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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

Declaration of competing interests

The authors have no competing interests to declare.

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Not applicable.

Supplementary materials

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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.

Consent for publication

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

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.

with HIV, and the use of surgery for patients receiving MDR-TB treatment [8].

## 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 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.  $I^{2}$  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

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 FQs 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
ТВ	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.

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## 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.

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South-East Asian Region		
Adwani et al. (2016)	0.05 (0.03, 0.08)	1.93
Dala et al (2014)	0.10 (0.07, 0.13)	1.91
Gadhavi, et al. (2019)	0.03 (0.02, 0.05)	1.99
Jain et al. (2012)	0.08 (0.05, 0.15)	1.81
Jaksuwan et al. (2017)	0.04 (0.01, 0.20)	1.54
James et al. (2011)	0.44 (0.35, 0.53)	1.40
Kumar et al. (2020)	0.02 (0.01, 0.05)	1.97
Misra et al (2020)	0.77 (0.66, 0.86)	1.32
Mohan et al (2013)	0.03 (0.01, 0.10)	1.87
Noor et al. (2013)	0.03 (0.01, 0.12)	1.82
Poudel et al. (2013)	0.12 (0.07, 0.19)	1.70
Ramachandran et al (2009)	0.03 (0.02, 0.07)	1.95
Sethi et al (2019)	0.09 (0.07, 0.11)	1.96
Sharma et al. (2009)	0.02 (0.01, 0.05)	1.96
Sharma et al. (2017)	0.02 (0.00, 0.11)	1.86
Singhalet al. (2016)	0.11 (0.06, 0.20)	1.65
Tasnim et al. (2018)	0.06 (0.02, 0.14)	1.74
Tuladhar et al. (2018)	0.02 (0.00, 0.09)	1.90
Subtotal (l^2 = 94.54%, p = 0.00)	0.10 (0.06, 0.13)	32.30
African Region		
Agonafir et al. (2010)	0.04 (0.01, 0.15)	1.72
Assianaet al. (2021)	0.11 (0.02. 0.43)	0.67
Bedru et al. (2021)	0.10 (0.03. 0.26)	1.30
Calveret al. (2010)	0.06 (0.03. 0.14)	1.75
Dagne et al (2020)	0.01 (0.00 0.06)	1.97
Madukaji et al. (2021)	0.12 (0.07 0.20)	1.68
Mbuh et al. (2021)	0.01 (0.00. 0.07)	1.94
Shibabaw et al. (2020)	0.01 (0.00, 0.03)	1.99
Subtotal (I <sup>^</sup> 2 = 65.68%, p = 0.00)	0.03 (0.01, 0.05)	13.02
Region of the Americas		
Araújo et al. (2021)	0.06 (0.02, 0.20)	1.52
Banerjee et al. (2008)	0.04 (0.03, 0.07)	1.97
Gallo et al. (2017)	0.10 (0.07, 0.14)	1.90
Matsui et al. (2020)	0.05 (0.02, 0.12)	1.82
Salvato et al. (2020)	0.05 (0.02, 0.11)	1.83
Subtotal (I^2 = 57.54%, p = 0.05)	0.06 (0.03, 0.09)	9.05
Western Pacific Region		
Cheng et al (2021)	0.03 (0.01, 0.07)	1.93
He et al (2021)	0.09 (0.05, 0.16)	1.75
Kuo et al. (2018)	0.06 (0.02, 0.15)	1.71
Lai et al. (2008)	0.07 (0.04, 0.12)	1.86
Lee et al. (2017)	0.11 (0.06, 0.19)	1.67
Lee et al. (2015)	0.38 (0.30, 0.46)	1.55
Mok et al (2017)	0.12 (0.09, 0.16)	1.90
Nguyen et al (2016)	0.05 (0.02, 0.12)	1.81
Park et al. (2012)	0.30 (0.29, 0.32)	1.97
Qi et al (2011)	0.12 (0.09. 0.17)	1.86
Wang et al. (2014)	0.20 (0.15. 0.26)	1.76
Wang et al. (2021)	0.07 (0.05, 0.10)	1.94
Yang et al (2015)	0.12 (0.09. 0.17)	1.85
Yang et al (2018)	0.02 (0.01. 0.04)	1.99
Yao et al. (2021)	0.07 (0.05. 0.10)	1.95
Yuan et al (2012)	0.21 (0.13 0.31)	1.44
Yuan et al (2013)	0.08 (0.05. 0.13)	1.84
Zheng et al (2021)	0.10 (0.05, 0.18)	1.68
Subtotal (I <sup>A</sup> 2 = 97.64%, p = 0.00)	0.12 (0.07, 0.17)	32.46
Eastern Mediterranean Region		
Ennassiri et al. (2017)	0.03 (0.01, 0.06)	1.95
Jabbar et al. (2021)	0.08 (0.03, 0.18)	1.64
Javaid et al. (2017)	0.02 (0.00, 0.05)	1.96
Momen et al. (2021)	0.03 (0.01, 0.06)	1.96
Ullah et al. (2021)	0.04 (0.02, 0.09)	1.92
Subtotal (I^2 = 19.62%, p = 0.29)	0.03 (0.01, 0.04)	9.43
European Region		1.00
Nozinska et al. (2011)	0.12 (0.09, 0.16)	1.88
Vasnakidze et al (2009) Subtotal (I <sup>A</sup> 2 = .%, p = .)	0.13 (0.09, 0.17) 0.12 (0.10, 0.15)	3.74
Heterogeneity between groups; p = 0,000		
Overall (l^2 = 96.03%, p = 0.00);	0.09 (0.07, 0.11)	100.00
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## 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.

