-Ottawa scale adapted for cross-sectional studies to assess the quality of the included studies. Newcastle-Ottawa scale rates the likelihood of bias in three domains of observational studies. These are the (1) selection of participants, (2) comparability, and (3) outcomes.

For each numbered item in the selection and outcome categories, a study receives up to one point, and for comparability, a study may receive up to two points [11]. For low-, moderate-, and high-quality studies, the corresponding scores of 0–3, 4–6, and 7–9 were given, respectively. We used the *I*-squared statistic (I^2) to assess the heterogeneity in the reported proportion. $I^2 \geq 50\%$ was used to indicate the presence of heterogeneity [12]. Moreover, a funnel plot was used to examine the possibility of publication bias.

Statistical analysis

We used the random-effects model to pool the proportion of pre-XDR-TB and XDR-TB and their 95% confidence interval (CI). The pooled proportion of pre-XDR-TB and XDR-TB in patients with MDR-TB was estimated using the "metaprop" command in STATA 14 (STATA Corporation, College Station, TX, USA). The estimates of pre-XDR-TB and XDR-TB pooled proportion were compared descriptively by the WHO regional categories and patient TB treatment history.

Results

Study selection

A total of 867 records were retrieved from the electronic and gray literature search and imported to EndNote reference manager. Of the total retrieved record, 389 remained after the duplicates were removed; Of 389 records, 298 were excluded by reviewing the title and abstract for population, intervention, and outcome difference with the current review. A total of 91 original articles were retrieved and fully articles were reviewed, and 27 were removed based on exclusion criteria. Finally, total of 64 articles were included in this review [5,13–75] (Figure 1).

Characteristics of the studies included in the review

Detailed characteristics of included studies are depicted in Table 1. The included studies were reported from 22 countries across the WHO regions. A total of 13 studies were reported from in India [14,23,27,31,33,35,44,45,54,57–59,61] and 11 from China [13,20,29,53,66,67,69,70,72–74]. A total of 20 studies were reported from the Western Pacific [13,20,21,29,36–39,46,49,51,53,66,67,69–74] and 18 from South-East Asian regions [14,23,27,31–33,35,44,45,50,52,54, 57–59,61–63]. A total of 12 studies reported from African region [15,16,18,19,22,24,25,41,43,48,60,68]. The remaining 14 studies were reported from the Eastern Mediterranean, Americas, and European regions [5,17,26,28,30,34,40,42,47,55,56,64,65,75].

The data were extracted from 64 studies involving a total of 12,711 patients with MDR-TB who were treated from 2003 to 2020, with publication years ranging from 2008 to 2021. The sample size of MDR-TB in the included studies varied from nine [16] to 2472 [51]. Among the 64 studies, 53 reported pre-XDR cases, whereas 57 reported XDR-TB cases.

Pooled proportion of pre-XDR-TB

The pooled proportion of pre-XDR-TB among MDR-TB cases was 26% (95% CI: 22–31; $I^2 = 97.31\%$). China had the highest proportion of pre-XDR-TB (66%) [13] and Ethiopia

the lowest (3%) [18]. In the Western Pacific, South-East Asian, Eastern Mediterranean, European, Americas, and African regions, the pooled proportions of pre-XDR-TB were 35% (95% CI: (95% CI: 24–41; I^2 = 96.2%), 30% (95% CI: 15–45; I^2 = 95.41%), 22% (95% CI: 5–39), 14% (95% CI: 10–19; I^2 = 65.25%), and 12% (95% CI: 7–17; I^2 = 79.68%), respectively (Figure 2).

In the current study, we also performed a subgroup analysis based on the treatment history of patients with MDR-TB (newly diagnosed and previously treated cases). In the newly diagnosed group, the data were extracted from 23 studies, with the sample sizes ranging from 14 [25] to 687 [57]. A study in China had the highest proportion of pre-XDR-TB (27%) [70], whereas Ethiopia and Cameroon had the lowest (1%) [43,60]. The pooled proportion of pre-XDR-TB among newly diagnosed MDR-TB cases was 9% (95% CI: 5–12; I^2 = 96.32%). In the previously treated group, the data were extracted from 19 studies with sample sizes ranging from 14 [25] to 687 [57]. Similarly, the highest proportion of pre-XDR-TB (47%) was reported in China (69), whereas Ethiopia and Cameroon had the lowest (3%) [18,43]. The pooled proportion estimate of pre-XDR-TB proportion was 13% (95% CI: 8–18; I^2 = 96.12%) (Figure 3).

Pooled proportion of XDR-TB

The proportion of XDR-TB was reported in all WHO regions. The estimated pooled proportion of XDR-TB among patients with MDR-TB was 9% (95% CI: 7–11; I^2 = 95.98%). The highest proportion of XDR-TB was reported in India (77%) [44] and the lowest in Ethiopia [60] and Cameron (1%) [43]. The pooled proportions of XDR-TB in the Western Pacific, South-East Asian, Americas, African, and Eastern Mediterranean regions were 12% (95% CI: 7–17; I^2 = 19.62%), 10% (95% CI: 6–13%; I^2 = 94.54%), 6% (95% CI: 3–9; I^2 = 57.54%), and 3% (95% CI: 1–5%; I^2 = 65.68%), 3% (95% CI: 1–4; I^2 = 19.62%), respectively (Figure 4).

In the current study, we performed a subgroup analysis based on the treatment history of patients with MDR-TB (newly diagnosed and previously treated cases). In the newly diagnosed group, the data were extracted from 23 studies with a sample size ranges from nine [16] to 2472 [51]. Whereas the data was extracted from 25 studies, with sample sizes ranging from 33 [75] to 2472 [51], on previously treated patients. The pooled estimates of XDR-TB among newly diagnosed patients with MDR-TB were 3% (95% CI: 2–5; I^2 = 93.58%) and 6% (95% CI: 4–8; I^2 = 95.62%) among previously treated patients (Figure 5).

Pooled proportion estimates of FQs, SLID, and new drugs (BDQ, CFZ, DLM, and LZD)

In this study, we estimated the pooled proportion of resistance to FQs, SLIDs, and new drugs among patients with MDR-TB. The highest proportion of FQs resistance was 77% [44], whereas the lowest proportion was 4% [15,37]. Furthermore, the highest proportion of SLIDs resistance was 40% [13], whereas the lowest proportion was 3% [50,62]. The overall pooled proportion of FQs resistance among MDR-TB cases were 27% (95% CI: 22–33; I^2 = 97.53%) and 11% (95% CI: 9–13; I^2 = 91.31%) SLIDs resistance (Figure 6).

