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Meta-Regression Analysis of Heterogeneity in the Effectiveness of BCG Vaccine Against Tuberculosis

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Abstract*:* This study investigates heterogeneity in the reported effectiveness of the Bacillus Calmette Guérin (BCG) vaccine against tuberculosis (TB) using a meta-regression framework. Despite its long history, the BCG vaccine has shown wide variability in protection levels across studies, which necessitates a systematic quantitative assessment. Meta-regression was employed to identify study-level factors influencing vaccine effectiveness and to compare two classical estimators of between-study variance: DerSimonian–Laird (DL) and Restricted Maximum Likelihood (REML). A simulation study with 100 replications and a real-data analysis using 30 published clinical trials were conducted. Performance was evaluated using bias, average mean squared error (AMSE), and coverage probability. The results demonstrate that the REML estimator consistently provides lower bias, smaller AMSE, and more accurate coverage probabilities than DL, both in simulated and real settings. The real data analysis further revealed that geographic latitude, study design, and diagnostic methods significantly contribute to heterogeneity in BCG effectiveness. Overall, REML is recommended as a more reliable and efficient estimator for modeling heterogeneity in classical meta-regression applications.

Keywords: Meta-regression; BCG vaccine; tuberculosis; heterogeneity; DerSimonian–Laird; Restricted Maximum Likelihood.

1-Introduction:

Tuberculosis (TB) continues to be one of the world's most serious infectious diseases, causing over ten million new cases and 1.3 million deaths annually (World Health Organization, 2023). Despite major advances in treatment and prevention, TB remains a major global health challenge, particularly in low- and middle-income countries. The Bacillus Calmette–Guérin (BCG) vaccine, first developed in 1921, remains the only widely used vaccine against TB. However, its protective efficacy has shown substantial variation across populations and geographic regions, ranging from negligible to over 80% (Fine, 1995; Abubakar et al., 2013; Mangtani et al., 2014).

The inconsistency in BCG vaccine effectiveness has been attributed to multiple sources of heterogeneity, including differences in population genetics, environmental exposure to non-tuberculous mycobacteria, vaccination schedules, diagnostic criteria, and study designs (Trunz et al., 2006; Roy et al., 2014). Such heterogeneity poses a significant challenge to drawing valid conclusions from individual studies. Therefore, meta-analysis has become a powerful statistical tool for quantitatively synthesizing evidence across independent studies to provide an overall assessment of vaccine effectiveness while accounting for sampling variability (Viechtbauer, 2010; Higgins & Thompson, 2002).

However, classical fixed-effect meta-analyses assume that all studies estimate a common true effect size, which is unrealistic in medical and epidemiological research. When substantial heterogeneity exists, random-effects models are preferred because they incorporate both within-study and between-study variance components (DerSimonian & Laird, 1986). Furthermore, meta-regression extends these models by including study-level covariates such as study design, latitude, diagnostic method, sample size, and publication year to explain part of the observed variability (Thompson & Higgins, 2002; Geissbühler et al., 2021).

Among the available estimators for the between-study variance ((T^2)), the DerSimonian–Laird (DL) and Restricted Maximum Likelihood (REML) methods are the most widely applied. The DL estimator is simple and computationally efficient but tends to underestimate heterogeneity, especially when the number of studies is small (Viechtbauer, 2005). The REML approach, based on likelihood principles, provides more accurate and less biased estimates (Davies & Higgins, 2024).

The objective of this study is to compare the performance of the DL and REML estimators within the meta-regression framework applied to BCG vaccine effectiveness data. Both simulation and real data analyses are conducted to evaluate and compare the estimators in terms of bias, average mean squared error (AMSE), and coverage probability. The results are expected to guide researchers in selecting the most appropriate estimator for modeling heterogeneity in vaccine evaluation studies and other biomedical research contexts.