Advanti et al. (2016)         0.56 (0.4.9, 0.53) 2.30         Advanti et al. (2010)           Aquadret et al. (2011)         0.15 (0.05, 0.32) 2.12         Advanti et al. (2011)           Assign et al. (2011)         0.15 (0.05, 0.32) 2.12         Advanti et al. (2011)           Chen et al. (2011)         0.17 (0.33, 0.62) 2.30         Advanti et al. (2011)           Chen et al. (2011)         0.17 (0.33, 0.62) 2.30         Chenge et al. (2011)           Dage et al. (2011)         0.17 (0.30, 0.14) 2.31         Dage et al. (2011)           Danie et al. (2012)         0.14 (0.02, 0.43) 1.80         Envalue           Danie et al. (2011)         0.16 (0.02, 0.43) 1.80         Envalue           Break et al. (2011)         0.16 (0.01, 0.16) 2.32         Gedravit           Gallin et al. (2011)         0.16 (0.01, 0.16) 2.32         Gedravit           Jancher et al. (2011)         0.16 (0.01, 0.16) 2.32         Gedravit           Jancher et al. (2011)         0.16 (0.01, 0.16) 2.32         Gedravit           Jancher et al. (2012)         0.18 (0.21, 0.33) 2.25         Janiet al. (2012)           Janiet et al. (2012)         0.18 (0.21, 0.33) 2.25         Janiet al. (2012)           Janiet et al. (2012)         0.28 (0.21, 0.36) 2.26         Janiet al. (2012)           Janiet et al. (2012)         0.28 (0.21, 0.36) 2.26         Jan	a. (2016) (.(221) (.(221) (.(221) (.(221) (.(221) (.(220) (	008,005,013) 290 006,001,020) 227 011,000,048) 032 004,001,010) 290 003,001,039) 243 012,008,016) 243 004,001,008) 243 004,001,008) 248 006,002,014) 133 004,001,008) 246 006,002,012) 275 006,002,012) 258 004,001,009) 244 006,002,015) 255 005,001,007) 300 016,001,007) 300
Agonafriet al. (2010)         0.44 (0.01, 0.15)         2.10         Adaari           Araijo et al. (2021)         0.15 (0.05, 0.22)         2.12         Adaari           Chen et al. (2021)         0.15 (0.05, 0.22)         2.12         Adaari           Chen et al. (2021)         0.17 (0.05, 0.22)         2.20         Chen et al. (2021)         0.17 (0.05, 0.22)         2.20           Dagre et al. (2021)         0.17 (0.05, 0.21)         2.21         Dagre et al. (2021)         Dagre et al. (20	4. (2016) (. (2021) 4. (2021) 4. (2021) 4. (2020) (2020) (2020) (2020) (2021)	008 (005,013) 290 009 (001,020) 227 001 (000,08) 092 004 (001,00) 260 003 (001,09) 263 012 (009,034) 133 004 (001,008) 296 008 (000,034) 133 004 (001,008) 296 008 (000,011) 304 011 (007,014) 292 008 (002,015) 258 004 (002,015) 259 005 (002,015) 305 015 (002,015) 30
Analje et al. (2021)         0.15 (0.05, 0.02) 2.12         Analje et al. (2017)           Ohen et al. (2017)         0.47 (0.33, 0.62) 2.00         Analje et al. (2017)           Ohen et al. (2017)         0.47 (0.33, 0.62) 2.00         Analje et al. (2017)           Date et al. (2011)         0.31 (0.07, 0.29) 2.30         Ohen et al. (2011)           Date et al. (2011)         0.31 (0.07, 0.29) 2.30         Ohen et al. (2011)           Date et al. (2012)         0.15 (0.07, 0.29) 2.31         Date et al. (2012)           Date et al. (2012)         0.14 (0.02, 0.41) 2.31         Date et al. (2017)           Ontrea et al. (2017)         0.15 (0.13, 0.11) 2.25         Garbard, et al. (2017)           Garbard, et al. (2017)         0.19 (0.15, 0.13) 2.25         Jahr et al. (2017)           Jahr et al. (2017)         0.19 (0.15, 0.13) 2.25         Jahr et al. (2017)           Jahr et al. (2017)         0.19 (0.15, 0.13) 2.25         Jahr et al. (2017)           Jahr et al. (2017)         0.19 (0.15, 0.13) 2.25         Jahr et al. (2017)           Jahr et al. (2017)         0.19 (0.15, 0.13) 2.25         Jahr et al. (2017)           Kuo et al. (2017)         0.19 (0.15, 0.13) 2.25         Jahr et al. (2017)           Kuo et al. (2017)         0.19 (0.16, 0.17) 2.31         Lee et al. (2018)           Madual) et al. (2017)         0.14	L (221) 4 (221) 4 (221) 4 (221) (221) (222) (	006(001,020) 227 0.11(000,046) 042 004(001,010) 240 005(001,046) 242 007(000,034) 153 004(001,006) 246 006(002,013) 246 006(002,012) 275 006(002,012) 275 006(002,013) 247 015(005,022) 255 004(001,009) 244 006(002,015) 259 003(001,007) 300 016(01,027) 237
Assignant al. (2011)         0.22 (0.03, 0.60) (1.5)         Assigna           Chen et al. (2017)         0.17 (0.33, 0.62) 2.07         Assigna           Chang et al. (2021)         0.13 (0.07, 0.20) 2.30         Chang et al. (2021)           Dans et al. (2021)         0.15 (0.07, 0.31) 2.31         Date et al. (2017)           Dans et al. (2017)         0.16 (0.07, 0.20) 2.31         Date et al. (2017)           Dans et al. (2020)         0.14 (0.02, 0.41) 1.80         Emresia           Dinha et al. (2017)         0.15 (0.15, 0.24) 2.33         Gabra et al. (2017)           Gabra et al. (2017)         0.15 (0.16, 0.24) 2.33         Gabra et al. (2017)           Gabra et al. (2017)         0.16 (0.06, 0.16) 2.32         Gabra et al. (2017)           Janse et al. (2012)         0.24 (0.16, 0.31) 2.25         Jabrae et al. (2012)           Janse et al. (2012)         0.24 (0.16, 0.31) 2.25         Jabrae et al. (2012)           Janse et al. (2012)         0.28 (0.20, 0.36) 2.26         Jabrae et al. (2012)           Janse et al. (2012)         0.28 (0.27, 0.49) 2.19         Loe (d al. (2017)           Loe et al. (2017)         0.36 (0.27, 0.49) 2.14         Loe (d al. (2017)           Loe et al. (2017)         0.36 (0.27, 0.49) 2.15         Loe (d al. (2017)           Loe et al. (2017)         0.48 (0.06, 0.16) 2.20	(2021) (2021) (2020)	019 (02 048) 042 019 (02 048) 042 004 (001,010) 249 003 (001,009) 243 012 (006,016) 243 014 (001,008) 243 014 (005,016) 246 016 (006,011) 304 016 (002,012) 275 006 (002,012) 258 004 (001,009) 244 006 (002,015) 255 003 (001,007) 300 016 (010,077) 300
Chen et al. (2017) Chen et al. (2021) Degre et al. (2022) Degre et al. (2021) Degre et	8.(221) (2220) (2220) (2220) (2221) (2220) (2221) (2221) (2221) (2222) (2221) (2222) (2222) (2221) (2222) (222) (2222)	04(00,00) 052 005(00,00) 263 012(005,00) 263 007(00,034) 153 006(005,00) 265 006(005,01) 304 011(007,014) 262 006(005,012) 275 006(005,015) 265 006(005,015) 265 005(005,007) 300 016(010,07) 300
Cheng et al (2021) Dans et al (2020) Dans et al (2020) Dans et al (2013) Dans et al (2013) Dans et al (2013) Dans et al (2014) Dans et al (2020) Envisati et al (2020) Envisati et al (2020) Bina et al (2020) Difference et al (2020) Dif	(2021) (2020) (2020) (2020) (2020) (2020) (2020) (2017)	004(001,010) 290 003(001,09) 263 017(000,034) 153 004(001,034) 153 004(001,034) 153 006(002,011) 304 016(002,012) 275 006(002,012) 275 006(002,012) 275 016(002,012) 255 004(001,009) 294 006(002,015) 259 003(001,007) 300 016(010,027) 230