In this study, we performed a subgroup analysis to estimate the pooled new drug resistance among patients with MDR-TB. The pooled proportion of new drugs resistance was

estimated from five studies for BDQ and LZD, four studies for DLM, and three studies for CFZ [13,29,67,71,74]. The sample size of the included studies ranged from 88 [74] to 425 [13]. The pooled proportion of resistance to new drugs among patients with MDR-TB was 5% (95% CI: 1–8; I^2 = 90.84%) for BDQ, 4% (95% CI: 0–10; I^2 = 84.27%) for CFZ, 5% (95% CI: 2–8; I^2 = 80.80%) for DLM, and 4% (95% CI: 2–10; I^2 = 67.39%) for LZD (Figure 7).

Publication bias

We assessed the publication bias using funnel plots with the effect size and their standard errors. Visual inspection showed that the presence of publication bias was observed for the majority of the estimation of pre-XDR-TB, with fewer studies clustered at the tip of the funnel and the others distributed to the right and left corners of the funnel. The funnel plot for XDR-TB patients was relatively symmetrical, with only few studies visible in the right corners (Figure 8).

Discussion

This systematic review and meta-analysis estimated the pooled proportion of pre-XDR and XDR-TB among patients diagnosed with MDR-TB from the study reported worldwide. The pooled proportions of XDR-TB among new patients with MDR-TB were 3% and 6% in previously treated patients. The pooled proportions of pre-XDR-TB among new patients with MDR-TB were 9% and 13% among previously treated patients. The overall pooled proportion of pre-XDR was 26%, whereas the proportion of XDR-TB was 9% among patients diagnosed with MDR-TB. The pooled proportion of FQs resistance was 27% and the proportion of SLIDs resistance was 11%. A considerable proportion of resistance to new drugs BDQ (5%), CFZ (4%), DLM (5%), and LZD (4%) were also reported worldwide.

In the current review, the pooled proportion of XDR-TB was 9%. This is relatively higher than the proportion reported by the WHO global TB report in 2019, in which the proportion of XDR-TB was 6.2% [4]. This substantial difference could be due to the fact that the current meta-analysis was based on the findings from published clinical studies that reported data from diverse patient populations in various settings. The data, therefore, effectively entails regional influences and different epidemiological factors contribute to drug resistance and do not involve selective sampling of patients. Moreover, the proportion reported in the current review might reflect the status of suspected isolates referred for resistance testing rather than the might actual prevalence that estimated from representative participates. In contrast, the proportion given by WHO is based on the estimation from the TB program report, which could lead to underestimation, whereas the current review is based on the primary studies reported by independent researchers worldwide, which could be more representative. The results of the current review findings were relatively similar to the 2018 WHO global TB report, in which the proportion of XDR-TB was 8.5% [76].

The proportion of XDR-TB among newly diagnosed patients with MDR-TB was 3% and 6% in previously treated patients. The combined proportion of pre-XDR-TB patients among the newly diagnosed patients with MDR-TB was 9% and 13% in the previously treated patients. The WHO estimate showed that 25,038 cases of pre-XDR-TB or XDR-TB were

detected worldwide in 2022 [3]. However, there is limited information on the burden of pre-XDR-TB and XDR-TB among MDR-TB cases based on their previous treatment history.

The findings of the current study showed that more than a quarter of patients with MDR-TB had pre-XDR-TB with the majority were resistant to FQs. The pooled proportion of pre-XDR-TB in the current review is higher than the WHO estimate of 2021 [77]. The study results show that the proportion of pre-XDR-TB is higher and strains remains a major global public health concern in the area of antimicrobial resistance.

Based on the subgroup analysis, there are differences in the proportion of pre-XDR and XDR-TB in the WHO-defined regions of the world. The Western Pacific and South-East Asian regions have the highest rates of pre-XDR-TB and XDR-TB proportion. These regions should primarily examine the major risk factors for the high rates of DR-TB and intensify their efforts to address factors associated with high prevalence of DR-TB. The Beijing family is highly prevalent in these two regions and could be among the factors associated with the high proportion of DR-TB in the region [61]. The higher proportion of pre-XDR and XDR-TB might be due to the considerable variation in the coverage of high MDR/RR-TB burden countries and the high burden of the Beijing family.

The current review determined the proportion of FQs resistance cases. The pooled proportion of FQs resistance among MDR-TB cases was 27%. This finding is higher than the estimate of WHO in 2019, in which the proportion of FQs was 20.8% [4]. This difference is most likely due to the fact that majority of the included publications being from countries with high proportion of DR-TB. In addition, the possible reasons behind the high proportion of FQs are access and indiscriminate use of some of the commonly available FQ antibiotics for the treatment of various infection diseases [78]. Furthermore, the pooled proportion of SLID resistance among patients with MDR-TB was found to be 11%. The proportion of FQs resistance was equal to resistance to SLID proportion. This might be due to the fact that injectable drugs are less frequently used than FQs to treat common infections.

WHO has updated the MDR-TB treatment recommendations, in which injectable drugs are replaced by new drugs (BDQ, CFZ, DLM, and LZD). The update is required because the SLIDs are associated with an increase in deaths, treatment failures, relapses, and severe side effects, including permanent hearing loss [79]. Despite the limited evidence on new drugs, five published studies were included in the current review. In the current review, the proportion of resistance to new drugs (BDQ, CFZ, DLM, and LZD) among patients with MDR-TB was considerable. The occurrence of drug resistance among these four new anti-TB drugs was highlighted by the relatively higher proportion of resistance to BDQ and DLM. The introduction of new drugs may represent a new era in the care of patients with DR-TB by minimizing the toxicity associated with injectable drugs, reducing the spread of disease, reducing mortality rates, and improving successful treatment outcomes [31]. However, our findings revealed that 4–5% of patients with MDR-TB developed resistance to new drugs. Our findings imply that appropriate strategies are required to reduce resistance acquired during treatment.

