Mortality risks in multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis: a systematic review and meta-regression analysis

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Abstract

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Global Health

Tuberculosis (TB) remains a leading cause of infectious disease mortality globally, and the emergence of drug-resistant strains poses a significant threat to TB control efforts. This study aimed to quantify the relative mortality risks associated with multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), in comparison to drug-susceptible TB (DS-TB) and MDR-TB, respectively. A systematic review was conducted following PRISMA guidelines, and eligible studies reporting comparative mortality outcomes were identified through PubMed, Embase, and Global Health databases.

A total of 62 studies were included in the meta-analysis. Random-effects models were used to pool relative risk estimates, and meta-regression analyses were conducted to explore the influence of contextual moderators such as country income group, HIV status, and urbanicity. Results showed that MDR-TB was associated with significantly higher mortality compared to DS-TB, particularly in low-income countries and among populations exclusively living with HIV. For XDR-TB versus MDR-TB,

urbanicity emerged as a significant moderator, with higher mortality observed in urban settings. XDR-TB exhibited consistently elevated mortality across most contexts, indicating the limited moderating effect of structural variables beyond urbanicity.

These findings highlight the disproportionate impact of drug resistance on vulnerable populations and underscore the urgency of expanding diagnostic and treatment capacity in high-burden, low-resource, and urban settings. This work contributes to the global evidence base supporting more equitable TB control strategies and context-specific public health interventions.

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Above all, I owe my deepest thanks to my family, and friends. Their love, sacrifices, and unwavering belief in me have been the foundation of all my accomplishments. This journey is as much theirs as it is mine.

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1. BACKGROUND

1.1 Context and Rationale

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is a preventable, treatable, and curable disease. However, TB, causing over one million deaths annually, has likely returned as the world's leading cause of death from a single infectious agent after three years when it was surpassed by coronavirus disease (COVID-19). [1,2]The increasing burden of drug-resistant TB, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), has emerged as a major challenge to global TB control efforts.[1] Drug resistance primarily arises from incomplete, inconsistent, or inappropriate treatment regimens, including poor adherence, drug stock-outs, and incorrect prescribing.[3] Additionally, primary transmission of resistant strains is becoming more common in some settings,[4] compounding the challenge of controlling TB globally.

In 2023, an estimated 400,000 people developed MDR/RR(Rifampicin-resistant)TB and approximately 150,000 deaths occurred globally.[2] Moreover, the rapid spread of drug-resistant TB has led to decreasing cure rates and reduced survival times, with MDR-TB cure rate at 56% and XDR-TB cure rate at 39%.[5]

Despite expanded diagnostic capacity in many countries, a substantial number of drug-resistant TB cases continue to be reported in high-burden such as Belarus and Russia.[2] Treating drug-resistant TB also places a significant strain on healthcare systems, with treatment costs estimated to be 20 times higher than those for drug-susceptible TB.[6] The limited availability of effective treatments, resource-intensive care requirements, and high mortality rates further emphasize the urgent need for strengthened global attention to drug-resistant TB.

The mortality risk of drug-resistant TB, compared with drug-susceptible TB (DS-TB), varies widely across studies and settings. For instance, the hazard ratio of mortality in MDR-TB patients compared to those with DS-TB was found to be 2 times higher in a study conducted in Tomsk Oblast, Russia[7], while it was 7.5 times higher in a study conducted in Lima, Peru.[8] Furthermore, a study conducted in Indonesia found that older age has been linked to poor treatment outcomes, such as death, with drug-resistant patients aged 60 years and above showing a hazard ratio of 3.48 compared to younger patients.[9] Consistently, another study conducted in Korea suggested that age is an independent predictor of mortality for drug-resistant TB patients.[10]

Evidence from survival analyses further highlights that this elevated mortality risk spans both HIV-positive and HIV-negative populations. A study conducted in Thailand among HIV-TB co-infected patients reported that those with MDR-TB were 12 times more likely to die than those without MDR-TB, emphasizing the lethal nature of drug resistance.[11]In another Thailand-based study of a predominantly HIV-negative TB population, MDR-TB was also independently associated with increased mortality (adjusted RR 2.8; 95% CI: 1.7–4.8), along with older age and social factors.[12] These findings suggest that HIV status may be an important source of heterogeneity in reported mortality risks.

Understanding the sources of variability is critical for improving TB management and informing targeted public health interventions. This research aims to fill this gap by identifying and quantifying the factors contributing to heterogeneity in mortality risk estimates for drug-resistant TB and drug-susceptible TB through a systematic review and meta-regression analysis.

1.2 Research Problem:

While numerous studies have examined the relative mortality risks of drug-susceptible TB (DS-TB), MDR-TB, and XDR-TB, the most recent systematic reviews on this topic were conducted in 2021 as integral components of the Global Burden of Disease (GBD) study. However, these previous systematic reviews did not explore the factors contributing to the substantial variation in mortality risk of drug-resistant TB across studies and settings. Additionally, significant advancements in treatment, diagnostics, and data availability since those reviews necessitate an updated review to reflect current evidence accurately. This systematic review synthesized the latest evidence and use meta-regression analysis to identify and quantify the sources of heterogeneity in drug-resistant TB mortality risk estimates. By building on the previous systematic reviews, this updated study aims to provide a more comprehensive and current understanding of drug-resistant TB mortality risk disparities, guiding more effective and targeted TB control strategies.

1.3 Specific Aims:

- To compare the reported mortality risks between XDR-TB and MDR-TB, and between MDR-TB and DS-TB across studies.
- To identify and quantify factors explaining heterogeneity in these mortality risk estimates using meta-regression analysis.

1.4 Research Questions:

- What are the pooled mortality risk estimates for XDR-TB vs MDR-TB and MDR-TB vs DS-TB?

- What study-level factors, such as geographic location, national income, patient demographics, and treatment protocols, explain heterogeneity in these estimates?

2. RESEARCH DESIGN AND METHODOLOGY

2.1 Study Setting and Search Strategy

We conducted a systematic review and meta-analysis adhering to PRISMA guidelines[13] and registered under PROSPERO (CRD42024619742). The review was conducted in collaboration with a multidisciplinary research team with expertise in global health, epidemiology, and systematic review methodology.

We searched two major electronic databases, PubMed and Embase. The PubMed search was limited to studies published between January 1, 2017, and December 31, 2024, because earlier data had already been captured in previous Global Burden of Disease (GBD) study updates. These earlier GBD systematic reviews primarily relied on PubMed searches and were combined with newly retrieved studies from this updated systematic review to ensure a comprehensive synthesis of both historical and current evidence. In contrast, the Embase search included studies published between January 1, 1990, and December 31, 2024.The search strategy was designed to identify studies related to tuberculosis (TB), multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), mortality, and comparative outcomes. The complete and final search terms used for the final review are included in the Appendix. There were no language restrictions, although only studies with English-language abstracts or titles were retrieved due to the use of English search terms.