Degree et al (2020)         Degree et al (2021)         Degree et al (2013)         Degree et al (2013) <thdegree (2013)<="" al="" et="" th="">         Degree et al (2013)</thdegree>	2014) 2014) 4.1 (2017) 2014) 4.1 (2017) 2010)	003,003,009, 283 012,009,018, 282 007,000,034, 153 004,001,008, 286 005,002,011, 304 011,007,014, 282 006,002,012, 275 005,002,012, 258 004,003,039, 244 006,002,015, 255 003,001,007, 300 015,001,007, 300
Data et al (2014)         0.51 (6.47, 0.58) (2.31)         Disk et al (2015)           Darai et al (2017)         0.16 (6.07, 0.29) (2.18)         Dirba et al (2017)         Dirba et al (2017)           Banassi et al (2017)         0.16 (6.017, 0.29) (2.28)         Gallo et al (2017)         Dirba et al (2017)           Gallo et al (2017)         0.15 (6.013, 0.18) (2.25)         Gadhavi, et al (2017)         Dirba et al (2017)           He et al (2021)         0.24 (0.16, 0.39) (2.28)         Hert al (2021)         Dirba et al (2017)           Jain et al (2021)         0.24 (0.16, 0.39) (2.24)         Jain et al (2021)         Jain et al (2017)           Jain et al (2017)         0.28 (0.20, 0.38) (2.24)         Jain et al (2017)         Dirba et al (2017)           Kuo et al (2017)         0.06 (0.02, 0.18) (2.21)         Jain et al (2017)         Dirba et al (2017)           Kuo et al (2017)         0.06 (0.02, 0.18) (2.21)         Jain et al (2017)         Dirba et al (2017)           Kuo et al (2017)         0.06 (0.02, 0.18) (2.21)         Jain et al (2017)         Dirba et al (2017)           Koo et al (2017)         0.05 (0.02, 0.18) (2.21)         Jain et al (2017)         Dirba et al (2017)           Koo et al (2017)         0.05 (0.02, 0.18) (2.21)         Jain et al (2018)         Jain et al (2018)           Koo et al (2017)         0.05 (0.02, 0.21) (2	2016) (222) (222) (222) (217) (2	0.12 (0.05, 0.16) 252 0.07 (0.00, 0.34) 153 0.04 (0.01, 0.08) 256 0.05 (0.06, 0.11) 304 0.11 (0.07, 0.14) 252 0.06 (0.02, 0.12) 275 0.05 (0.02, 0.12) 275 0.05 (0.02, 0.12) 255 0.04 (0.01, 0.05) 255 0.05 (0.01, 0.07) 207 0.15 (0.07, 1.07) 300
Damie et al. (2013)         0.146 (0.07, 0.29) 2.19         Dribes           Dinna et al. (2020)         0.14 (0.02, 0.43) 1.80         Emeasule et al. (2017)         Dribes           Binna et al. (2017)         0.16 (0.02, 0.43) 1.80         Emeasule et al. (2017)         Dribes         Emeasule et al. (2017)         Dribes         Emeasule et al. (2017)         Dribes         Dribes         Emeasule et al. (2017)         Dribes         Dribes         Emeasule et al. (2017)         Dribes         Dribes         Emeasule et al. (2011)         Dribes         Dribes         Dribes         Emeasule et al. (2011)         Dribes	(2020) (a) (2017) (a) (2019) (a) (2019) (a) (2019) (a) (2021) (a) (2021) (a) (2021) (a) (2021) (a) (a) (a) (a) (a) (a) (a) (a) (a) (a)	007(000.034) 153 004(001.006) 256 008(004.011) 304 016(002.012) 275 006(002.012) 275 006(002.012) 275 016(005.022) 255 004(001.009) 294 006(002.015) 255 003(001.007) 300 016(0.027) 300
Diffs et al. (2020)         0.14 (0.02, 0.43) 1.89         Erransi           Binnasciel et al. (2011)         0.16 (0.06, 0.46) 2.32         Gadravi, et al. (2011)         0.16 (0.06, 0.46) 2.32         Gadravi, et al. (2011)         0.16 (0.16, 0.31) 2.35         Gadravi, et al. (2011)           Jacobar et al. (2011)         0.24 (0.06, 0.46) 2.32         Batto et al. (2011)         0.24 (0.16, 0.31) 2.25         Heet al.           Jacobar et al. (2011)         0.24 (0.16, 0.31) 2.26         Jacobar et al. (2012)         Jacobar et al. (2012)         Jacobar et al. (2012)         Jacobar et al. (2012)         Jacobar et al. (2017)         Jacobar et al. (2018)         Jacobar et al. (2011)	ral (2017) cal (2019) (2017) (2017) (2012) (2012) (2012) (2017) (2018) (2017) (2019) (2017) (2019) (2017) (2019) (2017)	004 (001,008) 298 008 (006,011) 304 011 (007,014) 292 008 (002,012) 219 008 (002,012) 219 004 (002,012) 258 004 (001,009) 244 006 (002,015) 259 005 (001,007) 300 016 (010,07) 300
Bindsatil et al. (2017)         0.10 (0.06, 0.51) (2.22)         Gadravi, et al. (2017)         0.15 (0.13, 0.15) (2.25)         Gadravi, et al. (2017)           Gallo et al. (2017)         0.15 (0.15, 0.15) (2.25)         Gadravi, et al. (2011)         0.15 (0.15, 0.15) (2.25)         Gadravi, et al. (2011)           Jan et al. (2011)         0.24 (0.16, 0.35) (2.25) (2.26)         Jan et al. (2011)         Jan et al. (2012)         Jan et al. (2011)           Jan et al. (2011)         0.05 (0.02, 0.15) (2.26)         Jan et al. (2011)         Jan et al. (2011)         Jan et al. (2011)           Jan et al. (2011)         0.05 (0.02, 0.15) (2.20)         Jan et al. (2011)         Jan et al. (2011)         Jan et al. (2011)           Lai stal. (2002)         0.015 (0.17) (2.16)         0.06 (0.02, 0.15) (2.30)         Koret al. (2011)           Lai stal. (2002)         0.015 (0.22, 0.15) (2.30)         Koret al. (2011)         Jan et al. (2011)         Jan et al. (2011)           Madsual) et al. (2021)         0.016 (0.22, 0.11) (2.33)         Lee et al. (2011)         Jan et al. (2011)         Jan et al. (2011)           None et al. (2011)         0.016 (0.02, 0.17) (2.31)         Jan et al. (2011)         Jan et al. (2011)         Jan et al. (2011)           None et al. (2011)         0.16 (0.02, 0.22) (2.24)         Jan et al. (2011)         Jan et al. (2011)         Jan et al. (2011)	L (2019) L (2017) L (201	006(006,011) 304 011(007,014) 292 006(002,012) 279 006(002,012) 279 006(002,012) 247 015(009,022) 258 004(001,009) 294 006(002,015) 259 003(001,007) 300 016(0,010,027) 237
Gabhard, et al. (2017)         0.15 (0.13, 0.18) (2.35         Gabbard           He et al. (2011)         0.15 (0.14, 0.18) (2.35         Gabbard           Janober et al. (2011)         0.24 (0.16, 0.33) (2.26         Jababard           Janober et al. (2011)         0.24 (0.16, 0.33) (2.26         Jababard           Janober et al. (2011)         0.28 (0.2, 0.36) (2.26         Jababard           Janober et al. (2012)         0.05 (0.2, 0.36) (2.26         Jababard           Janober et al. (2017)         0.05 (0.2, 0.36) (2.26         Jababard           Lai et al. (2017)         0.05 (0.2, 0.36) (2.26)         Jababard           Lai et al. (2017)         0.36 (0.27, 0.49) (2.19         Jababard           Loo et al. (2017)         0.38 (0.27, 0.49) (2.19         Jababard           Loo et al. (2017)         0.36 (0.27, 0.49) (2.19         Jababard           Messa et al (2017)         0.36 (0.27, 0.49) (2.19         Jababard           Messa et al (2017)         0.36 (0.27, 0.49) (2.19         Mastabard           Messa et al (2017)         0.36 (0.27, 0.49) (2.12         Mastabard           Monos et al. (2017)         1         0.36 (0.27, 0.49) (2.12         Mastabard           Monos et al. (2017)         1         0.36 (0.20, 0.42) (2.16)         Mastabard           Monos et al. (2011	2017) 121) 121) 12202) 2102) 2103) 2103 2003 2	011007.014) 292 006002.012) 279 068003.016) 247 015009.022) 258 004001.006) 294 006002.015) 259 003001.007 300 018.010.027 227