Our review has several strengths. We used a random-effects model to address the problem of heterogeneity on the effect sizes between the included studies. In addition, we conducted a subgroup analysis using previous TB treatment history to determine the potential sources of heterogeneity. Although we cannot exclude the risk of publication bias, we used a sensitive search strategy and included a large number of studies. Moreover, we included a large number of studies that published from different parts of the world, which increases the generalizability of our findings. The current review study has some limitations. We included the studies that were published in English only, which could induce publication bias. In addition, the majority of the included studies were reported from the Western Pacific and South-East Asian regions, which could have overestimated the proportion of pre-XDR-TB and XDR-TB in this region and might have induced variation in the coverage of high MDR/RR-TB burden among the countries. Moreover, we did not evaluate the effect of HIV and other factors that could have predicted the proportion of pre-XDR-TB and XDR-TB due to the lack of data on potential predictors from the included studies. Despite these limitations listed previously, the current study results would not be affected by these limitations.

Conclusion

The current review study showed the presence of a higher proportion of pre-XDR-TB and XDR-TB than the WHO estimates. The highest proportions of pre-XDR-TB and XDR-TB were observed in the Western Pacific and South-East Asian regions. A considerable proportion of resistance to new drugs was also observed. Programmatic interventions are required to reduce the occurrence of pre-XDR-TB and XDR-TB. Countries should implement robust passive or active surveillance of DR-TB to understand the current burden of resistance to second-line and newly introduced drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of data and materials

All relevant data are available from the corresponding author upon request.

Abbreviations:

AFR	African region
AMR	Region of the Americas
BDQ	Bedaquiline

CFZ	Clofazimine
CI	Confidence interval
DLM	Delamanid
DR-TB	Drug-resistant tuberculosis
EMR	Eastern Mediterranean reegion
ES	Effect size
EUR	European region
FQs	Fluoroquinolone
INH	Isoniazid
LZD	Linezolid
MDR-TB	Multidrug-resistant tuberculosis
pre-XDR-TB	pre-extensively drug-resistant tuberculosis
RIF	Rifampicin
SEAR	South-East Asian region
SLID	Second-line injectable drug
TB	Tuberculosis
WHO	World Health Organization
WPR	Western Pacific region
XDR-TB	Extensively drug-resistant tuberculosis

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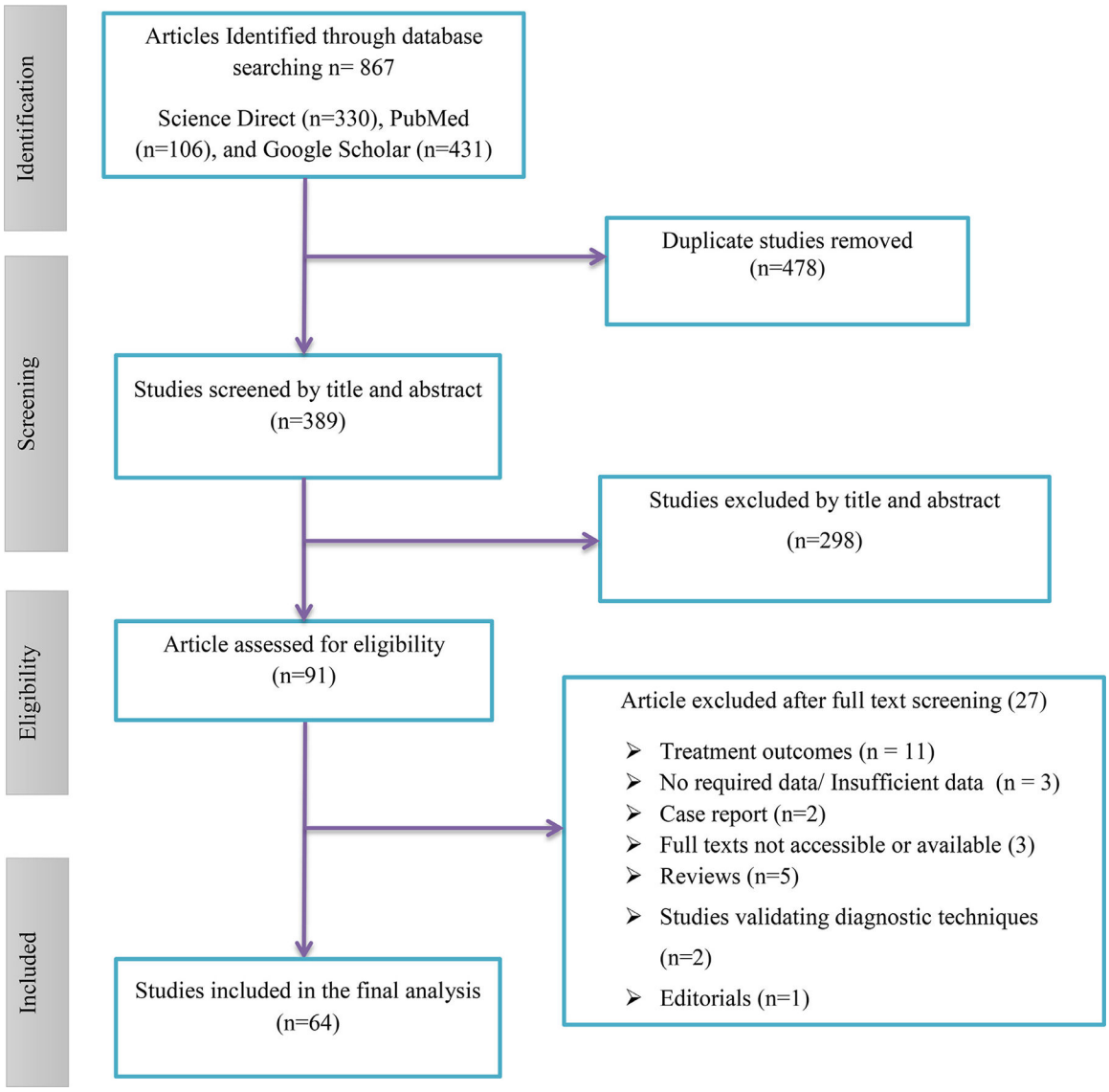


Figure 1.

Flowchart describing the selection of studies for the systematic review and meta-analysis of extensively drug-resistant-TB and pre- extensively drug-resistant-TB TB in globally. TB, tuberculosis.