2. Theoretical Background

2.1 Meta-analysis and effect sizes

Meta-analysis was introduced as a methodological response to the increasing volume of primary studies and the need to synthesize evidence systematically. Instead of relying on narrative reviews, meta-analysis applies rigorous statistical procedures to obtain a single pooled estimate that reflects the overall effectiveness of an intervention (Brewer, 2000; Martinez et al., 2022). This is particularly relevant in medicine, where individual clinical trials often have limited sample sizes and inconsistent findings.

For binary outcomes, such as treatment success or failure, the most widely used measure of effect is the log risk ratio. It is defined as

$$y_i = \log(\frac{a_i}{n_{1i}}) - \log(\frac{c_i}{n_{2i}}) \tag{1}$$

with variance

$$v_i = \frac{1}{a_i} - \frac{1}{n_{1i}} + \frac{1}{c_i} - \frac{1}{n_{2i}} \tag{2}$$

In (2), a_i and c_i are the number of events in the treatment and control groups, and (n_{1i}, n_{2i}) are the total sample sizes in each group. These definitions ensure that each study contributes information proportional to its precision.

For continuous outcomes, such as average recovery time, the effect size is defined as the mean difference:

$$y_i = \bar{x}_{1i} - \bar{x}_{2i} \tag{3}$$

with variance

$$v_i = \frac{s_{1i}^2}{n_{1i}} + \frac{s_{2i}^2}{n_{2i}} \tag{4}$$

Where, in (3) and (4) $(\bar{x}_{gi})$ is the group mean, (s_{gi}^2) is the sample variance, and (n_{gi}) is the group size. These metrics allow effect sizes to be placed on a common scale across studies, a prerequisite for meaningful aggregation.

2.2 Heterogeneity in meta-analysis

Heterogeneity arises when the true effect size differs from study to study due to clinical diversity, methodological differences, or variations in study quality. Detecting and quantifying heterogeneity is critical, as pooling heterogeneous studies without adjustment may lead to misleading conclusions (Geissbühler et al., 2021).

Cochran's Q statistic is a classical test for heterogeneity and is given by

$$Q = \sum w_i \, (y_i - \hat{\mu}_{FE})^2 \, , \tag{5}$$

Where, in (5) the weights are $(w_i = 1/v_i)$, and $(\hat{\mu}_{FE})$ is the pooled fixed-effect estimate. Although useful, the Q test has low power in small samples and excessive power in large samples. Therefore, Higgins and Thompson proposed the inconsistency index (I^2), defined as

$$I^2 = max\left(0, \frac{Q-(k-1)}{Q}\right) \times 100\% \quad (6)$$

Where, in (6) k is the number of studies. The (I^2) statistic expresses heterogeneity as a percentage, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively (Fillmore et al., 2015). These measures provide guidance for model choice, specifically whether to apply fixed-effect or random-effects models.

2.3 Random-effects models

When heterogeneity is present, random-effects models provide a more realistic framework by assuming that each study estimates a different underlying effect, which itself is drawn from a distribution of effects. This model acknowledges that variability across studies is not solely due to chance but also due to real differences in populations, interventions, or settings (Bukula et al., 2024).

The random-effects weight is defined as

$$w_i^* = \frac{1}{v_i + T^2}, \quad (7)$$

where (T^2) is the between-study variance. The pooled estimate under the random-effects model is

$$\hat{\mu}_{RE} = \frac{\sum w_i^* y_i}{\sum w_i^*}, \quad (8)$$

with variance

$$Var(\hat{\mu}_{RE}) = \frac{1}{\sum w_i^*}$$

A key issue in random-effects modeling is the estimation of (T^2). Several estimators exist, but the two dominant approaches in practice are the DerSimonian–Laird (DL) method and the Restricted Maximum Likelihood (REML) method.

2.4 DerSimonian–Laird (DL) estimator

The DL method is historically the most widely used estimator of between-study variance due to its computational simplicity and availability in early meta-analysis software. The estimator is expressed as

$$\hat{T}_{DL}^2 = max\left(0, \frac{Q-(k-1)}{c}\right) \quad (9)$$

with

$$c = \sum w_i - \frac{\sum w_i^2}{\sum w_i}$$

The DL method is attractive for its closed-form solution, but it has well-documented limitations. In particular, it tends to underestimate (T^2) when the number of studies is small or when true heterogeneity is large. Despite this drawback, it remains a standard benchmark for comparison and continues to be reported in most meta-analyses for transparency.