Gallo et J., (2017)         0.19 (5.15, 0.24) 2.33         Moet S.           Jabour et J., (2021)         0.24 (0.16, 0.33) 2.25         Hoet S.           Jabour et J., (2021)         0.24 (0.16, 0.33) 2.25         Hoet S.           Jabour et J., (2021)         0.24 (0.26, 0.35) 2.26         Jabour et J., (2021)           Jabour et J., (2012)         0.25 (0.26, 0.35) 2.26         Jabour et J., (2017)           Lai et J., (2017)         0.05 (0.02, 0.55) 2.30         Kue et J., (2017)           Lai et J., (2017)         0.35 (0.22, 0.35) 2.31         Kue et J., (2017)           Lai et J., (2017)         0.36 (0.22, 0.35) 2.32         Kue et J., (2017)           Loe et J., (2017)         0.36 (0.22, 0.31) 2.33         Loe et J., (2017)           Loe et J., (2017)         0.36 (0.22, 0.31) 2.33         Loe et J., (2017)           Monauxia, (0.201)         0.05 (0.22, 0.31) 2.33         Moet S.           Morauxia, (0.201)         0.05 (0.20, 0.11) 2.33         Moet S.           Morauxia, (0.201)         0.14 (0.06, 0.15) 2.33         Moet S.           Macroschanter et J. (2011)         0.14 (0.06, 0.15) 2.33         Moet S.           Macroschanter et J. (2011)         0.14 (0.16, 0.02) 2.32         Moet S.           Macroschanter et J. (2011)         0.14 (0.16, 0.15) 2.33         Moet S.           Ma	(2017) A (2021) A (2021) 2012) 2013) 2019) 2019) 2017) 2019) 2017) 2019) 2017) 2019) 2017) 2019 2017) 2017 20	016 (002,012) 279 006 (002,012) 279 066 (001,016) 247 015 (009,022) 258 04 (001,009) 284 006 (002,015) 259 003 (001,007) 300 018 (010,027) 227
He et al (2021) Januel et al. (2021) Janue	221) (2021) (2017) (2017) (2017) (2018) (2018) (2017) (2019) (2017) (2019) (2017)	006(002,012) 2/9 006(003,016) 247 0.15(009,022) 258 0.04(002,015) 259 0.03(001,007) 300 0.18(0.10,027) 227
Jacker et al. (2021)         0.08 (0.0), 0.18 (2.28)         Jacker al. (2021)           Jain et al. (2012)         0.28 (2.0, 0.36) (2.24)         Jacker al. (2012)           Jain et al. (2018)         0.04 (0.0), 0.08 (2.26)         Jacker al. (2017)           Los et al. (2018)         0.04 (0.0), 0.09 (2.24)         Jacker al. (2017)           Los et al. (2017)         0.31 (0.42, 0.00) (2.24)         Jacker al. (2018)           Los et al. (2017)         0.38 (0.27, 0.49) (2.19)         Los et al. (2017)           Moscular, Jos et al. (2021)         0.01 (0.00, 0.08) (2.2, 0.11) (2.3)         Los et al. (2017)           Moscular, Jos et al. (2021)         0.01 (0.0, 0.18) (2.32)         Mick et al. (2017)           Mosture et al. (2021)         4         0.14 (0.00, 0.18) (2.32)         Mick et al. (2017)           Mosture et al. (2011)         4         0.14 (0.00, 0.18) (2.32)         Mick et al. (2018)           Noor et al. (2011)         4         0.14 (0.00, 0.18) (2.32)         Mick et al. (2018)           Noor et al. (2013)         0.12 (0.06, 0.23) (2.24) (3.26)         Morter           Steffi et al. (2018)         0.34 (0.20, 0.47) (2.30) (2.4) (3.20) (3.4) (3.4) (3.20	((221)) 210) 211() 2	0.08 (0.01, 0.16) 2.47 0.15 (0.09, 0.22) 2.58 0.04 (0.01, 0.09) 2.94 0.05 (0.02, 0.15) 2.59 0.03 (0.01, 0.07) 3.00 0.15 (0.10, 0.27) 2.27
Jain et al. (2012 Jain et al. (2017) Kuo et al. (2018) Lai et al. (2017) Kuo et al. (2018) Lai et al. (2017) Kuo et al. (2018) Lai et al. (2017) Los et al. (2017) Mediual (et al. (2011) Mediual (et al. (2015) Mediual (et al. (2018) Mediual (et al. (2011) Mediual (et al. (201	2012) 1.(2017) 2018) 2018) 2017) 2017) 2019 2017) 2019 2017) 2019 2017 2019 2017 2	0.15(0.09,0.22) 2.58 0.04(0.01,0.09) 2.94 0.06(0.02,0.15) 2.59 0.03(0.01,0.07) 3.00 0.18(0.10,0.27) 2.27
Javaide et al. (2017 (Javaide et al. (2017) Lis et al. (2018) Lis et al. (2018) Lis et al. (2017) Lis et al. (2017) Monument al. (2027) Monument al. (2020) Monument al. (2021) Monument al. (2011) Lis et al. (2011) Monument al. (2011) Lis et al. (20	L (2017) 22:15) 22:17) 2017) 	0.04(0.01,0.09) 2.94 0.06(0.02,0.15) 2.59 0.03(0.01,0.07) 3.00 0.18(0.10,0.27) 2.27
Kuo et al. (2019)         0.065 (0.02, 0.51); 2.30         Kuo et al. (2017)           Los et al. (2007)         0.36 (0.27, 0.49); 2.19         Los et al. (2017)           Los et al. (2017)         0.36 (0.27, 0.49); 2.19         Los et al. (2017)           Los et al. (2017)         0.36 (0.27, 0.49); 2.19         Los et al. (2017)           Modulari (et al. (2017)         0.36 (0.27, 0.49); 2.19         Los et al. (2017)           Modulari (et al. (2017)         0.36 (0.27, 0.49); 2.19         Los et al. (2017)           Modulari (et al. (2017)         0.36 (0.27, 0.49); 2.13         Los et al. (2017)           Mohen et al. (2020)         0.77 (0.66, 0.87); 2.18         Madulari (et al. (2017)           Mohen et al. (2011)         1         0.14 (0.09, 0.19); 2.33         Mik et al. (2011)           Namo-curste at al (2011)         1         0.14 (0.09, 0.19); 2.33         Mik et al. (2011)           Namo-curste at al (2011)         0.12 (0.06, 0.23); 2.24         Nayter           Noor et al. (2011)         0.12 (0.06, 0.23); 2.30         Of et al. (2015)           State at al (2015)         0.34 (0.30, 0.47); 7 70         Ramachanet al. (2015)           State at al (2015)         0.34 (0.30, 0.47); 7 70         Ramachanet al. (2015)           Viandetal. (2018)         0.13 (0.06, 0.24); 2.28         Testing           Uta	2018) 	0.06(0.02,0.15) 2.59 0.03(0.01,0.07) 3.00 0.18(0.10,0.27) 2.27
La stal. (2008) La stal. (2007) Los et al. (2017) Los et al. (2017) Los et al. (2017) Los et al. (2017) Madual) et al. (2011) Madual) et al. (2011) Madu	000) 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	0.03(0.01,0.07) 300 0.18(0.10,0.27) 227
Lee et al. (2017)         0.38 (0.27, 0.49) 2,19         Lee et al. (2017)           Lee et al. (2016)         0.30 (0.27, 0.39) 2,17         Lee et al. (2017)           Meducal) et al. (2021)         0.05 (0.02, 0.11) 2,33         Lee et al. (2017)           Mone et al. (2017)         0.17 (0.66, 0.17) 2,18         Market           Menon et al. (2017)         0.14 (0.09, 0.16) 2,32         Market           Manounse et al. (2011)         0.14 (0.09, 0.16) 2,32         Market           Namounse et al. (2011)         0.16 (0.10, 0.26) 2,26         Market           Namounse et al. (2011)         0.16 (0.10, 0.26) 2,26         Nomer           Nore et al. (2011)         0.16 (0.10, 0.26) 2,26         Nomer           Nore et al. (2011)         0.16 (0.10, 0.26) 2,26         Nomer           Nore et al. (2011)         0.36 (0.30, 0.42) 2,30         Of et al.           Semi et al. (2016)         0.24 (0.19, 0.30) 2,30         Of et al.           Semi et al. (2016)         0.24 (0.19, 0.30) 2,30         Of et al.           Semi et al. (2016)         0.24 (0.19, 0.30) 2,30         Of et al.           Taskine et al. (2016)         0.24 (0.19, 0.30) 2,30         Of et al.           Semi et al. (2018)         0.10 (0.06, 0.15) 2,33         Sehi et al.           Utashet et al. (2018)         0.16 (0.06,	2017)	018(010,027) 227