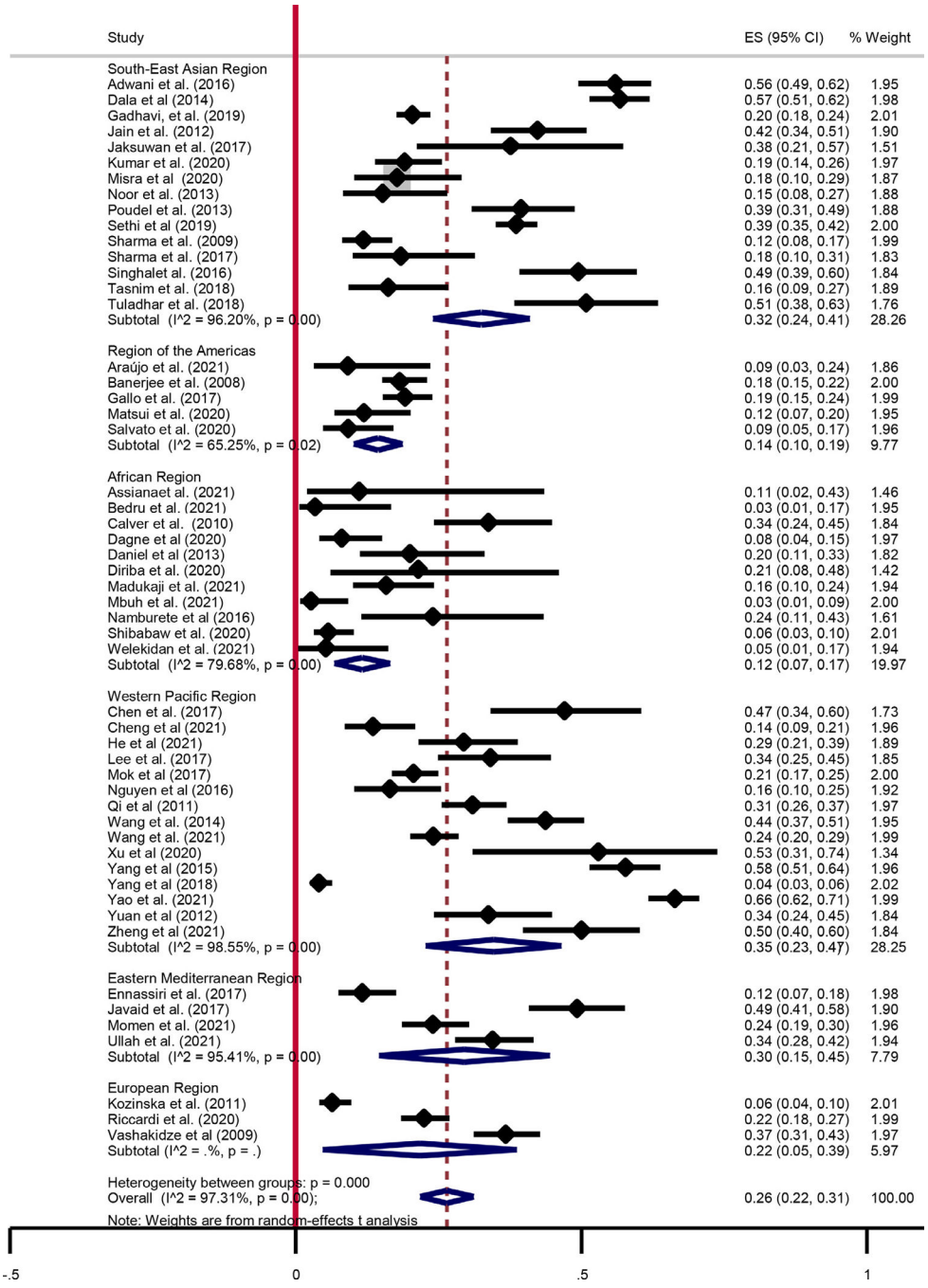


Figure 2.

Summary of pooled estimates of pre-extensively drug-resistant-tuberculosis among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size. New diagnosed cases Previously treated diagnosed cases.

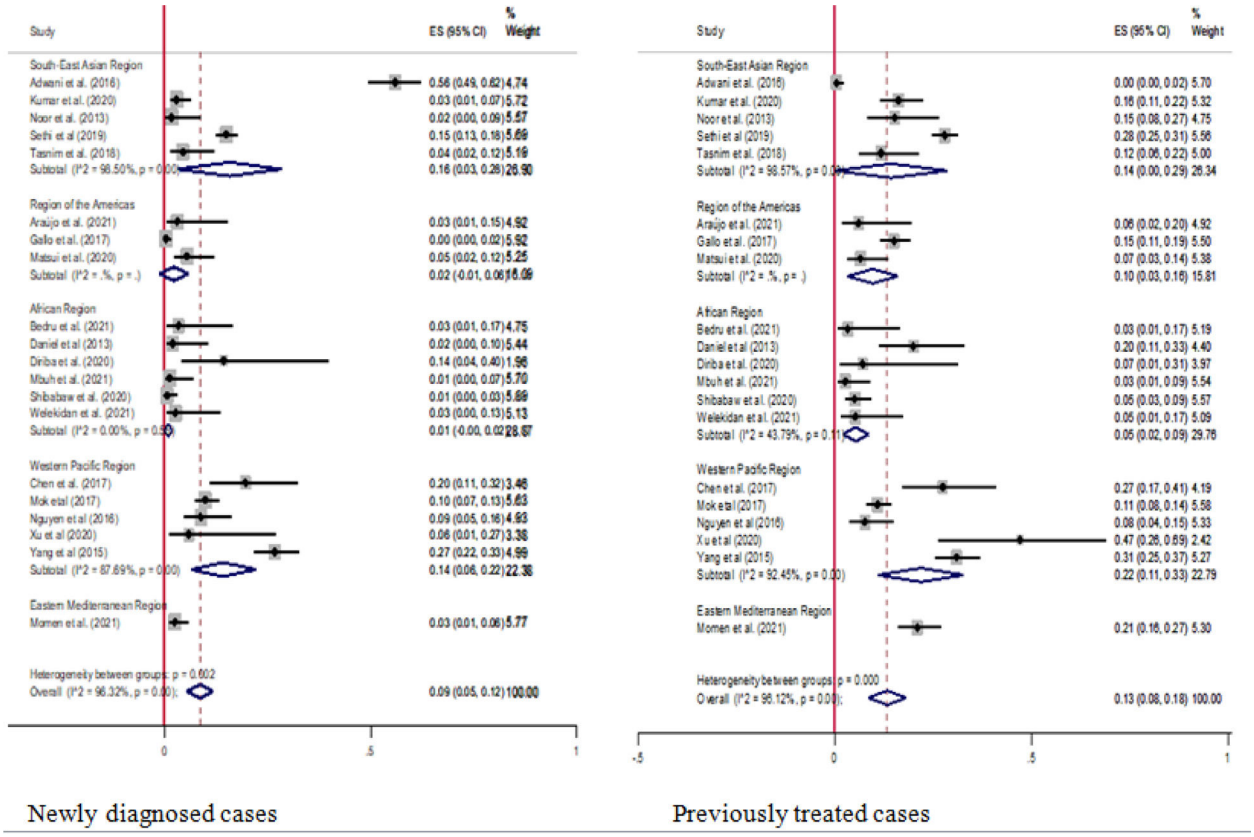


Figure 3.