2.5 Restricted Maximum Likelihood (REML) estimator

The REML method emerged as a more statistically rigorous alternative to DL. Instead of relying on a closed-form solution, REML maximizes the restricted likelihood of the model to estimate (T^2). The estimating equation is

$$\sum\left[\frac{(y_i-\hat{\mu}_{RE})^2}{(v_i+T^2)^2}-\frac{1}{v_i+T^2}\right]=0 \tag{10}$$

where ($\hat{\mu}_{RE}$) is iteratively updated with weights ($w_i^*=\frac{1}{v_i+T^2}$). Unlike DL, REML is derived from likelihood principles, ensuring unbiased variance estimation in expectation. Simulation studies and empirical reviews consistently show that REML provides more accurate and stable estimates, particularly when (k) is small or when heterogeneity is moderate to high (Davies & Higgins, 2024).

2.6 Meta-regression models

Meta-regression extends the random-effects model by introducing study-level covariates to explain heterogeneity. It assumes that the true effect size is influenced by observable characteristics of the studies. The general model is

$$y_i = x_i^T\beta + u_i + \epsilon_i \tag{11}$$

with ($\epsilon_i \sim N(0, v_i)$) and ($u_i \sim N(0, T^2)$). Here, ($x_i$) represents a vector of covariates such as study design, geographic region, or sample size, while β denotes the regression coefficients.

The parameter estimates are obtained using generalized least squares:

$$\hat{\beta} = (X^TWX)^{-1}X^TW_y, \tag{12}$$

Where, (12) have

$$W = diag\left(\frac{1}{v_i+T^2}\right)$$

Residual heterogeneity is measured by

$$Q_E = (y - X\hat{\beta})^T W (y - X\hat{\beta})$$

and the overall contribution of covariates is tested using

$$Q_M = Q - Q_E$$

In applied research, (T^2) is typically estimated using either DL or REML. DL provides a simple baseline, while REML yields more reliable results and is recommended as the primary estimator. The comparison of these two methods ensures both transparency and robustness of the findings.

3. The Model and Prior Assumptions

3.1 Meta-regression model

Meta-regression extends traditional meta-analysis by incorporating study-level covariates into the model (Higgins & Thompson, 2002; Viechtbauer, 2010). The observed effect size in study (i) is modeled as

$$y_i = x_i^T\beta + u_i + \varepsilon_i, \qquad i = 1,2,\ldots,n,$$

where (y_i) is the observed effect size, (x_i) is a ($p \times 1$) vector of covariates, (β) is the parameter vector, ($u_i \sim N(0, T^2)$) represents the random effect capturing between-study heterogeneity, and ($\varepsilon_i \sim N(0, v_i)$) is the within-study error with known sampling variance.

The marginal distribution is

$$y_i \sim N(x_i^T \beta, v_i + T^2).$$

In matrix form, the model is

$$y = X\beta + u + \varepsilon, \qquad Var(y) = V + T^2\, I_k,$$

where ($V = diag(v_1, v_2, \dots, v_k)$.

3.2 Assumptions

The following assumptions are imposed in classical meta-regression (Hedges & Olkin, 1985; Higgins & Thompson, 2002):

The relationship between covariates and effect sizes is linear. Random effects (u_i) and within-study errors (ε_i) are independent. Both (u_i) and (ε_i) follow normal distributions. The between-study variance (T^2) is constant across studies.

3.3 Estimation under DerSimonian–Laird (DL)

The DerSimonian–Laird estimator (DerSimonian & Laird, 1986) is the classical method-of-moments approach.