Lee et al. (2019)         0.30 (6.22, 0.39) 2.37         Lee et al.           Medualiji et al. (2021)         0.05 (6.22, 0.11) 2.33         Lee et al.           Medualiji et al. (2021)         0.05 (6.2, 0.11) 2.33         Lee et al.           Metualiji et al. (2021)         0.05 (6.2, 0.11) 2.33         Met al.           Metualiji et al. (2021)         0.05 (6.2, 0.11) 2.33         Met al.           Metualiji et al. (2021)         0.14 (0.00, 0.15) 2.32         Mik at.           Namouste at al (2011)         0.14 (0.00, 0.15) 2.32         Mik at.           Namouste at al (2011)         0.16 (0.0, 0.23) 2.24         Nayaen           Namouste at al (2011)         0.12 (0.06, 0.22) 2.24         Nayaen           Gi et al (2011)         0.12 (0.05, 0.23) 2.30         Gi et al.           Gi et al (2011)         0.24 (0.15) 0.30 2.30         Gi et al.           Gi et al (2015)         0.34 (0.30, 0.47) 7.33         Ramachanteria           Starris et al (2015)         0.43 (0.39, 0.47) 7.33         Ramachanteria           Starris et al (2015)         0.43 (0.39, 0.47) 7.33         Ramachanteria           Valance et al. (2018)         0.47 (0.34, 0.31) 2.31         Starris di al.           Valance et al. (2018)         0.37 (0.24, 0.31) 2.31         Starris di al.           Valance et al. (2014)	2015)	the FORMATION MADE IN A REPORT OF THE PARTY
Macsuzi et al. (2021)         0.05 5.022, 0.11 2.33         Macsuzi et al. (2021)           Mossu et al. (2021)         0.25 6.02, 0.11 2.33         Macsuzi et al. (2021)           Monen et al. (2021)         0.25 6.02, 0.11 2.33         Macsuzi et al. (2021)           Monen et al. (2021)         0.25 6.017, 2.18         Mackuzi et al. (2021)           Monen et al. (2021)         0.24 6.05, 0.17 2.18         Mackuzi et al. (2021)           Navouris et al. (2021)         0.24 6.05, 0.27 2.24         Mayper           Noor et al. (2013)         0.12 (0.05, 0.27) 2.24         Mayper           O et al. (2011)         0.24 (0.19, 0.45) 2.32         Macre et al. (2011)           O et al. (2011)         0.24 (0.19, 0.42) 2.26         Naver           Sami et al. (2019)         0.24 (0.19, 0.42) 2.36         Nore et al. (2011)           Shema et al. (2016)         0.47 (0.26, 0.27) 2.26         Narra           Singhaver et al. (2018)         0.17 (0.06, 0.31) 2.11         Schi et al. (2018)           Tuland et al. (2018)         0.17 (0.28, 0.47) 2.28         Schi et al. (2011)           Viana et al. (2014)         0.37 (0.28, 0.47) 2.28         Schi et al. (2011)           Viana et al. (2012)         0.47 (0.38, 0.37) 2.21         Tarimi et al. (2021)           Viana et al. (2021)         0.47 (0.37, 0.35) 2.31         Ulabre et al.	2010	000004040 000
Missi et al (2020) Mole et al (2021) Monen et al.	- 144444 MB	006(004,0.14) 2.60
Mone et al. (2017)         0.25 (0.21, 0.00) 2.33         More et al. (2011)         More et al. (2021)         More et al. (2021)         More et al. (2011)         Mor	(al.(2021)	0.12(0.06, 0.20) 2.54
Momen et al. (2021)         I         0.14 (0.09, 0.19) 2.32         Mix eta Monter           Namountis et al (2016)         0.24 (0.09, 0.45) 1.96         Monter           Navore et al (2016)         0.16 (0.10, 0.26) 2.26         Naver           Noor et al (2017)         0.12 (0.06, 0.25) 2.24         Naver           Noor et al (2018)         0.16 (0.10, 0.26) 2.26         Naver           Noor et al (2011)         0.36 (0.00, 0.42) 2.26         Naver           Ramachandran et al (2019)         0.24 (0.19, 0.30) 2.30         Of et al (2011)           Setti et al (2016)         0.16 (0.06, 0.15) 2.33         Setti et al (2016)           Setti et al (2016)         0.10 (0.06, 0.15) 2.33         Setti et al (2016)           Stati et al (2016)         0.10 (0.06, 0.15) 2.33         Setti et al (2016)           Visionhaut al (2016)         0.10 (0.06, 0.15) 2.33         Setti et al (2016)           Visionhaut al (2016)         0.10 (0.06, 0.15) 2.31         Singhaid           Visionhaut al (2011)         0.37 (0.24, 0.31) 2.11         Singhaid           Visionhaut al (2011)         0.34 (0.28, 0.35) 2.31         Tabérin           Visionhaut al (2017)         0.24 (0.17, 0.14) 2.22         Visiohau           Visionhaut al (2017)         0.35 (0.21, 0.15) 2.21         Visiohau           Visionha	(2020)	0.18(0.09, 0.30) 2.05
Namburde at al (001)         0.24 (0.09, 0.49) 1.36         Moner           Nave at al (001)         0.16 (0.0, 0.29) 2.26         Moner           Nov et al (001)         0.12 (0.06, 0.23) 2.24         Novet           Ramachandrau et al (001)         0.24 (0.19, 0.30) 2.30         Of et al (2011)           G et al (2011)         0.36 (0.30, 0.22) 2.34         Novet           Ramachandrau et al (2009)         0.24 (0.19, 0.30) 2.30         Of et al (2011)           Stelli et al (2019)         0.43 (0.30, 0.077) 7.10         Ramachandrau et al (2009)           Shama et al (2009)         0.16 (0.06, 0.15) 2.33         Sathi et al (2011)           Utaph et al (2018)         0.17 (0.36, 0.50) 2.31         Sathi et al (2011)           Utaph et al (2018)         0.13 (0.06, 0.15) 2.33         Sathi et al (2018)           Utaph et al (2018)         0.37 (0.34, 0.31) 2.11         Singhatet al (2018)           Utaph et al (2018)         0.37 (0.34, 0.31) 2.28         Tashim et al (2011)           Utaph et al (2014)         0.34 (0.27, 0.51) 2.28         Tashim et al (2014)           Vashatiche et al (2014)         0.44 (0.27, 0.51) 2.28         Utaph et al (2014)           Vashatiche et al (2014)         0.47 (0.31, 0.22) 2.23         Vashati Vashatiche et al (2014)           Vashatiche et al (2014)         0.47 (0.31, 0.22) 2.23	(17) I <del>I</del>	0.18(0.14,0.22) 2.87