Pooled estimates of pre-extensively drug-resistant-tuberculosis among new and previous treated multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

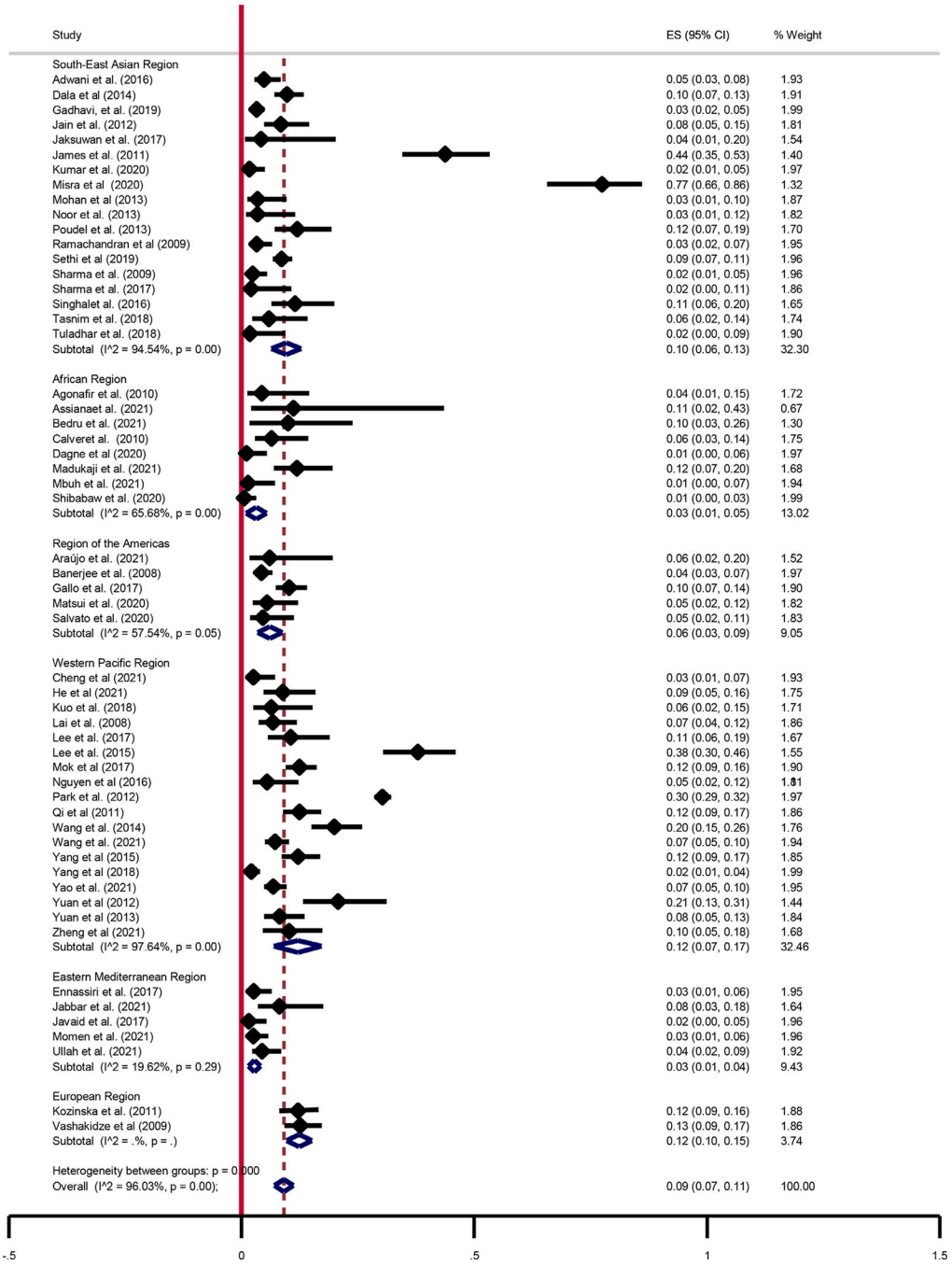
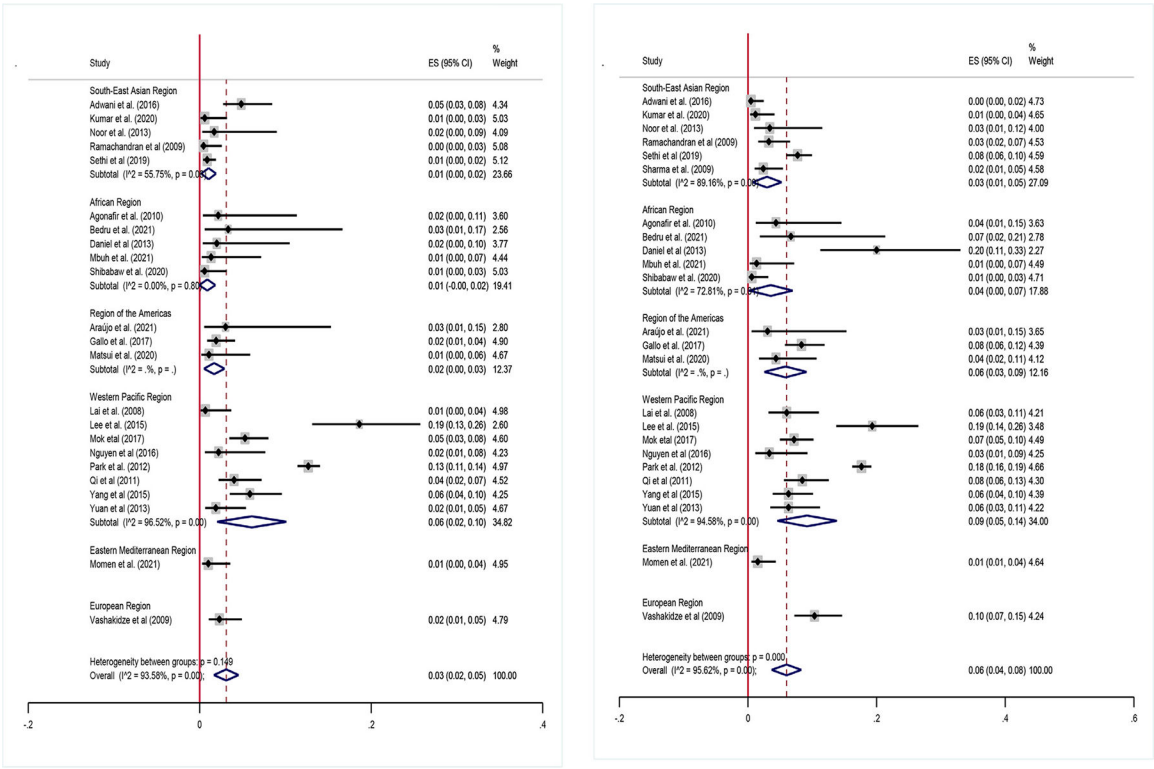


Figure 4.