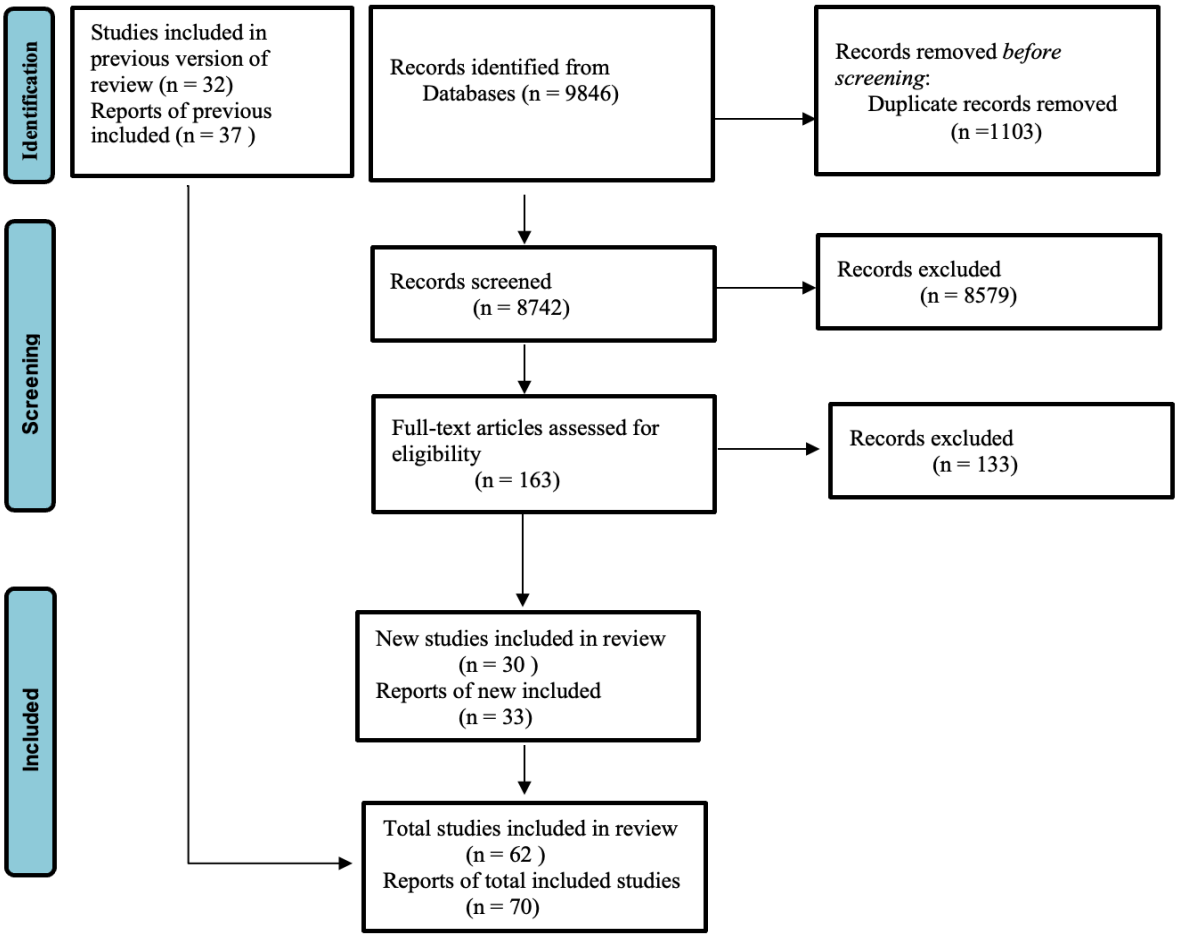

Figure 1

Updated PRISMA flow diagram showing the identification, screening, and inclusion process for studies comparing MDR-TB vs. DS-TB and XDR-TB vs. MDR-TB.

2.1.1 Study Selection Criteria

We included observational studies with comparative designs, specifically cohort studies, that reported on mortality associated with MDR-TB relative to drug-susceptible TB, or XDR-TB relative to MDR-TB.

2.1.2 Study Population

We included studies involving individuals of any age, sex, or geographic location. HIV-positive individuals were included only if HIV status was consistent across comparison groups. For this systematic review, we included only studies that compare the mortality risk of either: 1) MDR-TB to DS-TB, or 2) XDR-TB to MDR-TB. We excluded studies that focused solely on MDR-TB or XDR-TB without comparing the specified groups, studies investigating only on mono-drug resistant TB, and studies limited to narrowly defined or non-generalizable populations (e.g., military personnel, cancer patients, prison populations).

2.1.3 Exposure and Comparator Groups

This review did not evaluate interventions. Instead, the exposures of interest were the presence of MDR-TB or XDR-TB infection. Comparator groups included either drug-susceptible TB or MDR-TB patients, depending on the comparison of interest.

2.1.4 Outcome of Interest

The primary outcome was TB-related mortality, defined as death attributed to tuberculosis, using either clinical determination or ICD-coded cause of death.

2.2 Data Collection and Screening Procedures

2.2.1 Data collection

All search results were imported into **DistillerSR** (version 2.35, DistillerSR Inc.) for deduplication, screening, and extraction. Studies were identified through systematic database searches across multiple electronic sources. A total of 9,846 records were initially retrieved. No

additional records were identified through other sources, such as grey literature or manual reference checks. After removing duplicates, 8743 records remained for screening.

2.2.2 Screening Procedure

Title and abstract screening was initially conducted by a single reviewer (Ye H Naing). To assess consistency in applying the inclusion and exclusion criteria, a second reviewer (Huong Chu) independently screened a random 10% subset of records. Discrepancies were resolved through consensus discussions. This dual screening approach helped validate the screening process before proceeding with bulk review. Then, DistillerSR's prioritization tools were used to rank higher-priority articles for early review. Potential screening errors were flagged and reviewed for resolution. Screening continued until 20% of the studies had been manually screened. At that point, DistillerSR's artificial intelligence (AI) feature was activated to support the screening of the remaining records.

The PRISMA flowchart (Figure 1) illustrates the study selection process, which began with 9,846 records identified from database searches. After the removal of duplicates, 8,743 records were screened. Following title and abstract screening, 8,579 records were excluded, and full-text review was conducted for the remaining studies. 30 of the full-text articles met the inclusion criteria for qualitative synthesis, and the final number of studies included in the quantitative synthesis is reported in the flowchart.

2.2.3 Full-Text Review and Data Extraction

Once the screening process was complete, the studies that met the inclusion criteria underwent full-text review and data extraction. YN manually reviewed the full-text articles of studies that met the inclusion criteria. The extracted data included relative risk, odds ratio, or

hazard ratio, and HIV prevalence rate. Additional contextual and demographic variables were also recorded, including country income classification, urbanicity status, and mortality type (TB-specific or all-cause). For country classification by income group, we utilized the World Bank's income group classification, based on the economic status at the end of the study period.

Relevant data were extracted by a single reviewer (YN), and studies not meeting the eligibility criteria were excluded. After the first five extractions were completed, a second reviewer (HC) verified the accuracy of the extracted data and resolved any discrepancies regarding exclusions. Once initial consistency was confirmed, HC continued to verify all exclusions and randomly audited one extraction for every 5 to 10 studies to ensure ongoing accuracy and reliability.

2.3 Data Analysis

2.3.1 Meta-Analysis

All statistical analyses were conducted using the R statistical software. The metafor package was utilized for performing the meta-analysis and meta-regression. In the main analysis, we included studies reporting risk ratios (RRs), odds ratios (ORs), or hazard ratios (HRs), assuming that ORs and HRs approximated RRs due to the low incidence of the outcome of interest. To evaluate the robustness of this assumption, we conducted a sensitivity analysis (see Section 2.3.3) focused on the subset of studies for which conversion to RRs was feasible and compared the results to those of the main model. The risk ratios from individual studies—whether directly reported or approximated—were log-transformed to satisfy the assumption of approximate normality required for the statistical model.

A random-effects meta-analysis was performed on the log-transformed RRs using the Restricted Maximum Likelihood (REML) estimator for the between-study variance (tau^2). This approach was chosen to account for anticipated heterogeneity among the studies, assuming that the true effect sizes vary across studies beyond what would be expected from sampling error alone. Statistical heterogeneity was evaluated using Cochran's Q, I2 statistic, and the tau2 estimate. The pooled log RR was subsequently back-transformed to the RR scale to facilitate interpretation.

2.3.2 Meta-regression Analysis

To explore potential sources of heterogeneity, we conducted mixed-effects meta-regression analyses based on the theoretical relevance of variables and data availability. The included categorical moderators were country income group (low-, lower-middle-, upper-middle-, and high-income), region (Sub-Saharan Africa [SSA], non-SSA, and high-income), HIV sample composition (HIV-negative sample, HIV-positive sample, and Mixed sample) and urbanicity (urban-only, rural-only, and mixed settings). In addition, to examine how mortality risk has changed over time in relation to evolving treatment standards, we created a new variable, which was treatment regimen period, based on the study end year. Studies were grouped into three periods reflecting major milestones in global TB treatment guidance: pre-2010, 2010–2018, and post-2019. Each covariate was tested individually to assess its association with effect size and contribution to between-study variance.

2.3.3 Sensitivity Analysis

To test the robustness of the analytic estimates, we conducted a sensitivity analysis focused on the effect measure conversion. While we initially aimed to convert all ORs and HRs

to RRs, some studies did not provide sufficient data for conversion. Therefore, in the main model, unconverted ORs and HRs were treated as approximations of RRs. As a sensitivity analysis, we re-estimated the pooled effect using only the subset of studies for which conversion to RR was feasible and compared the results to those of the main model. This allowed us to evaluate whether the assumption of approximate equivalence across effect measures materially influenced the findings. We also tested the influence of different between-study variance estimators by repeating the meta-analysis using the DerSimonian–Laird (DL) and Maximum Likelihood (ML) estimators, in addition to REML. These analyses were conducted to evaluate whether the overall findings were sensitive to the choice of estimator and inclusion of approximated effect measures. Lastly, we examined whether the type of mortality outcomes impacted the effect measure. Specifically, studies reporting all-cause mortality were excluded and the analysis was repeated using only studies reporting TB-specific mortality to assess the stability of the findings.

2.3.2 Subgroup Analysis

We conducted subgroup analysis stratified by HIV sample composition to examine how HIV sample composition influenced the pooled mortality risk estimates. Studies were categorized into three groups based on reported HIV status of the participants: HIV-positive only samples, HIV-negative samples, and mixed samples. Separate random-effects meta-analyses were conducted within each subgroup using the restricted maximum likelihood (REML) estimator.