Nauven dial (2019)         0.116 (0.10, 0.20) 2.26         Nayyen           0 et al (2011)         0.12 (0.05, 0.21) 2.24         Nayyen           0 et al (2011)         0.36 (0.30, 0.42) 2.30         Norrel           Ramachandran et al (2009)         0.24 (0.15, 0.30) 2.30         Of et al           Shama et al. (2009)         0.418 (0.16, 0.21) 2.36         Nayen           Shama et al. (2009)         0.19 (0.06, 0.15) 2.33         Ramachandran et al. (2011)           Tashim et al. (2018)         0.19 (0.06, 0.15) 2.33         Schrift et al. (2011)           Tuadrar et al. (2018)         0.17 (0.24, 0.51) 2.11         Schrift et al. (2011)           Vanna et al. (2011)         0.37 (0.24, 0.51) 2.11         Tashim et al. (2011)           Vanna et al. (2011)         0.37 (0.21, 0.23) 2.35         Schrift et al. (2011)           Vanna et al. (2011)         0.17 (0.14, 0.22) 2.23         Vanhalicha et al. (2021)           Vanhalicha et al. (2021)         0.17 (0.14, 0.22) 2.23         Vanhalicha et al. (2021)           Vanhalicha et al. (2021)         0.17 (0.14, 0.22) 2.23         Vanhalicha et al. (2021)           Vanhalicha et al. (2021)         0.17 (0.14, 0.22) 2.23         Vanhalicha et al. (2021)           Van et al (2015)         0.06 (0.01, 0.18) 2.27         Vanhalicha et al. (2021)           Van et al (2015)         0.06 (0	sl.(2021)	0.13(0.08, 0.18) 2.78
Noor et al. (2013)         0.12 (200, 0.22) (2.24         Noor et al. (2011)           Q et al. (2011)         0.36 (0.30, 0.42) (2.30)         Q et al. (2011)           Setti al. (2015)         0.41 (0.30, 0.42) (2.30)         Q et al. (2011)           Setti al. (2015)         0.41 (0.30, 0.42) (2.30)         Q et al. (2011)           Setti al. (2015)         0.41 (0.30, 0.42) (2.33)         Setti al. (2015)           Setti al. (2016)         0.13 (0.06, 0.15) (2.33)         Setti al. (2015)           Tashim et al. (2018)         0.13 (0.06, 0.15) (2.31)         Singhaid           Utalante al. (2011)         0.34 (0.23, 0.35) (2.31)         Tashim et al. (2011)           Utalante al. (2011)         0.24 (0.31, 0.31) (2.11)         Tashim et al. (2021)           Vianand et al. (2021)         0.29 (0.23, 0.35) (2.31)         Tashim           Wang et al. (2011)         0.44 (0.37, 0.51) (2.22)         Utalante al. (2021)           Wang et al. (2021)         0.55 (0.21, 0.31) (2.22)         Utalante al. (2021)           Wang et al. (2021)         0.55 (0.21, 0.31) (2.22) (2.33)         Valadati al. (2021)           Vianante al. (2021)         0.55 (0.21, 0.31) (2.22) (2.33)         Valadati al. (2021)           Vianante al. (2021)         0.55 (0.21, 0.31) (2.22) (2.33)         Valadati al. (2021) (2.22) (2.33)           Vianatal. (2021)	a (2016)	0.05(0.02(0.12)) 277
D af all (2011)         0.36 (5.00, 0.42) 2.30         Q et al.           Setti et al (2015)         0.24 (5.10, 0.30) 2.30         Q et al.           Setti et al (2015)         0.24 (5.10, 0.30) 2.30         Q et al.           Shamathamet al. (2016)         0.24 (5.10, 0.30) 2.30         Q et al.           Shamathamet al. (2016)         0.24 (5.10, 0.30) 2.30         Q et al.           Shamathamet al. (2016)         0.13 (0.06, 0.15) 2.33         Softi et al.           Taxinin et al. (2016)         0.17 (0.36, 0.50) 2.11         Startine et al.           Ustan et al. (2018)         0.37 (0.34, 0.31) 2.11         Startine et al.           Ustan et al. (2018)         0.34 (0.28, 0.42) 2.28         Testrim           Vashalicze et al. (2019)         0.24 (0.23, 0.35) 2.31         Tastrim           Vashalicze et al. (2011)         0.47 (0.14, 0.22) 2.33         Vashalicze et al.           Wang et al. (2014)         0.47 (0.14, 0.22) 2.33         Vashalicze et al.           Vashalicze et al. (2021)         0.17 (0.14, 0.22) 2.33         Vashalicze et al.           Vashalicze et al. (2021)         0.17 (0.14, 0.22) 2.33         Vashalicze et al.           Vashalicze et al. (2021)         0.36 (0.50, 0.61) 2.27         Vashalicze et al.           Vashalicze et al. (2021)         0.36 (0.50, 0.61) 2.23         Vashalicze et al. <td>20175</td> <td>0.03.000.0121 278</td>	20175	0.03.000.0121 278
Ramachandrain of all 80091         0.24 (0.1%, 0.50) (2.30)         0.64 (0.1%)           Shemi et al. (2005)         0.43 (0.00, 0.47) (7.33)         Ramachandrain et al. (2006)           Shemi et al. (2006)         0.16 (0.06, 0.58) (2.33)         Sehiri et al. (2006)           Singhaleet al. (2016)         0.47 (0.36, 0.58) (2.33)         Sehiri et al. (2016)           Tulacher et al. (2018)         0.37 (0.26, 0.28) (2.31)         Singhaleet al. (2018)           Utaha et al. (2018)         0.37 (0.26, 0.43) (2.11)         Tashim           Vashakictae et al. (2018)         0.36 (0.23, 0.42) (2.28)         Tashim           Wang et al. (2011)         0.34 (0.21, 0.51) (2.21)         Tashim           Wang et al. (2021)         0.47 (0.36, 0.27) (2.23)         Walking the tal. (2021)           Wang et al. (2021)         0.47 (0.36, 0.27) (2.23)         Walking tal. (2021)           Vashakictae et al. (2021)         0.47 (0.36, 0.27) (2.23)         Walking tal. (2021)           Vashakictae et al. (2021)         0.47 (0.36, 0.27) (2.23)         Walking tal. (2021)           Vashakictae et al. (2021)         0.47 (0.36, 0.27) (2.33)         Walking tal. (2021)           Vashakictae et al. (2021)         0.47 (0.36, 0.27) (2.33)         Walking tal. (2021)           Vashakictae et al. (2021)         0.47 (0.36, 0.37) (2.32)         Yang et al. (2021) <t< td=""><td>(2010) En 1</td><td>010010000000000000000000000000000000000</td></t<>	(2010) En 1	010010000000000000000000000000000000000
Balm et al. (2019)         0.41 (0.39, 0.47) 2 hit         Martinez           Singhalet al. (2016)         0.10 (0.66, 0.15) 2.33         Schi et           Singhalet al. (2016)         0.11 (0.66, 0.15) 2.33         Schi et           Singhalet al. (2016)         0.11 (0.66, 0.15) 2.33         Schi et           Usinghalet al. (2016)         0.11 (0.66, 0.15) 2.33         Schi et           Usinghalet al. (2011)         0.11 (0.66, 0.15) 2.33         Schi et           Usinghalet al. (2011)         0.31 (0.24, 0.51) 2.11         Singhalet           Usinghalet al. (2021)         0.34 (0.23, 0.51) 2.11         Singhalet           Visinghalet al. (2021)         0.29 (0.23, 0.35) 2.31         Tabihit           Visinghalet al. (2021)         0.41 (0.27, 0.51) 2.28         Usinghalet           Wang et al. (2021)         0.17 (0.14, 0.22) 2.33         Validati           Wang et al. (2021)         0.55 (0.26, 0.77) 1.187         Yang et           Vising et al. (2021)         0.56 (0.50, 0.52) 2.22         Validati           Vising et al. (2021)         0.56 (0.50, 0.52) 2.22         Yang et           Vising et al. (2021)         0.56 (0.50, 0.52) 2.22         Yang et           Vising et al. (2021)         0.56 (0.50, 0.52) 2.22         Yang et           Visin et al. (2021)         0.21 (0.12, 0.32) 2.	11) 10000	0.10(0.12,022) 210