Pooled estimates of extensively drug-resistant-tuberculosis among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.



New diagnosed cases Previously treated diagnosed cases

Figure 5.

Pooled estimates of extensively drug-resistant-tuberculosis among new and previous treated multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

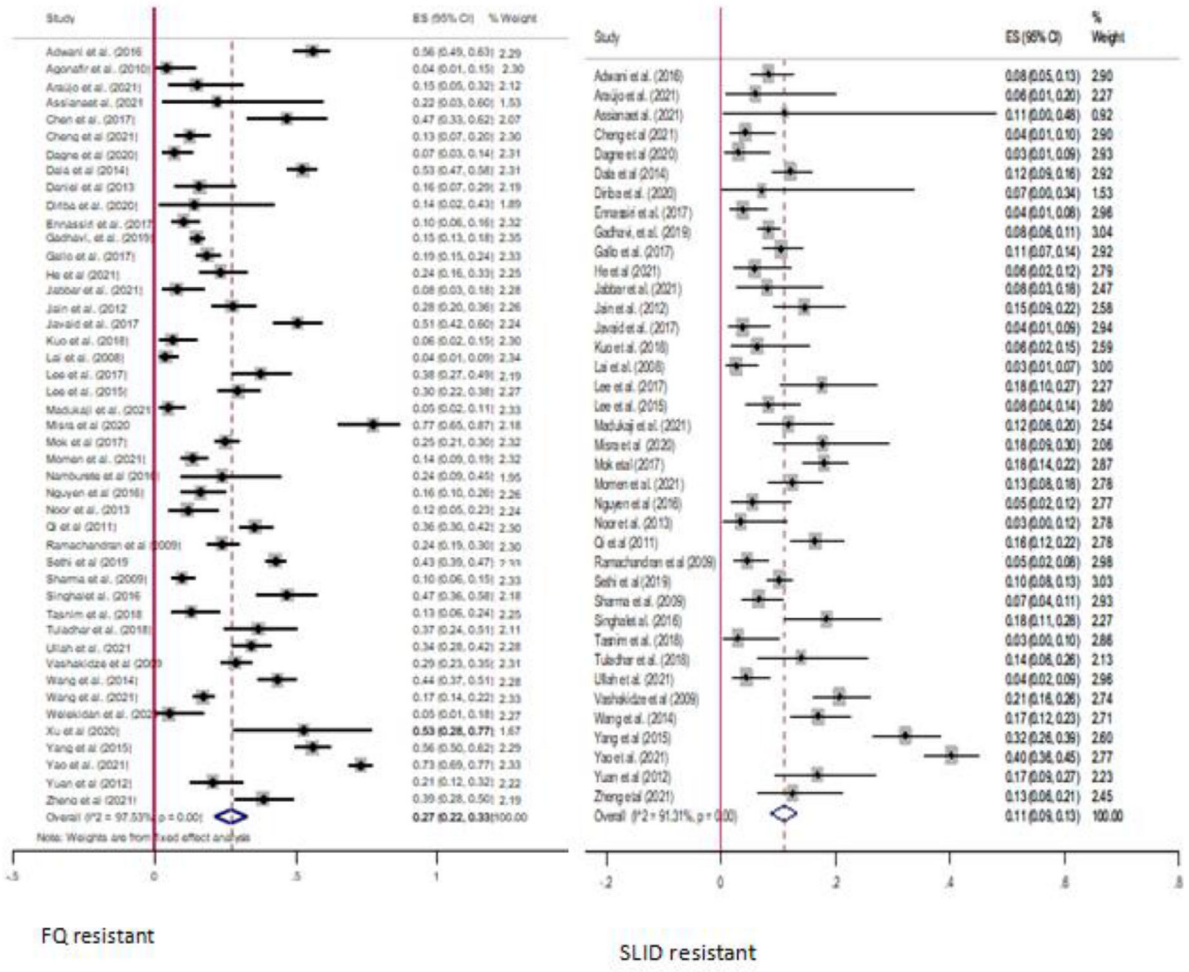


Figure 6.

Summary of pooled estimates of FQs resistance and SLIDs resistance among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size; FQs, fluoroquinolone; SLID, second-line injectable drug.