3. RESULT

3.1 Pooled Mortality Risk Estimate: MDR-TB Versus DS-TB

A random-effects meta-analysis of 43 studies estimated the relative mortality risk of MDR-TB compared to DS-TB. The pooled log risk ratio (log RR) was 1.1626 (SE = 0.0954), corresponding to a risk ratio (RR) of 3.20 (95% CI: 2.65–3.86). This indicates that individuals with MDR-TB had more than three times the risk of mortality compared to those with DS-TB ($p < 0.0001$). There was substantial heterogeneity across studies ($\tau^2 = 0.2231$, $I^2 = 74.07\%$, $Q(42) = 131.85$, $p < 0.0001$), prompting further exploration through moderator analyses. The forest plot summarizing these results is presented in Figure 2.

A mixed-effects meta-regression incorporating World Bank income group classification significantly explained variation in effect sizes, accounting for 19.55% of between-study heterogeneity ($R^2 = 19.55\%$) (Table 1). The model used low-income countries as the reference category, with an intercept of 2.026, which corresponds to a relative risk (RR) of 7.59 for mortality among individuals with MDR-TB compared to those with DS-TB. Relative to low-income countries, lower-middle-income countries had a regression coefficient of -0.970 ($p=0.016$), resulting in a log RR of 1.056 ($RR \approx 2.88$). Similarly, upper-middle-income countries had a coefficient of -1.079 ($p = 0.002$), corresponding to a log RR of 0.947 ($RR \approx 2.58$), while high-income countries had a coefficient of - 0.843 ($p = 0.014$), corresponding to a log RR of 1.183 ($RR \approx 3.27$).

In a separate meta-regression model including only HIV status as a moderator, studies that exclusively enrolled HIV-positive participants showed significantly higher mortality risk compared to mixed-population studies ($\beta = 0.91$, $p = 0.0385$). However, HIV-negative samples

did not significantly differ from the reference (β = 0.041, p = 0.877). This model explained 4.79% of the between-study heterogeneity (R^2 = 4.79%).

When HIV status was included alongside income group in a joint model, the effect of HIV positivity attenuated and was no longer statistically significant (β = 0.627,p = 0.1512). In contrast, income group remained a statistically significant moderator in the joint model, indicating that it is more consistent and robust. These findings suggest that the income level may confound the relationship between HIV status and mortality risk. Full model estimates are presented in Table 1.

Additional covariates, such as region and urbanicity, were tested in separate meta-regression models. Urbanicity did not significantly explain between-study heterogeneity (p > 0.05).

Table 1

Log-Transformed Relative Risk Estimates by Income Group, HIV Status, and Combined Income + HIV Status in Meta-Regression Models Comparing MDR-TB to DS-TB

Moderator	Category	Meta-regression coefficient (β), p-value
Income Group	Intercept	2.026
	Lower-middle income	–0.970, *p* = 0.016 *
	Upper-middle income	–1.079, *p* = 0.002 *
	High-income	–0.843, *p* = 0.014 *
	Low-income	Ref.
		R^2 = 19.55%
HIV	Intercept	1.1094
	HIV-Negative sample	0.041, *p* = 0.8766
	HIV-Positive sample	0.910, *p* = 0.0385 *
	Mixed population	Ref.
		R^2 =4.79%

Income + HIV	Intercept	1.886	
	Lower-middle income	-0.849, p= 0.0414 *	
	Upper-middle income	-0.965, p= 0.0074 *	
	High-income	-0.743, p= 0.0353 *	
	HIV-Negative sample	0.0823, p= 0.7527	
	HIV-Positive sample	0.627, p= 0.1512	
			R^2 = 17.49

*Note: log(RR)= log-transformed relative risk; Ref.= Reference category; * = statistically significant*

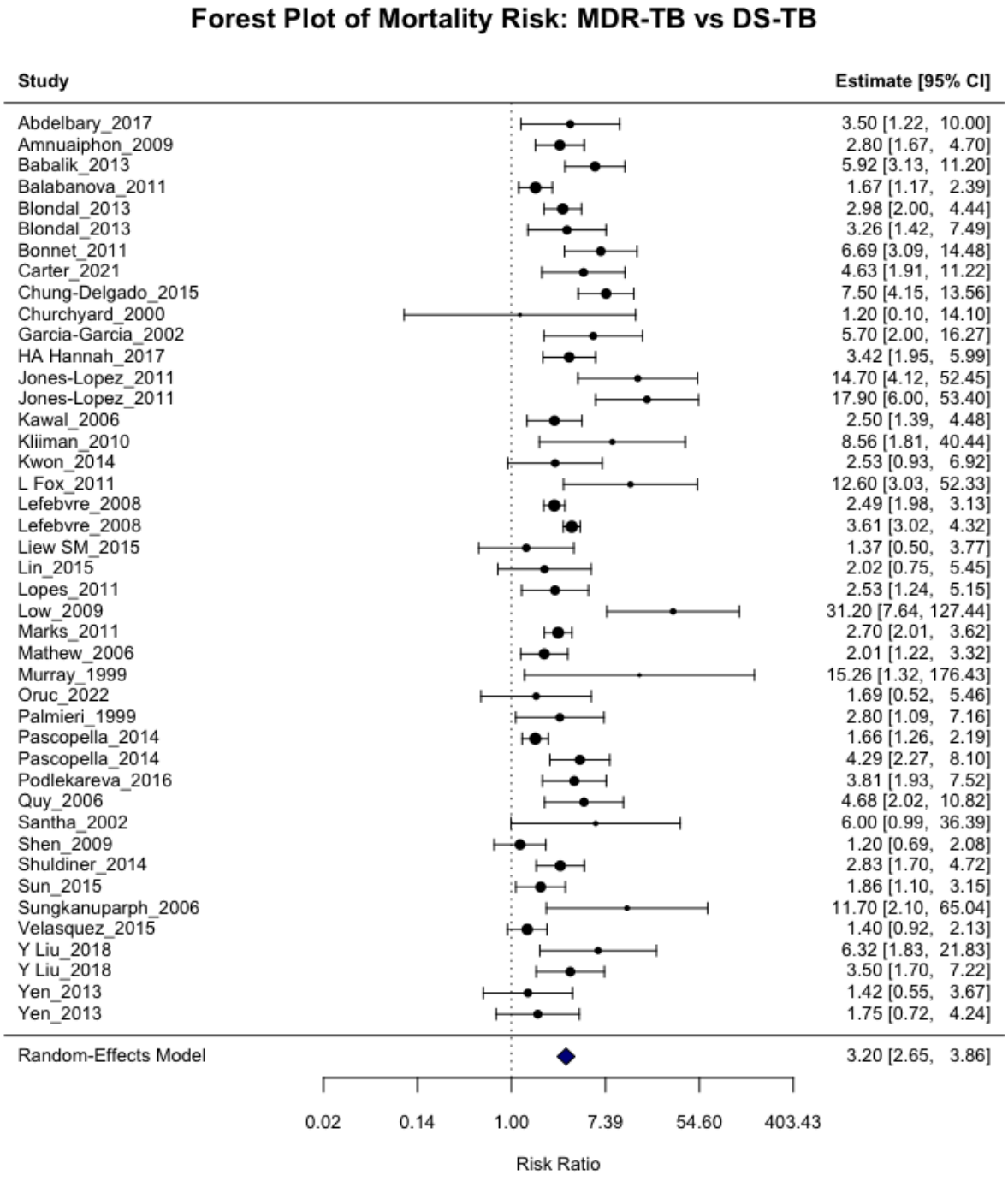

Figure 2

Forest plot of relative risk of mortality comparing MDR-TB to DS-TB

3.2 Pooled Mortality Risk Estimate: XDR-TB Versus MDR-TB

A random-effects meta-analysis of 27 studies was conducted to estimate the relative mortality risk of extensively drug-resistant tuberculosis (XDR-TB) compared to multidrug-resistant tuberculosis (MDR-TB). The pooled log risk ratio (log RR) was 0.9033 (SE = 0.1028), which corresponds to a RR of 2.47 (95% CI: 2.02–3.02), indicating that patients with XDR-TB had more than twice the risk of mortality compared to those with MDR-TB. The association was statistically significant ($p < 0.0001$). Substantial between-study heterogeneity was observed ($\tau^2 = 0.1295$, $I^2 = 84.63\%$, $Q(26) = 157.03$, $p < 0.0001$), suggesting that effect sizes varied considerably across studies. Figure 2 displays the forest plot summarizing individual study results and the overall pooled estimate for this comparison.

Meta-regression analysis was also conducted using the same covariates as in the MDR-TB vs. DS-TB model, including income group, region, HIV status and urbanicity. However, in the XDR-TB vs. MDR-TB comparison, only urbanicity emerged as a statistically significant moderator, while the other covariates did not significantly explain the observed heterogeneity.