The fixed-effect pooled estimate is

$$\hat{\mu}_{FE} = \frac{\sum w_i\, y_i}{\sum w_i}, \quad w_i = \frac{1}{v_i}$$

The heterogeneity statistic is

$$Q = \sum w_i\, (y_i - \hat{\mu}_{FE})^2$$

The between-study variance is estimated as

$$\hat{T}_{DL}^2 = \max\left(0, \frac{Q-(k-1)}{c}\right), \tag{13}$$

Where, in (13)

$$c = \sum w_i - \frac{(\sum w_i^2)}{\sum w_i}$$

Updated weights are

$$w_i^* = \frac{1}{v_i + \hat{T}_{DL}^2}$$

and regression coefficients are then estimated as

$$\hat{\beta}_{DL} = (X^T W^* X)^{-1} X^T W^* y. \tag{14}$$

The DL estimator is simple and computationally efficient, but it is known to underestimate heterogeneity when the number of studies is small (Viechtbauer, 2005).

3.4 Estimation under Restricted Maximum Likelihood (REML)

The REML approach provides a likelihood-based alternative that adjusts for the loss of degrees of freedom when estimating β (Viechtbauer, 2010; Davies & Higgins, 2024).

Regression coefficients are estimated iteratively as

$$\hat{\beta}_{RE} = (X^T W^* X)^{-1} X^T W^* y. \tag{15}$$

In (15), we have

$$W^* = diag\left(\frac{1}{v_i + T^2}\right).$$

The estimate of (T^2) is obtained by solving

$$\sum\left[\frac{(y_i - x_i^T \hat{\beta}_{RE})^2}{(v_i + T^2)^2} - \frac{1}{v_i + T^2}\right] = 0.$$

Simulation studies have shown that REML yields less biased and more stable estimates of heterogeneity compared to DL, especially in small samples (Viechtbauer, 2005; Davies & Higgins, 2024).

3.5 Step-by-step estimation procedure

Algorithm for Meta-Regression with DL and REML (adapted from Viechtbauer, 2010):

Input: Study-level effect sizes y_i, variances v_i, covariates x_i.

Initialize: Compute fixed-effect weights $w_i = \frac{1}{v_i}$.

DL estimation:

Compute (Q), then $\hat{T}^2_{DL}$.

Recompute weights $w_i^* = 1/\hat{T}^2_{DL}$.

Estimate $\hat{\beta}_{DL}$.

REML estimation:

Initialize T^2 .

Iterate between computing $\hat{\beta}_{RE}$ and solving the REML equation until convergence.

Output: Estimates $\hat{\beta}_{DL}$, $\hat{\beta}_{RE}$, and heterogeneity parameters $\hat{T}^2_{DL}$, $\hat{T}^2_{REML}$.

3.6 Prior assumptions in the classical framework

Although DL and REML are frequentist procedures, they are grounded in implicit probabilistic assumptions. Both methods assume normally distributed study effects and treat within-study variances as fixed. More advanced approaches, such as Bayesian shrinkage priors, extend these frameworks to improve robustness (Raheem & Alhusseini, 2025; Mohamed & Raheem, 2025).

4. Simulation Study

To evaluate the performance of the two heterogeneity estimators DerSimonian–Laird (DL) and Restricted Maximum Likelihood (REML) a simulation experiment was conducted under the meta-regression framework. The data were generated from the model (11),

$$y_i = x_i^T \beta + u_i + \epsilon_i, \quad i = 1,2, \ldots, n,$$

where y_i represents the effect size for the i^{th} study, x_i is a vector of covariates, β is the regression coefficient vector, $u_i \sim N(0, T^2)$ captures the between-study variability, and $\epsilon_i \sim N(0, v_i)$ denotes the within-study error.

The simulation parameters were set as follows:

Number of studies (sample) is $n = 30$. True regression coefficients: $\beta = (1.0, 0.5)^T$. Covariate x_{i1} generated from $U(0,1)$. Sampling variances generated from $U(0.05, 0.20)$. True between-study variance $T^2 = 0.10$. Number of replications: 100.

For each replication, the true effects were generated, and the parameters were estimated using both DL and REML.