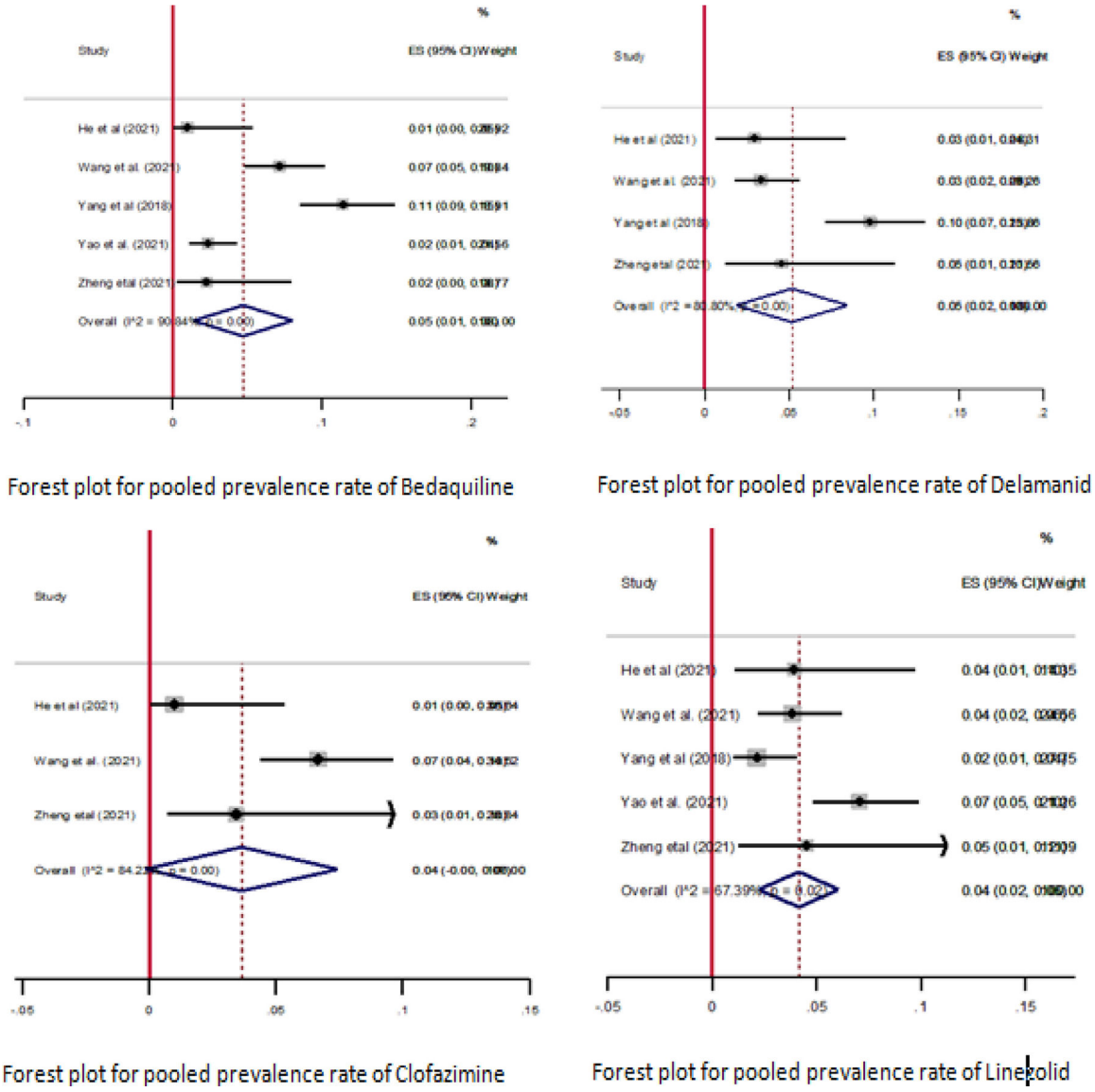


Figure 7.

Summary of the pooled prevalence of new drug resistance among multi drug-resistant-tuberculosis patients. CI, confidence interval; ES, effect size.

Figure 8.

Funnel plots analyzing publication bias among studies evaluated for pre-XDR-TB and XDR-TB. XDR-TB, extensively drug-resistant-tuberculosis

Table 1

Characteristics of the individual studies on XDR-TB and pre-XDR-TB among DR-TB patients in globally included in the current systematic review and meta-analysis.

First author, year	Study design	Country	WHO regions	Study period	MDR-TB	XDR-TB	Pre-XDR-TB	XDR-TB New	XDR-TB Previous treated	Pre-XDR-TB New	Pre-XDR-TB Previous treated	FQs resistance	SLIDs resistance
Adwani et al. [14]	cross-sectional	India	SEAR	2014	227	11	127	11	0	127	0	127	19
Agonafir et al. [15]	cross-sectional	Ethiopia	AFR	2005–2006	46	2	0	0	2	0	0	2	0
Araujo et al. [75]	cross-sectional	Brazil	AMR	2013–2019	33	2	3	1	1	1	2	5	2
Elion Assiana et al. [16]	cross-sectional	Congo	AFR	2018–2019	9	1	1	NR	NR	NR	NR	2	1
Banerjee et al. [17]	cross-sectional	California	AMR	1993–2006	424	18	77	NR	NR	NR	NR	NR	NR
Bedru et al. [18]	cross-sectional	Ethiopia	AFR	2017–2018	30	3	1	1	2	0	1	NR	NR
Calver et al. [19]	cross-sectional	South Africa	AFR	2003–2005	77	5	26	NR	NR	NR	NR	NR	NR
Chen et al. [20]	cross-sectional	China	WPR	2014 – 2015	51	0	24	0	0	10	14	24	0
Cheng et al. [21]	cross-sectional	Cambodia	WPR	2012–2017	118	3	16	NR	NR	NR	NR	15	5
Dagne et al. [20]	cross-sectional	Ethiopia	AFR	2019	99	1	8	NR	NR	NR	NR	7	3
Dala et al. [21]	cross-sectional	India	SEAR	2005–2013	340	33	193	NR	NR	NR	NR	179	41
Daniel et al. [24]	cross-sectional	Nigeria	AFR	2007–2011	50	0	10	0	10	0	10	8	NR
Diriba et al. [25]	cross-sectional	Ethiopia	AFR	2019	14	0	3	0	0	2	1	2	1
Ennassiri et al. [26]	cross-sectional	Morocco	EMR	2015	155	4	18	NR	NR	NR	NR	16	6
Gadhav et al. [27]	cross-sectional	India	SEAR	2019	700	23	143	NR	NR	NR	NR	106	58
Gallo et al. [28]	cross-sectional	Brazil	AMR	2011–2013	313	32	60	6	26	1	47	59	33
He et al. [29]	cross-sectional	China	WPR	2015	102	9	30	NR	NR	NR	NR	24	6
Jabbar et al. [30]	cross-sectional	Pakistan	EMR	2016–2017	62	5	0	NR	NR	NR	NR	5	5