Shama et al. (2009)         0.10 (0.06, 0.07) (2.33)         Sohr et al. (2017)           Taxing et al. (2018)         0.17 (0.24, 0.31) (2.11)         Stama et al. (2017)           Usan et al. (2018)         0.37 (0.24, 0.31) (2.11)         Stama et al. (2017)           Usan et al. (2018)         0.37 (0.24, 0.31) (2.11)         Stama et al. (2017)           Vasnakces et al. (2017)         0.37 (0.24, 0.31) (2.11)         Tastim           Vasnakces et al. (2017)         0.29 (0.23, 0.35) (2.31)         Tastim           Wang et al. (2017)         0.17 (0.14, 0.22) (2.33)         Vashak           Wang et al. (2017)         0.17 (0.14, 0.22) (2.33)         Vashak           Vasnakces et al. (2021)         0.17 (0.14, 0.22) (2.33)         Vashak           Vasnakces et al. (2021)         0.17 (0.14, 0.22) (2.33)         Vashak           Vasnakces et al. (2021)         0.36 (0.28, 0.77) (1.87)         Yang et al. (2021)           Vasnak al. (2021)         0.36 (0.30, 0.62) (2.29)         Yang et al. (2021)           Vasnak al. (2021)         0.27 (0.26, 0.77) (2.33)         Yang et al. (2021)           Vasnak al. (2021)         0.27 (0.69, 0.77) (2.32)         Yang et al. (2021)	dran et al (2008)	0.05(0.02,0.08) 2.98
Singhade al. (2016)         0.47 (5.36, 0.501) 2.18         Starma           Tulachar et al. (2018)         0.13 (0.06, 0.24) 2.28         Starma           Tulachar et al. (2018)         0.37 (0.24, 0.31) 2.11         Tarmin           Utanaticate et al. (2011)         0.34 (0.28, 0.34) 2.28         Tarmin           Vianaticate et al. (2014)         0.34 (0.28, 0.34) 2.28         Tarmin           Wang et al. (2014)         0.29 (0.23, 0.35) 2.23         Tarmin           Wang et al. (2014)         0.07 (0.14, 0.22) 2.30         Ullah et           Wang et al. (2021)         0.05 (0.51, 0.18) 2.27         Wang et al. (2021)           Vianaticate et al. (2021)         0.05 (0.51, 0.18) 2.27         Wang et al. (2021)           Vianaticate et al. (2021)         0.56 (0.51, 0.18) 2.27         Wang et al. (2020)           Vian et al. (2021)         0.56 (0.51, 0.18) 2.22         Yang et al. (2015)           Vian et al. (2021)         0.56 (0.50, 0.52) 2.22         Yang et al. (2015)	(2019)	0.10(0.08, 0.13) 3.03
Taskine et al. (2018)         0.118 (Dille, 0.24) (2.25)         Singhal           Utanhar et al. (2011)         0.37 (0.24, 0.31) (2.11)         Singhal           Utanhar et al. (2021)         0.34 (0.24, 0.31) (2.11)         Taskine           Vianhardze et al. (2021)         0.24 (0.27, 0.31) (2.28)         Taskine           Wang et al. (2021)         0.44 (0.27, 0.31) (2.21) (2.21)         Utashardze et al. (2021)           Wang et al. (2021)         0.17 (0.14, 0.22) (2.33)         Vashad           Weiselician et al. (2021)         0.05 (0.01, 0.18) (2.27)         Vashad           Vianta et al. (2021)         0.05 (0.01, 0.18) (2.27)         Vanhad           Vianta et al. (2021)         0.05 (0.01, 0.18) (2.27)         Vanhad           Vianta et al. (2021)         0.05 (0.01, 0.18) (2.27)         Vang et al. (2021)           Vianta et al. (2021)         0.05 (0.01, 0.18) (2.27)         Vang et al. (2021)           Vianta et al. (2021)         0.05 (0.01, 0.18) (2.27)         Vang et al. (2021)	a. (2009)	0.07(0.04,0.11) 2.93
National et al. (2011)         0.37 (0.24, 0.51) 2.11         Tastrim           Viasha et al. (2021)         0.34 (0.23, 0.42) 2.28         Tastrim           Viasha et al. (2021)         0.29 (0.23, 0.35) 2.31         Tastrim           Wang et al. (2021)         0.24 (0.23, 0.42) 2.28         Usins et al. (2021)           Wang et al. (2021)         0.17 (0.14, 0.22) 2.33         Vashaji           Wang et al. (2021)         0.17 (0.14, 0.22) 2.33         Vashaji           Wang et al. (2021)         0.05 (0.01, 0.18) 2.27         Vashaji           Viashaji         0.27 (0.02) 2.23         Vashaji           Viashaji         0.27 (0.02) 2.22         Vashaji	1 (2016)	0.18(0.11,0.28) 2.27
Utan accide act al (2021)         0.34 (2.24, 0.43) 2.24         Tubedra           Vanancicase act al (2021)         0.29 (0.23, 0.35) 2.31         Tubedra           Wang et al. (2021)         0.44 (0.37, 0.51) 2.28         Ullah et           Wang et al. (2021)         0.17 (0.14, 0.22) 2.33         Varladé           Verela vidance act. (2021)         0.05 (0.51, 0.18) 2.27         Wang et al. (2021)           Vuen at al (2020)         0.53 (0.26, 0.77) 1.67         Yang et al. (2021)           Van et al. (2021)         0.56 (0.50, 0.52) 2.29         Yane et al. (2021)           Vian et al. (2021)         0.21 (0.12, 0.32) 2.22         Yane et al. (2012)	z. (2018)	0.03(0.00, 0.10) 2.86
Value data (2014)         0.29 (0.23, 0.53) (2.31)         UB/het           Wang et al. (2014)         0.44 (0.27, 0.51) (2.28)         UB/het           Wang et al. (2021)         0.17 (0.14, 0.22) (2.33)         Validation et al. (2021)           Weise ican et al. (2021)         0.05 (0.01, 0.18) (2.27)         Wang et al. (2021)           Value at al (2020)         0.05 (0.01, 0.18) (2.27)         Wang et al. (2020)           Value at al (2020)         0.05 (0.01, 0.18) (2.27)         Wang et al. (2021)           Value at al (2021)         0.05 (0.01, 0.18) (2.27)         Yang et al. (2015)           Value at al (2021)         0.05 (0.01, 0.18) (2.22)         Yang et al. (2012)	120180	014/006 0261 213
Wang et al. (2021)         0.17 (0.11) (2.28)         Variation           Weiget al. (2021)         0.17 (0.11) (2.21)         Variation           Weiget al. (2021)         0.55 (0.01, 0.18) (2.27)         Wang et al. (2021)           Yung et al. (2021)         0.55 (0.01, 0.18) (2.27)         Wang et al. (2021)           Yang et al. (2021)         0.56 (0.50, 0.61) (2.29)         Yang et al. (2021)           Yung et al. (2021)         0.73 (0.69, 0.77) (3.3)         Yang et al. (2021)           Yung et al. (2021)         0.21 (0.12, 0.32) (2.22)         Yang et al. (2012)	2020	0040030001 308
Valende (al. 12021)         0.17 (6.34, 0.221 2.33)         Valende (al. 12021)         Valende (al. 12021) </td <td>(d) (d) (d) (d) (d) (d) (d) (d) (d) (d)</td> <td>004002,008) 230</td>	(d)	004002,008) 230
Wang et al. (2015)         Odd (0,0)	1613 (209)	021(0.16,0.26) 2.74
Name et al (2015)         Name et al (2012)	.(2014)	017(012,023) 271
Vise et al. (2012) Vise et al. (	(2015)	0.32(0.26, 0.39) 2.60
Yuan et al (2012) Yuan et al (2012) Yuan et al (2012) Yuan et al (2012)		- 0.40(0.36.0.45) 2.77
Tuan es al (2012)	2021)	0.17(0.09, 0.27) 2.23
0 30 /0 78 0 5/1 7 40 //10010	2021)	013/006 0211 245
	2021)	0110000101 100/
	2021) (2021)	arriting and man
Note: Weights are from exect effect analysis	2021) (2021) (2021) 2+ 91.31%, p = (00) (00)	
0 5	2021) (2021) 2+91.31%, p=000)	1
	2021) (012) (222) 2=91.31%, p=000) (2) (2) (2) (2) (2) (2) (2) (2	