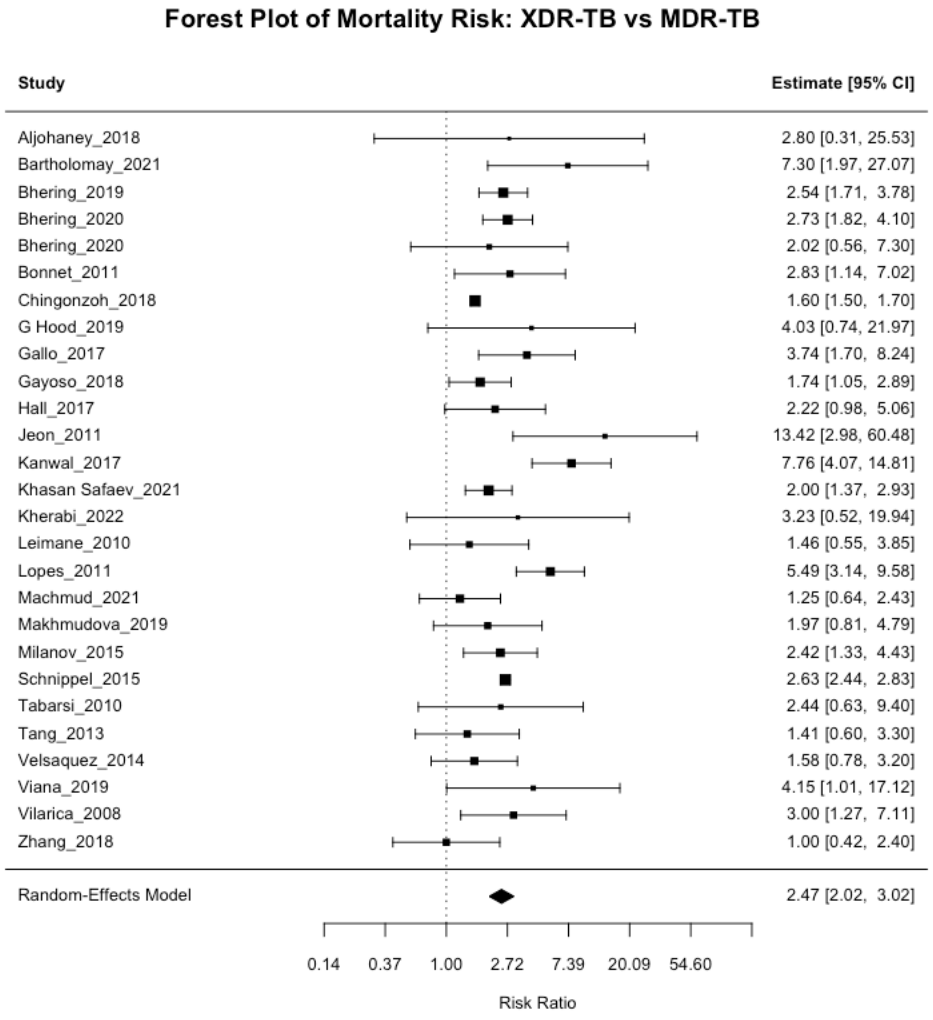

Figure 3

Forest plot of relative risk of mortality comparing XDR-TB to MDR-TB

A mixed-effects meta-regression using urbanicity as a moderator explained 40.59% of the between-study heterogeneity. “Urban only” was used as the reference category, with an intercept of 1.757, which corresponds to an RR of 5.79 for mortality among individuals with XDR-TB compared to those with MDR-TB. In comparison, studies conducted in mixed setting (including both rural and urban areas) had a significantly lower low risk ratio, with a regression of -0.919 (p= 0.0167) .The full results are presented in Table 2.

Table 2

Log-Transformed Relative Risk Estimates by Income Group, and Urbanicity in Meta-Regression Models Comparing XDR-TB to MDR-TB

Moderator	Category	Meta-regression coefficient (β), p-value
Income Group	Intercept	0.678
	Lower-middle income	0.294, $p = 0.6406$
	Upper-middle income	0.115, $p = 0.8463$
	High-income	0.599, $p = 0.3436$
	Low-income	Ref.
		$R^2 = 0\%$
Urbanicity	Intercept	1.757
	Rural only	
	Mixed	–0.919, $p = 0.0167$ *
	Urban only	Ref.
		$R^2 = 40.59\%$

*Note: log(RR)= log-transformed relative risk; Ref.= Reference category; * = statistically significant*

3.3 Sensitivity Analysis

The sensitivity analysis using converted risk ratios (RRs) from odds ratios (ORs) and hazard ratios (HRs) produced pooled estimates that were consistent with the main model, suggesting that inclusion of different effect measures did not substantially influence the results. The pooled RR was 3.01 (95% CI: 2.35-3.86) for MDR-TB vs DS-TB, and 2.23 (95%CI: 1.98-2.50) for XDR-TB vs MDR-TB. The corresponding forest plots illustrating these results are presented in the Appendix Figures to visually compare the effect sizes and confidence intervals across studies.

Additionally, when comparing across three τ^2 estimators—Restricted Maximum Likelihood (REML), DerSimonian–Laird (DL), and Maximum Likelihood (ML)—the pooled RRs remained stable (RR = 3.14–3.20), with I^2 values ranging from 68.1% to 74.1%. These findings confirm that the overall mortality risk estimate is robust to both the handling of effect measure types and the choice of heterogeneity estimator.

When we conducted the sensitivity analysis stratified by mortality type, we observed that the pooled relative risk remained robust. For the RR for XDR-TB vs MDR-TB was 2.42 (95% CI: 1.92–3.06) and for MDR vs DS was 3.22 (95% CI: 2.34–4.42)**,** suggesting that the elevated risk persisted even when restricted to TB-attributable deaths. These findings further support the robustness of the main results.

3.4 Subgroup Analysis

We conducted subgroup analyses stratified by HIV status to explore whether the association between drug-resistant TB and mortality risk varied by HIV composition. In the MDR-TB vs. DS-TB comparison, the relative risk was notably higher in studies that exclusively included HIV-positive participants (RR = 8.67, 95% CI: 2.79–26.92), compared to those with mixed HIV populations (RR = 2.96, 95% CI: 2.44–3.59) and those limited to HIV-negative samples (RR = 3.13, 95% CI: 1.94–5.04). (Figure 4)

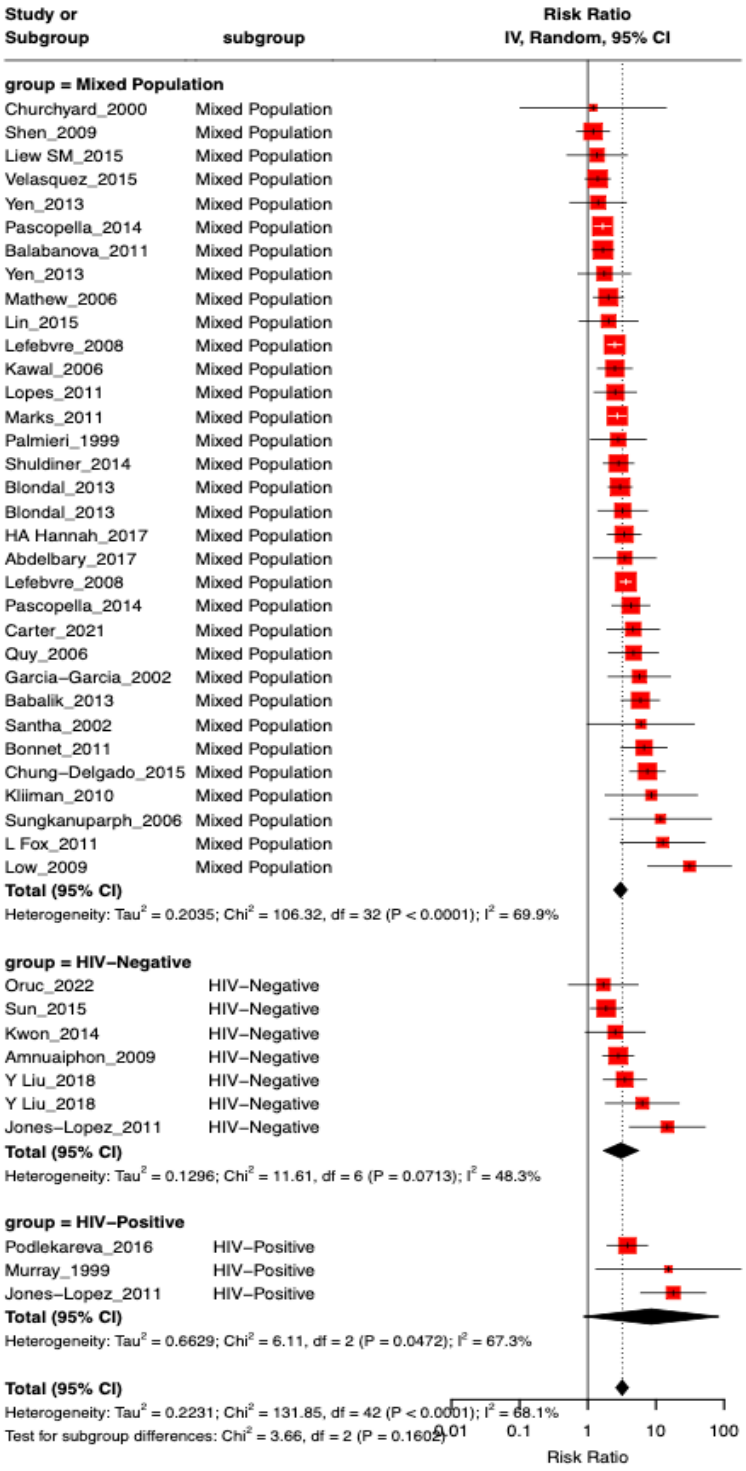

Figure 4

Forest plot showing subgroup analysis of mortality risk stratified by HIV status in the comparison of MDR-TB vs DS-TB