First author, year	Study design	Country	WHO regions	Study period	MDR-TB	XDR-TB	Pre-XDR-TB	XDR-TB New	XDR-TB Previous treated	Pre-XDR-TB New	Pre-XDR-TB Previous treated	FQs resistance	SLIDs resistance
Jain et al. [31]	retrospective	India	SEAR	2007–2009	130	11	55	NR	NR	NR	NR	36	19
Jaksuwan et al. [32]	cross-sectional	Thailand	SEAR	2005–2012	24	1	9	NR	NR	NR	NR	NR	NR
James et al. [33]	cross-sectional	India	SEAR	2003 – 2007	103	45	0	NR	NR	NR	NR	NR	NR
Javaid et al. [34]	cross-sectional	Pakistan	EMR	2011–2012	132	2	65	NR	NR	NR	NR	67	5
Kozinska et al. [5]	cross-sectional	Poland	EUR	2000–2009	297	36	19	NR	NR	NR	NR	NR	NR
Kumar et al. [35]	cross-sectional	India	SEAR	2014–2016	173	3	33	1	2	5	28	NR	NR
Kuo et al. [36]	cross-sectional	Taiwan	WPR	2011–2015	63	4	0	NR	NR	0	0	4	4
Lai et al. [37]	cross-sectional	Taiwan	WPR	2000–2006	150	10	0	1	9	NR	NR	6	4
Lee et al. [38]	cross-sectional	South Korea	WPR	2011–2017	85	9	29	NR	NR	NR	NR	32	15
Lee et al. [39]	cross-sectional	Korea	WPR	2006–2013	145	55	0	27	28	0	0	43	12
Macedo et al. [40]	cross-sectional	Portugal	EUR	2008–2010	50	12	0	NR	NR	NR	NR	NR	NR
Madukaji et al. [41]	cross-sectional	Nigeria	AFR	2018–2019	101	12	16	NR	NR	NR	NR	5	12
Matsui et al. [42]	cross-sectional	Brazil	AMR	2016–2017	92	5	11	1	4	5	6	NR	NR
Mbuh et al. [43]	cross-sectional	Cameroon	AFR	2016–2017	75	1	2	0	1	0	2	NR	NR
Misra et al. [44]	cohort study	India	SEAR	2017–2019	62	48	11	NR	NR	NR	NR	48	11
Mohan et al. [45]	cross-sectional	India	SEAR	2012	87	3	0	NR	NR	NR	NR	NR	NR
Mok et al. [46]	cross-sectional	Korea	WPR	2010–2014	378	47	78	20	27	37	41	96	68
Momen et al. [47]	cross-sectional	Morocco	EMR	2015–2018	200	5	48	2	3	5	42	27	25
Namburete et al. [48]	cross-sectional	Mozambique	AFR	2014–2015	25	0	6	0	0	NR	NR	6	0

First author, year	Study design	Country	WHO regions	Study period	MDR-TB	XDR-TB	Pre-XDR-TB	XDR-TB New	XDR-TB Previous treated	Pre-XDR-TB New	Pre-XDR-TB Previous treated	FQs resistance	SLIDs resistance
Nguyen et al. [49]	cross-sectional	Vietnamese	WPR	2011	91	5	15	2	3	8	7	15	5
Noor et al. [50]	cross-sectional	Bangladesh	SEAR	2011–2012	59	2	9	0	2	0	9	7	2
Park et al. [51]	retrospective	Korea	WPR	2008	2,472	749	0	313	436	0	0	NR	NR
Poudel et al. [52]	cross-sectional	Nepal	SEAR	2007–2010	109	13	43	NR	NR	NR	NR	NR	NR
Qi et al. [53]	cross-sectional	China	WPR	2009–2011	249	31	77	10	21	NR	NR	89	41
Ramachandran et al. [54]	cross-sectional	India	SEAR	2005	216	7	0	0	7	NR	NR	52	10
Riccardi et al. [55]	retrospective	Italy	EUR	2000–2015	370	0	83	0	0	NR	NR	NR	NR
Salvato et al. [56]	cross-sectional	Brazil	AMR	2013–2014	87	4	8	NR	NR	NR	NR	NR	NR
Sethi et al. [57]	cross-sectional	India	SEAR	2018	687	59	265	6	53	103	192	295	70
Sharma et al. [58]	retrospective	India	SEAR	2003	211	5	25		5	NR	NR	21	14
Sharma et al. [59]	cross-sectional	India	SEAR	2014–2016	49	1	9	NR	NR	NR	NR	NR	NR
Shibabaw et al. [60]	cross-sectional	Ethiopia	AFR	2016–2018	176	1	10	1	0	1	9	NR	NR
Singhal et al. [61]	cross-sectional	India	SEAR	2012–2013	87	10	43	NR	NR	NR	NR	41	16
Tasnim et al. [62]	cross-sectional	Bangladesh	SEAR	2016–2017	68	4	11	1	3	3	8	9	2
Tuladhar et al. [63]	cross-sectional	Nepal	SEAR	2015	57	1	29	NR	NR	NR	NR	21	8
Ullah et al. [64]	retrospective	Pakistan	EMR	2019–2020	180	8	62	NR	NR	NR	NR	62	8
Vashakidze et al. [65]	cross-sectional	Georgia	EUR	2005–2007	261	33	96	6	27	NR	NR	75	54
Wang et al. [66]	cross-sectional	china	WPR	2008–2012	206	41	90	NR	NR	NR	NR	90	35
Wang et al. [67]	cross-sectional	china	WPR	2020	391	28	94	NR	NR	NR	NR	68	NR
Welekidan et al. [68]	cross-sectional	Ethiopia	AFR	2018–2019	38	0	2	NR	NR	NR	2	2	0
Xu et al. [69]	cross-sectional	China	WPR	2015–2018	17	0	9	NR	NR	1	8	9	NR

First author, year	Study design	Country	WHO regions	Study period	MDR-TB	XDR-TB	Pre-XDR-TB	XDR-TB New	XDR-TB Previous treated	Pre-XDR-TB New	Pre-XDR-TB Previous treated	FQs resistance	SLIDs resistance
Yang et al. [70]	cross-sectional	China	WPR	2008–2009	239	29	138	14	15	64	74	134	77
Yang et al. [71]	cross-sectional	Korea	WPR	2017	420	9	17	NR	NR	NR	NR	NR	NR
Yao et al. [13]	cross-sectional	China	WPR	2018–2019	425	29	282	NR	NR	NR	NR	311	171
Yuan et al. [72]	cross-sectional	China	WPR	2010–2011	77	16	26	NR	NR	NR	NR	16	13
Yuan et al. [73]	cross-sectional	China	WPR	2010–2011	159	13	0	3	10	NR	NR	NR	NR
Zheng et al. [74]	cross-sectional	China	WPR	2014–2016	88	9	44	NR	NR	NR	NR	34	11

AFR, African region; AMR, region of the Americas; DR-TB, drug-resistant tuberculosis; EMR, Eastern Mediterranean eegion; EUR, European region; FQs, fluoroquinolone; MDR-TB, multidrug-resistant tuberculosis; SEAR, South-East Asian region; SLID, second-line injectable drug; WPR, Western Pacific region; XDR-TB, extensively drug-resistant tuberculosis.