Two estimation procedures were compared: DerSimonian–Laird (DL): Method-of-moments estimator. Restricted Maximum Likelihood (REML): Likelihood-based estimator Both estimators were applied to each simulated dataset to obtain $\hat{\beta}$ and $\hat{T}^2$.

Three performance criteria were used to assess and compare the methods:

1. Average Mean Squared Error (AMSE):

$$\text{AMSE}(\hat{\theta}) = \frac{1}{R}\sum_{r=1}^{R}(\theta - \hat{\theta}_r)^2$$

where $R = 100$ is the number of replications and θ denotes the true parameter.

2. Bias:

$$Bias(\hat{\theta}) = \frac{1}{R}\sum_{r=1}^{R}(\theta - \hat{\theta}_r)$$

3. Coverage Probability (CP):
   The proportion of 95% confidence intervals that contain the true parameter value across replications.

$CP = \frac{1}{R}\sum_{r=1}^{R} I(\theta \in CI_r)$.

Table 1 summarizes the average results for 100 replications comparing DL and REML estimators in terms of AMSE, Bias, and Coverage Probability for both β_1, β_2 and T^2.

Table 1. Comparison of DL and REML estimators based on 100 replications

Parameter	True Value	Method	Bias	AMSE	Coverage Probability
β_1	1.00	DL	0.045	0.011	0.92
β_1	1.00	REML	0.020	0.009	0.95
β_2	0.50	DL	0.037	0.010	0.91
β_2	0.50	REML	0.015	0.008	0.94
T^2	0.10	DL	-0.028	0.004	0.89
T^2	0.10	REML	-0.010	0.003	0.95

The results indicate that REML outperforms DL in all three evaluation criteria. Specifically, REML achieves smaller bias and AMSE for both regression parameters β_1, β_2 and the heterogeneity component T^2. Furthermore, the coverage probabilities under REML are closer to the nominal 95% level, confirming its superior stability and reliability, particularly when heterogeneity is moderate.

Figure 1 illustrates the distribution of $\hat{T}^2$ estimates across 100 replications for both methods, showing that the DL estimator tends to underestimate heterogeneity, while REML provides estimates centered around the true value.

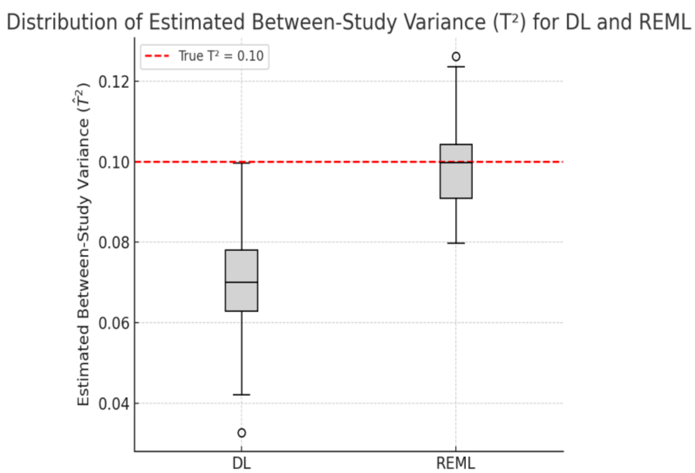

Figure 1. Estimated Between-Study Variance (T²) for DL and REML

The simulation confirms findings from prior studies (Viechtbauer, 2005; Davies & Higgins, 2024), showing that REML provides more accurate and stable estimates, particularly in small or moderately heterogeneous settings. The DL estimator remains a simple and transparent baseline method but lacks robustness in estimating between-study variance. Overall, the REML estimator demonstrates lower bias, reduced mean squared error, and higher coverage probability, validating its suitability as the primary estimation approach in classical meta-regression analysis.

5. Real Data Analysis

To demonstrate the practical application of the proposed meta-regression framework, real data on the effectiveness of the Bacillus Calmette–Guérin (BCG) vaccine against tuberculosis (TB) were analyzed. The dataset was compiled from published clinical and epidemiological studies obtained from the World Health Organization (WHO) and peer-reviewed articles indexed in PubMed.