In the XDR-TB vs. MDR-TB comparison, the pooled estimates were more consistent across subgroups: RR = 2.35 (95% CI: 1.86–2.98) for mixed HIV samples, RR = 2.73 (95% CI: 1.59–4.69) for HIV-negative, and RR = 2.02 (95% CI: 0.41–9.88) for HIV-positive populations. The wider confidence interval in the HIV-positive subgroup reflects the small number of contributing studies and limits the precision of the estimate. These findings suggest that mortality risks associated with drug-resistant TB are consistently elevated across HIV strata, with potentially higher mortality among HIV-positive individuals, particularly in the MDR-TB context. (Figure 5)

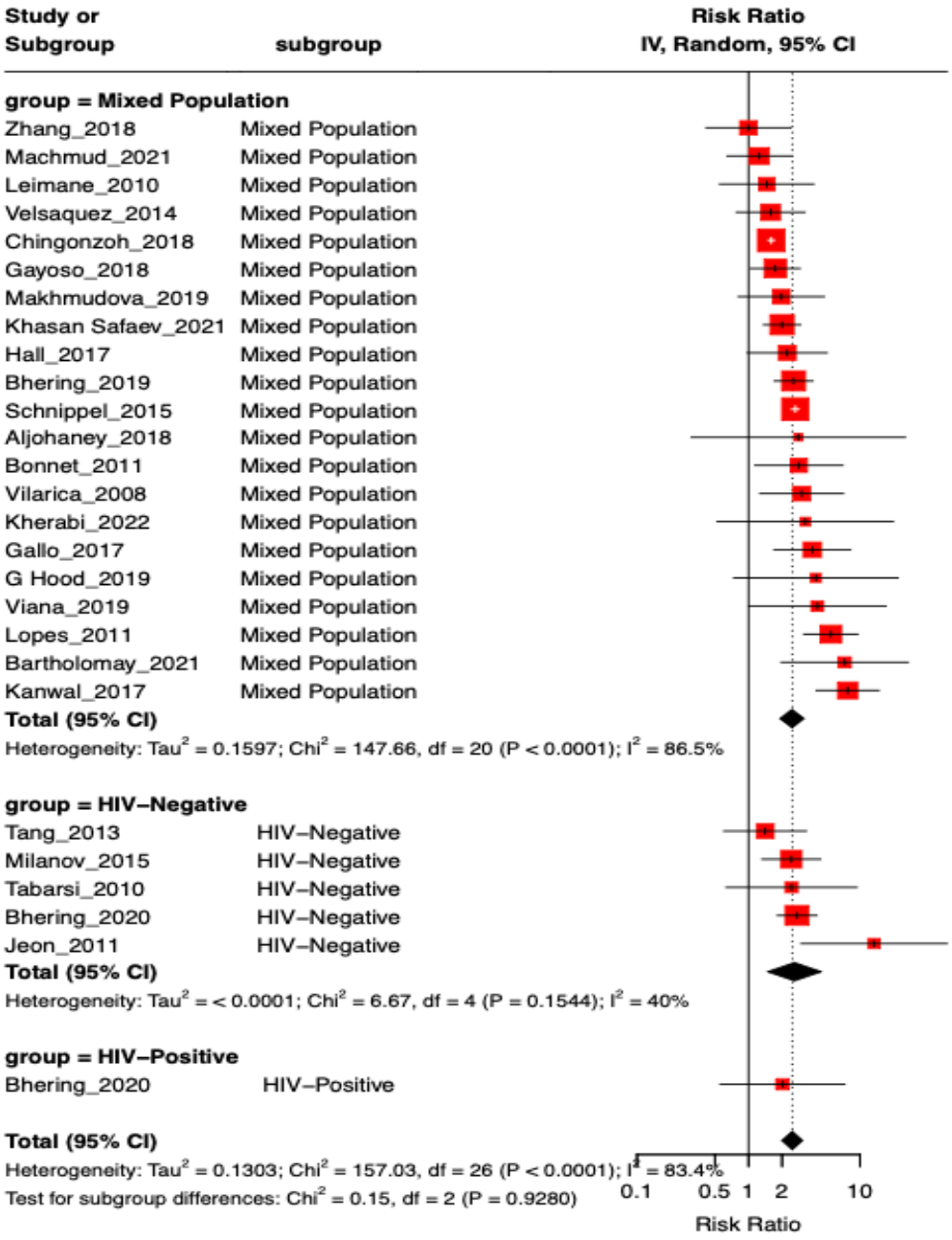

Figure 5

Forest plot showing subgroup analysis of mortality risk stratified by HIV status in the comparison of XDR-TB vs MDR-TB

4. DISCUSSION

4.1 Summary of Key Findings

In this study, we utilized and updated an existing Global Burden of Disease (GBD) database to examine the relative mortality risk of MDR-TB compared to (DS-TB), as well as XDR-TB compared to MDR-TB. For the MDR vs DS comparison, the analysis included 28 existing studies and 15 newly added studies, totaling 43 articles. For the XDR vs MDR comparison, 9 existing studies and 18 newly added studies were included, resulting in a total of 27 studies. We further investigated study-level factors that may explain heterogeneity in the reported effect sizes through meta-regression analysis.

Overall, the pooled relative risk of mortality associated with MDR-TB compared to DS-TB was 3.20 (95%CI: 2.65-3.86), indicating that a more than threefold increased risk. The corresponding relative mortality risk for XDR-TB compared to MDR-TB was 2.47 (95% CI: 1.84–3.31), highlighting the further escalation of mortality risk with more severe resistance. These findings underscore the global mortality burden posed by drug-resistant TB. While global efforts have contributed to a 23% reduction in TB-related deaths between 2015 and 2023, progress has been uneven.[2] Despite progress in some countries toward the WHO End TB Strategy milestones for 2020, treatment outcomes remain suboptimal in many high-burden settings. Achieving global TB targets will require addressing key systemic gaps, including poor early linkage to care, insufficient support for treatment adherence, undiagnosed drug resistance, and limited integration of HIV care and TB services.

4.2 Explaining Heterogeneity: Study-Level Moderators

One of the most crucial findings in the MDR-TB vs DS-TB analysis was the significant variation in mortality risk across country income groups. In this context, income group refers to the World Bank's country-level classification (i.e., low-, lower-middle-, upper-middle-, and high-income countries) based on gross national income per capita, rather than individual or household socioeconomic status. Relative risks varied substantially by income group, with studies from low-income countries reporting higher mortality risks compared to those from middle- and high-income settings. This likely reflects systemic disparities in early detection, and overall health system capacity to manage drug-resistant TB.

In contrast, income group did not significantly explain differences in mortality risk in the XDR-TB vs. MDR-TB comparison. This implies that the step-up in mortality risk from MDR to XDR-TB may be consistently severe across settings regardless of income group classification. The lack of significance may reflect the universal clinical challenges of treating XDR-TB, including limited drug options and high toxicity profiles, even in higher-resource contexts. These findings point to the urgent need for novel therapeutic options and more equitable global access to effective treatment regimens for XDR-TB.

We also assessed whether HIV status influenced the relative mortality risk between drug-resistant TB categories. In these models, HIV status was treated as a study-level characteristic, not an individual-level variable. In the MDR-TB vs. DS-TB comparison, meta-regression indicated that studies exclusively including HIV-positive participants showed significantly higher mortality risk compared to mixed-population studies (log risk ratio = 0.91, $p = 0.0385$). However, this association attenuated and was no longer statistically significant ($p = 0.15$) when

HIV status was included alongside income group in a joint model, suggesting that part of the observed effect may be confounded by national income level or healthcare system differences.

In contrast, no statistically significant differences were found by HIV status XDR-TB vs. MDR-TB comparison. However, this should not be interpreted to mean that HIV is unimportant as a risk factor for TB mortality. Individual-level studies have demonstrated substantially elevated mortality among HIV-positive individuals with MDR-TB—for example, a study conducted in Brazil reported an adjusted excess hazard ratio of 1.46 (95% CI: 1.05 –1.96) for people living with HIV compared to HIV-negative patients.[14] These findings highlight the limitations of study-level meta-analysis in capturing within-study variation and underscore the need for individual participant data (IPD) meta-analyses to more precisely assess the interaction between HIV status and drug resistance on TB mortality.