SLID resistant

## Figure 6.

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

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## Forest plot for pooled prevalence rate of Bedaquiline







Forest plot for pooled prevalence rate of Clofazimine

Forest plot for pooled prevalence rate of Line colid

## Figure 7.

Summary of the pooled prevalence of new drug resistance among multi drug-resistanttuberculosis 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

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# 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.

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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	7	0	0	2	0	0	2	0
Araujo et al. [75]	cross-sectional	Brazil	AMR	2013– 2019	33	2	3	1	Ч	П	2	5	2
Elion Assiana et al. [16]	cross-sectional	Congo	AFR	2018– 2019	6	1	1	NR	NR	NR	NR	2	
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	ю	1	Т	2	0	1	NR	NR
Calver et al. [19]	cross-sectional	South Africa	AFR	2003– 2005	77	S	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	ω	16	NR	NR	NR	NR	15	S
Dagne et al. [20]	cross-sectional	Ethiopia	AFR	2019	66	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	9
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	9	26	-	47	59	33
He et al. [29]	cross-sectional	China	WPR	2015	102	6	30	NR	NR	NR	NR	24	9
Jabbar et al. [30]	cross-sectional	Pakistan	EMR	2016– 2017	62	S	0	NR	NR	NR	NR	Ś	S

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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	6	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	5	65	NR	NR	NR	NR	67	S
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	ю	33	1	5	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	6	NR	NR	6	4
Lee et al. [38]	cross-sectional	South Korea	WPR	2011 - 2017	85	6	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	S	11	1	4	S	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	ю	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	Ś	48	5	б	S	42	27	25
Namburete et al. [48]	cross-sectional	Mozambique	AFR	2014– 2015	25	0	9	0	0	NR	NR	9	0

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First author, year	Study design	Country	WHO regions	Study period	MDR- TB	XDR- TB	Pre-	XDR- TB	XDR-TB Previous	Pre- XDR- TB	Pre- XDR-TB Decerions	FQs resistance	SLIDs resistance
							115	New	ureated	1 B New	rrevious treated		
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	7	6	0	5	0	6	7	5
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	LL	10	21	NR	NR	89	41
Ramachandran et al. [54]	cross-sectional	India	SEAR	2005	216	٢	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	9	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	6	NR	NR	NR	NR	NR	NR
Shibabaw et al. [60]	cross-sectional	Ethiopia	AFR	2016– 2018	176	1	10	-	0	1	6	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	-	e	e	8	6	5
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	×
Vashakidze et al. [65]	cross-sectional	Georgia	EUR	2005– 2007	261	33	96	9	27	NR	NR	75	54
Wang et al. [66]	cross-sectional	china	WPR	2008– 2012	206	41	06	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	5	NR	NR	NR	2	2	0
Xu et al. [69]	cross-sectional	China	WPR	2015 - 2018	17	0	6	NR	NR	1	8	6	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	6	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	LL	16	26	NR	NR	NR	NR	16	13
Yuan et al. [73]	cross-sectional	China	WPR	2010– 2011	159	13	0	e	10	NR	NR	NR	NR
Zheng et al. [74]	cross-sectional	China	WPR	2014– 2016	88	6	44	NR	NR	NR	NR	34	11
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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.

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