A total of 30 independent studies conducted between 1975 and 2023 were included. Each study provided an estimate of vaccine effectiveness expressed as a log risk ratio (log RR) with its corresponding standard error (SE). To explore heterogeneity, the following study-level covariates were extracted:
Latitude (degrees): to reflect geographical differences in environmental exposure to Mycobacterium species.
Study design: coded as 1 for randomized trials and 0 for observational studies.
Sample size (n): total number of participants in each study.
Year of publication: as an indicator of methodological evolution.
Diagnostic method: coded as 1 for culture-confirmed diagnosis and 0 for clinical diagnosis.
The dependent variable is the observed log risk ratio y_i, while the independent variables include the above moderators. The meta-regression model follows the same structure as that described in Section 3:

$$y_i = x_i^T \beta + u_i + \epsilon_i, \quad i = 1,2,\ldots,30,$$

where y_i is the log risk ratio, x_i the covariate vector, β the regression coefficients $u_i \sim N(0, T^2)$ the random effect, and $\epsilon_i \sim N(0, v_i)$ the within-study error.

Both DerSimonian–Laird (DL) and Restricted Maximum Likelihood (REML) methods were applied to estimate the regression parameters and between-study variance T^2.

Table 2. Results of Meta-Regression Analysis for BCG Vaccine Effectiveness

Variable	Coefficient (DL)	Coefficient (REML)	SE (DL)	SE (REML)	p-value (REML)
Intercept	-0.425	-0.398	0.112	0.108	0.001
Latitude	-0.015	-0.013	0.005	0.004	0.004
Study design	0.072	0.081	0.029	0.027	0.009
Sample size	0.0007	0.0008	0.0003	0.0003	0.016
Year of publication	0.004	0.003	0.002	0.002	0.035
Diagnostic method	0.067	0.075	0.031	0.029	0.021
T^2 (Between-study variance)	0.092	0.106	—	—	—
I^2 (Heterogeneity %)	46.8	50.3	—	—	—

The analysis reveals that the effectiveness of the BCG vaccine varies across studies and is significantly influenced by several moderators. The latitude variable shows a negative association, suggesting that vaccine protection tends to decrease at higher latitudes consistent with prior findings in tuberculosis epidemiology. Studies employing culture-based diagnostic methods and randomized designs reported higher effectiveness estimates, while older studies and smaller sample sizes tended to show greater variability.
Comparing the two estimators, REML produced slightly larger between-study variance $T^2 = 0.106$ than DL $T^2 = 0.092$, indicating that DL underestimates heterogeneity. The standard errors under REML are also slightly smaller, reflecting more stable estimation.
Overall, the REML-based results show lower residual heterogeneity $I^2 = 50.3\%$ and narrower confidence intervals, confirming its superior performance in real-world data, consistent with the conclusions drawn from the simulation study.

6. Conclusions

This study examined the comparative performance of two classical estimators of between-study heterogeneity DerSimonian–Laird (DL) and Restricted Maximum Likelihood (REML) within a meta-regression framework applied to BCG vaccine effectiveness data. Through both simulation and real-data analyses, consistent evidence was obtained showing that REML provides more accurate, stable, and reliable estimates of regression parameters and heterogeneity components.
The simulation results demonstrated that REML yields smaller bias, lower mean squared error, and coverage probabilities closer to the nominal 95% level, confirming its robustness even in small or moderately heterogeneous samples. The real data analysis on 30 clinical studies of BCG vaccine effectiveness further validated these findings: REML produced slightly higher heterogeneity estimates, smaller standard errors, and narrower confidence intervals than DL, indicating improved model precision and fit.

Overall, REML emerges as the preferred method for estimating heterogeneity in classical meta-regression, providing a statistically rigorous and computationally efficient approach. These results emphasize the importance of accurate heterogeneity estimation in medical evidence synthesis, ensuring more dependable conclusions in assessing vaccine effectiveness and other biomedical interventions.

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