Then, we examined urbanicity as a potential moderator of mortality risk. Studies were categorized based on whether their populations were from urban-only, rural-only, or mixed (urban and rural) settings. In the XDR-TB vs. MDR-TB analysis, urbanicity emerged as a significant moderator. Specifically, studies conducted in mixed settings showed a significantly lower relative mortality risk compared to those conducted exclusively in urban populations. This suggests that mortality associated with XDR-TB may be higher in fully urban settings, possibly due to factors such as higher rates of transmission in densely populated areas, or delayed diagnosis despite proximity to health services. However, we should also consider that relatively few studies were conducted exclusively in mixed setting, which may have limited the power to detect differences. No significant differences by urbanicity were observed in the MDR-TB vs. DS-TB comparison. These findings indicate that geographic context may influence XDR-TB outcomes and should be considered in the design of targeted TB control strategies.

Lastly, we assessed whether evolving global treatment standards for drug-resistant TB have contributed to changes in mortality risk over time. Despite substantial advancements in treatment strategies, meta-regression analysis showed that the treatment period variable explained none of the between-study-heterogeneity (R^2=0.00%). This may reflect delays in the uptake of new regimens, especially in low-resource settings where diagnostic capacity, drug availability, and health system readiness vary substantially. It is also important to note that treatment period classification was based on the study end year as a proxy, and the specific regimens used in each study were not consistently reported.

4.3 Sensitivity Analysis

To assess the robustness of the pooled mortality risk estimate, we conducted two sensitivity analyses. Studies that originally reported ORs or HRs were converted to approximate RRs using log transformations. The pooled estimates based on these converted RRs remained similar, indicating that the inclusion of different effect measures did not introduce substantial bias.

Second, we compared heterogeneity estimates across three tau-squared (τ^2) estimators: restricted maximum likelihood (REML), DerSimonian-Laird (DL), and maximum likelihood (ML). The pooled RR remained stable across estimators (RR = 3.14–3.20), with I^2 ranging from 68.1% to 74.1%. These findings indicate that the main result is robust to both the choice of effect measure and the method of heterogeneity estimation.

In addition, we restricted to analysis to studies that reported TB-specific mortality, excluding those that reported all-cause mortality and those with missing values for TB-mortality type. The pooled risk ratios from these restricted models remained consistent with the main

estimates for both MDR-TB vs DS-TB and XDR-TB vs MDR-TB comparisons, suggesting that the inclusion of different mortality definitions did not substantially bias the results.

4.4 Subgroup Analysis

In our subgroup analysis, the mortality risk was highest in studies with only HIV-positive participants, indicating that having TB-HIV coinfection may lead to worse outcomes. However, there were only a few studies in this group, which makes the result less precise, the pattern still points to a possible added risk from HIV. These findings highlight the importance of integrated TB-HIV care, particularly in high-burden settings, and point to the need for further research using individual-level data to better quantify this interaction.

4.4 Strengths and Limitations of the study

This study serves as an updated evidence base by incorporating recent studies and providing comparative estimates for both MDR-TB vs. DS-TB and XDR-TB vs. MDR-TB. As a result, it offers a more accurate reflection of the current global landscape of drug-resistant TB mortality. Furthermore, by including data from diverse geographic regions and income settings, the study enhances the generalizability of the findings across various TB-affected contexts.

However, this study has several limitations to be acknowledged. First, we did not conduct a formal risk of bias assessment for the included studies. Additionally, our inclusion criteria required that studies report relative measures of mortality risk (e.g., risk ratios, hazard ratios, or odds ratios) comparing MDR-TB vs. DS-TB or XDR-TB vs. MDR-TB. As a result, we excluded studies that reported only absolute mortality rates without a comparison group. While this

approach ensured consistency and allowed for pooled effect estimation, it may have limited the breadth of included evidence.

We also attempted to evaluate changes in mortality risk over time based on treatment availability. However, most studies did not report detailed information on the specific regimens used. To address this, we approximated treatment eras based on the study's end year, using broad milestones corresponding to major WHO guideline changes. While this allowed for general comparisons, it may not accurately reflect when newer regimens were adopted in practice, as treatment implementation varies by country and program.

Lastly, although we aimed to explore whether age could explain some of the observed heterogeneity, we were unable to examine its impact due to inconsistent reporting of age distributions across studies. Several studies did not report mean or median age, and those that did used varying formats, limiting comparability and precluding subgroup or meta-regression analysis based on age.

4.5 Implications for Policy and Practice

The findings from this meta-analysis have several important implications for TB control efforts globally. The consistently elevated mortality risk associated with XDR-TB across regions suggests a widespread challenge in effectively managing extensively drug-resistant TB. While our study did not directly assess health system characteristics, the variation observed in MDR-TB mortality across income groups and geographic settings may reflect underlying differences in healthcare infrastructure, access to diagnostics, and treatment availability. These contextual factors warrant further investigation and should be considered when designing strategies to reduce mortality disparities. Collectively, these highlight the need to tailor TB control strategies

to specific regional and health system contexts, while also promoting global coordination in areas such as drug procurement and resistance surveillance.

5. CONCLUSION

This study systematically assessed and synthesized evidence comparing mortality risks across drug-resistant TB categories. We found that both MDR-TB and XDR-TB are associated with significantly higher mortality compared to their respective reference groups (DS-TB and MDR-TB), with the highest risks seen in XDR-TB cases. While some variation exists for MDR-TB depending on contextual factors, XDR-TB outcomes appear universally poor, suggesting a more urgent need for programmatic interventions.

Sensitivity analyses confirmed the robustness of our findings, and meta-regression highlighted important sources of heterogeneity. These insights can inform TB program design, particularly in prioritizing high-risk populations and optimizing resource allocation. Future research should aim to incorporate individual-level data and explore the effectiveness of newer treatment regimens in reducing mortality in drug-resistant TB.

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7. APPENDIX

7.1 Search strategy

We use the following search string to help identify eligible studies that report the measures of interest. The search string below is that used for PubMed, which we then edited and replicated for Embase.

PubMed:

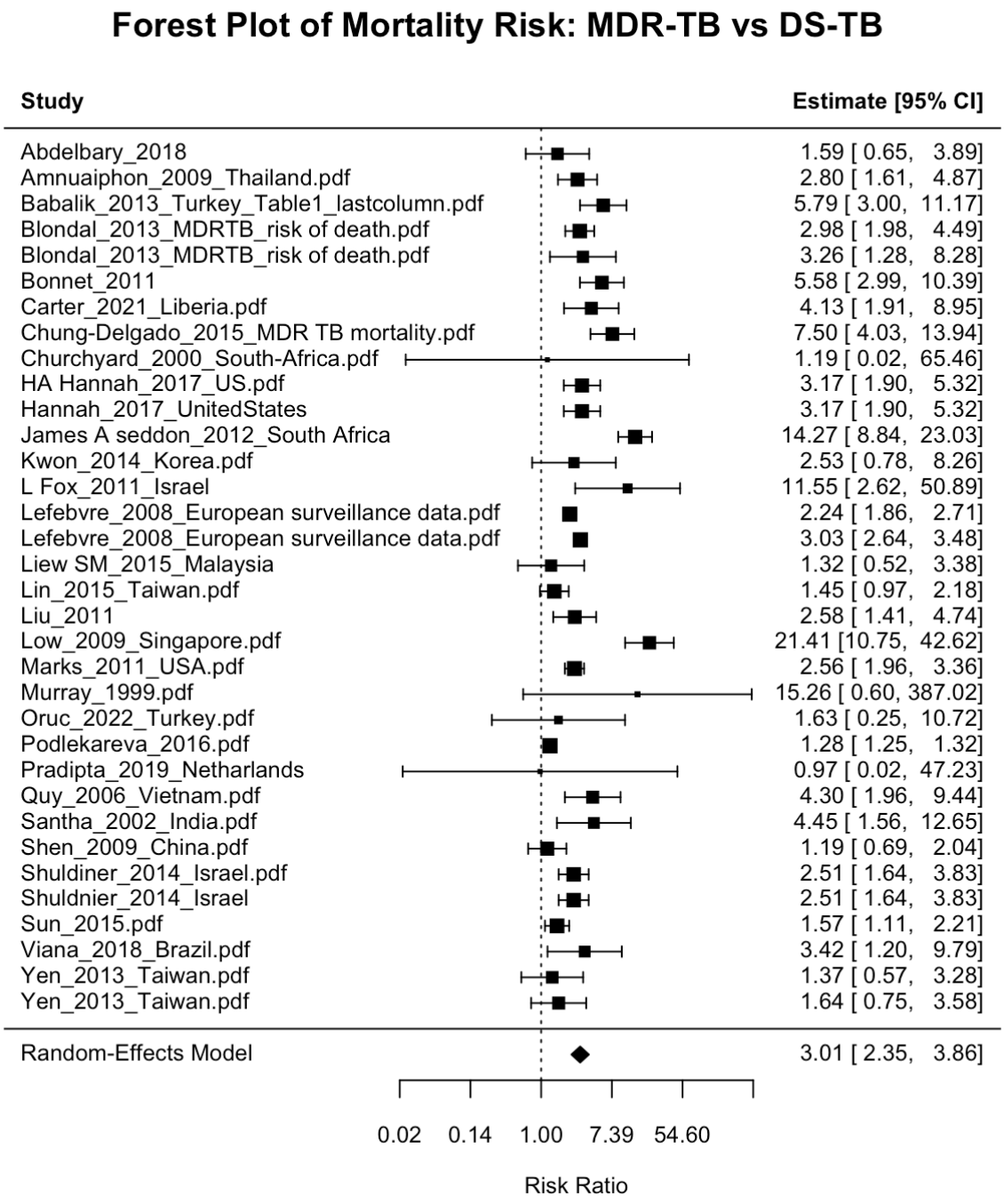
("tuberculosis"[MeSH Terms] OR ("tuberculosis, multidrug-resistant"[MeSH Terms])) AND ("risk"[MeSHTerms] OR "risk"[Title/Abstract]) AND ("mortality"[MeSH Terms] OR "cause specific mortality"[Title/Abstract] OR "cause-specific mortality"[Title/Abstract] OR death*[Title/Abstract]) NOT (animals[MESH] NOT humans[MESH])("2017/01/01"[PDAT]:"2024/09/03"[PDAT])

EMBASE:

('tuberculosis'/exp OR 'multidrug resistant tuberculosis'/exp) AND ('risk'/exp OR 'risk':ti,ab,kw) AND ('mortality'/exp OR 'cause specific mortality':ti,ab,kw OR 'cause-specific mortality':ti,ab,kw OR 'death*':ti,ab,kw) NOT ('animal'/exp NOT 'human'/exp) AND [1990-2024]/py

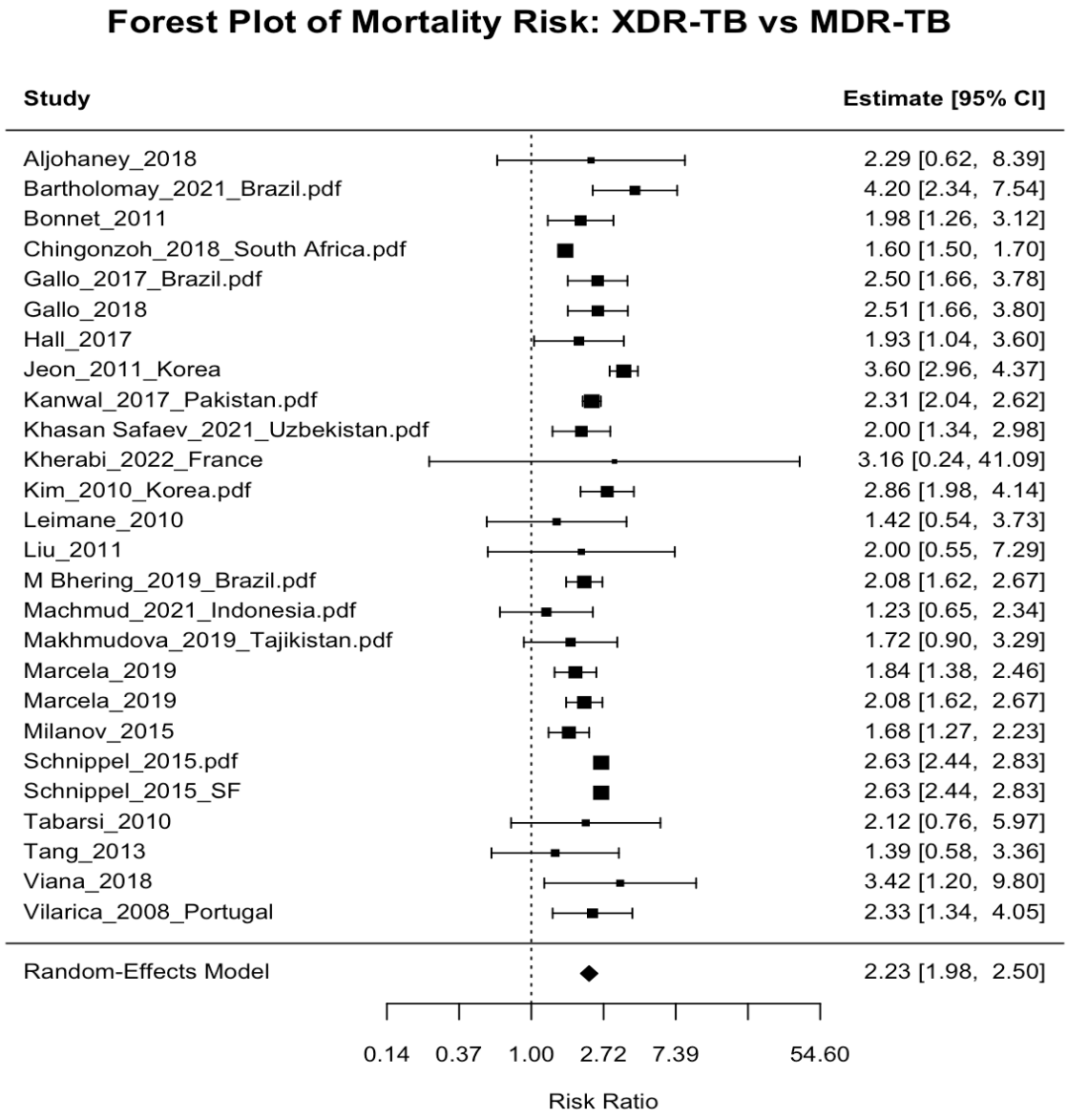
7.2 Sensitivity analysis results of mortality risk for MDR compared to DS-TB and XDR-TB compared to MDR-TB

These two forest plots present the pooled risk ratio and 95% confidence intervals under a sensitivity analysis that included studies reporting effect estimates converted from odds ratios or hazard ratios. The results were consistent with the main analysis.



Appendix Figure 1

Forest plot of mortality risk for MDR-TB versus DS-TB based on a sensitivity analysis that included studies reporting effect estimates converted from odds ratios or hazard ratios to relative risks.



Appendix Figure 2

Forest plot of mortality risk for XDR-TB versus MDR-TB based on a sensitivity analysis that included studies reporting effect estimates converted from odds ratios or hazard ratios to relative risks.

Table1:

Characteristics of the studies included in the meta-analysis of MDR-TB vs DS-TB comparison

Study Name	HIV Status	Country	Income level	Urbanicity	Time Period	Age	Sample size	Event type	Effect size	Lower	Upper
HA Hannah_2017	Mixed population	USA	High Income	Mixed Setting	2009 - 2013	0 to 99	52175	OR	3.42	1.95	5.99
Abdelbary_2017	Mixed population	Mexico	Upper Middle Income	Mixed Setting	2006 - 2013	18 to 99	8431	OR	3.5	1.2	9.8
Y Liu_2018	HIV-Negative	China	Upper Middle Income	Mixed Setting	2004 - 2015	0 to 99	2741	HR	6.32	1.83	21.84
Y Liu_2018	HIV-Negative	China	Upper Middle Income	Mixed Setting	2004 - 2015	0 to 67	2741	HR	3.5	1.7	7.24
Carter_2021	Mixed population	Liberia	Low Income	Mixed Setting	2015 - 2015	14 to 67	337	HR	4.632	1.913	11.217
Oruc_2022	HIV-Negative	Turkey	Upper Middle Income	Mixed Setting	2018 - 2019	34 to 67	382	HR	1.691	1.224	12.751
Liew SM_2015	Mixed population	Malaysia	Upper Middle Income	Mixed Setting	2012 - 2012	0 to 99	21582	OR	1.37	0.5	3.79
Pascopella_2014	Mixed population	USA	High Income	Mixed Setting	1994 - 2008	0 to 99	34534	OR	1.66	1.26	2.2
Pascopella_2014	Mixed population	USA	High Income	Mixed Setting	1994 - 2008	0 to 99	34534	OR	4.29	2.27	8.1
Shuldnier_2014	Mixed population	Israel	High Income	Mixed Setting	2000 - 2010	0 to 99	4555	OR	2.83	1.7	4.72
Lopes_2011	Mixed population	Portugal	High Income	Mixed Setting	1999 - 2019	16 to 95	1917	OR	2.53	1.244	5.148
Balabanova_2011	Mixed population	Russia	Upper Middle Income	Mixed Setting	2002 - 2003	0 to 99	880	HR	1.67	1.17	2.39
L Fox_2011	Mixed population	Israel	High Income	Mixed Setting	2002 - 2003	0 to 99	590	OR	12.6	3.03	52.27

Kliiman_2010	Mixed population	Estonia	High Income	Mixed Setting	2003 - 2005	0 to 99	1107	HR	8.56	1.81	40.4
Sungkanuparph_2006	Mixed population	Thailand	Lower Middle Income	Mixed Setting	1999 - 2004	15 0 to 99	225	HR	11.7	2.1	64.9
Amnuaiphon_2009	HIV-Negative	Thailand	Lower Middle Income	Mixed Setting	2004 - 2006	0.667 0 to 97	2463	RR	2.8	1.7	4.8
Blondal_2013	Mixed population	Estonia	High Income	Mixed Setting	2002 - 2011	25 to 64	1902	RR	2.98	2	4.44
Blondal_2013	Mixed population	Estonia	High Income	Mixed Setting	2002 -2011	25 to 64	1902	RR	3.26	1.42	7.5
Chung-Delgado	Mixed population	Peru	Upper Middle Income	Urban Only	2000 - 2012	18 to 99	1232	RR	7.5	4.1	13.4
Garcia-Garcia_2002	Mixed population	Mexico	Upper Middle Income	Mixed Setting	1995 - 2000	12 to 97	454	RR	5.7	2	16.3
Kawal_2006	Mixed population	Peru	Upper Middle Income	Mixed Setting	1999 - 2001	0 to 99	287	RR	2.5	1.4	4.5
Low_2009	Mixed population	Singapore	High Income	Mixed Setting	2000 - 2007	0 to 99	6752	RR	31.2	7.64	127.47
Lefebvre_2008	Mixed population	EU		Mixed Setting	2002 - 2004	0 to 99	39240	RR	2.49	1.98	3.12
Lefebvre_2008	Mixed population	Eu		Mixed Setting	2002 - 2004	0 to 99	39240	RR	3.61	3.02	4.32
Mathew_2006	Mixed population	Russia	Upper Middle Income	Mixed Setting	2002 - 2004	18 to 99	1916	RR	2.01	1.22	3.32
Palmieri_1999	Mixed population	Italy	High Income	Mixed Setting	1987 - 1996	0 to 99	118	RR	2.8	1.1	7.2
Quy_2006	Mixed population	Vietnam	Low Income	Mixed Setting	1998 - 2000	16 to 99	1131	RR	4.68	2.02	10.8
Jones-Lopez_2011	HIV-Negative	Uganda	Low Income	Mixed Setting	2003 - 2007	18 to 99	288	RR	14.7	4.1	52.2
Jones-Lopez_2011	HIV-Positive	Uganda	Low Income	Mixed Setting	2003 - 2007	18 to 99	288	RR	17.9	6	53.4

Marks_2011	Mixed population	USA	High Income	Mixed Setting	1997 - 2005	0 to 99	146253	RR	2.7	2	3.6
Yen_2013	Mixed population	Taiwan	Upper Middle Income	Urban Only	2005 - 2010	18 to 99	4438	RR	1.42	0.55	3.68
Yen_2013	Mixed population	Taiwan	Upper Middle Income	Urban Only	2005 - 2010	18 to 99	4438	RR	1.75	0.72	4.23
Sun_2015	HIV-Negative	China	Upper Middle Income	Mixed Setting	2001 -2010	18 to 99	234	RR	1.86	1.09	3.13
Churchyard_2000	Mixed population	South Africa	Upper Middle Income	Rural Only	1993 - 1997	18 to 65	2236	RR	1.2	0.1	13.8
Santha_2002	Mixed population	India	Low Income	Mixed Setting	1999 - 2000	14 to 87	676	RR	6	0.9	33.1
Shen_2009	Mixed population	China	Upper Middle Income	Urban Only	2000 - 2004	11 to 99	7999	RR	1.2	0.7	2.1
Murray_1999	HIV-Positive	South Africa	Upper Middle Income	Rural Only	1995 - 1996	18 to 65	376	RR	15.26	1.32	176.46
Velasquez_2015	Mixed population	Peru	Upper Middle Income	Mixed Setting	2005 - 2008	0 to 99	1211	RR	1.4	0.92	2.13
Kwon_2014	HIV-Negative	Korea	High Income	Mixed Setting	2009 - 2010	18 to 99	2481	RR	2.5313	0.9265	6.9161
Babalik_2013	Mixed population	Turkey	Upper Middle Income	Urban Only	2006 - 2009	18 to 99	11186	RR	5.92	3.13	11.2
Lin_2015	Mixed population	Taiwan	Upper Middle Income	Urban Only	2006 - 2011	65 to 99	2546	RR	2.02	0.75	5.45
Podlekareva_2016	HIV-Positive	EU		Mixed Setting	2011 - 2013	16 to 99	834	RR	3.81	1.93	7.51
Bonnet_2011	Mixed population	Georgia	Lower middle Income	Mixed Setting	2003 - 2005	0 to 18	326	RR	6.69281046	3.09374909	14.4787798

Table 3

Characteristics of the studies included in the meta-analysis of XDR-TB vs MDR-TB comparison

Study Name	HIV Status	Country	Income	urbanicity	Time Period	Age	Sample size	Event type	Effect size	Lower	Upper
Aljohaney_2018	Mixed population		High income	Mixed Setting	2011- 2016	0 to 99	23	RR	2.8	0.3071	25.5253
Bartholomay_2021	Mixed population	Brazil	Upper middle income	Mixed Setting	2013 - 2014	15 to 99	980	OR	7.3	1.97	27.09
Bhering_2020	HIV-Negative	Brazil	Upper middle income	Mixed Setting	2000 - 2016	0 to 99	2155	HR	2.73	1.82	4.11
Bhering_2020	HIV-Positive	Brazil	Upper middle income	Mixed Setting	2000 - 2016	0 to 99	2155	HR	2.02	0.56	7.32
Bonnet_2011	Mixed population	Georgia	Lower middle income	Mixed Setting	2003 - 2005	0 to 18	326	RR	2.8333	1.1431	7.0226
Chingonzoh_2018	Mixed population	South Africa	Upper middle income	Mixed Setting	2011 - 2013	18 to 99	3729	RR	1.6	1.5	1.7
G Hood_2019	Mixed population	USA	High Income	Mixed Setting	2004 - 2013	0 to 99	8209	OR	4.03	0.74	21.99
Gallo_2017	Mixed population	BRA	Upper middle income	Mixed Setting	2011 - 2013	0 to 99	345	OR	3.74	1.7	8.25
Gayoso_2018	Mixed population	Brazil	Upper middle income	Mixed Setting	2005 -2012	0 to 99	3802	HR	1.74	1.05	2.9
Hall_2017	Mixed population	South Africa	Upper middle income	Mixed Setting	2005 - 2008	0 to 17	340	RR	2.2227	0.9758	5.0628
Jeon_2011	HIV-Negative	Korea	High Income	Mixed Setting	2004 - 2004	0 to 99	202	HR	13.42	2.98	60.53
Kanwal_2017	Mixed population	Pakistan	Lower middle income	Urban Only	2010 - 2015	10 to 86	1136	OR	7.76	4.06	14.79
Khasan Safaev_2021	Mixed population	Uzbekistan	Lower middle income	Mixed Setting	2016 - 2017	0 to 99	15769	RR	2	1.4	3

Kherabi_2022	Mixed population	France	High Income	Mixed Setting	2006 - 2019	0 to 99	298	OR	3.23	0.52	19.81
Leimane_2010	Mixed population	Lativia	Upper middle income	Mixed Setting	2000 - 2004	0 to 99	1027	RR	1.4568	0.5511	3.8513
Lopes_2011	Mixed population	Portugal	High Income	Mixed Setting	1999 -2009	16 to 95	1917	OR	5.487	3.143	9.579
Bhering_2019	Mixed population	Brazil	Upper middle income	Mixed Setting	2000 - 2016	0 to 99	2268	OR	2.54	1.36	3.01
Machmud_2021	Mixed population	Indonesia	Lower middle income	Mixed Setting	2010 - 2015	18 to 99	553	HR	1.25	0.65	2.45
Makhmudova_2019	Mixed population	Tajikistan	Low income	Mixed Setting	2012 - 2013	18 to 99	601	OR	1.97	0.81	4.78
Milanov_2015	HIV-Negative	Bulgaria	Upper middle income	Mixed Setting	2009 - 2010	0 to 99	50	RR	2.4231	1.3253	4.4302
Schnippel_2015	Mixed population	South Africa	Upper middle income	Mixed Setting	2009 - 2011	0 to 99	17697	RR	2.63	2.45	2.84
Tabarsi_2010	HIV-Negative	Iran	Upper middle income	Urban Only	2004 -2007	20 to 85	51	RR	2.4375	0.6319	9.4018
Tang_2013	HIV-Negative	China	Upper middle income	Mixed Setting	2006 -2011	21 to 84	586	RR	1.4100	0.6026	3.2991
Velsaquez_2014	Mixed population	Russia	High Income	Mixed Setting	2000 -2004	0 to 99	614	RR	1.58	0.78	3.2
Viana_2019	Mixed population	Brazil	Upper middle income	Mixed Setting	2012 - 2013	15 to 99	191	RR	4.15	1.0061	17.1181
Vilarica_2008	Mixed population	Portugal	High Income	Mixed Setting	1999 -2007	0 to 99	132	OR	3	1.269	7.12
Zhang_2018	Mixed population	China	Upper middle income	Mixed Setting	2009 -2013	0 to 99	136	HR	1	0.4	2.3