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# Reevaluating the Role of BCG Vaccine in COVID-19 Protection: A Comprehensive Meta-Analysis and Systematic Review

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Abstract

This study aimed to undertake a meta-analysis of the BCG vaccine's efficacy in preventing COVID-19 infection and its complications. Data from multiple previously conducted studies are compiled for meta-analysis. 12 studies pertaining to COVID-19 infection in general, 9 studies pertaining to COVID-19 patients requiring hospital treatment, 3 studies pertaining to COVID-19 patients requiring ICU treatment, and 8 studies pertaining to COVID-19 mortality rates were included in the analysis. The meta-analysis revealed no association between the administered BCG vaccine with COVID-19 infection (p-value = 0.4494). However, there is a trend towards protection against COVID-19 infections requiring hospitalization (p-value = 0.1856). In addition, the results showed a protective trend against COVID-19-associated mortality, although it did not reach the generally accepted level of statistical significance (p-value = 0.0966). There was a low degree of heterogeneity between the studies included in each analysis, as determined by heterogeneity analyses. To substantiate these findings, additional research with improved designs and larger samples is required. The conclusion of the study was that the BCG vaccine may provide protection against COVID-19 that necessitates hospitalization and mortality, but these findings must be confirmed by additional research.

Keywords: BCG vaccination, COVID-19, Meta-analysis, Randomized controlled trials, Protective efficacy

## 1. Introduction

The COVID-19 virus has caused a global pandemic since late 2019. Vaccine development continues to be carried out in an effort to eradicate the COVID-19 virus. Several research links the role of several previous vaccines that are able to provide protection against bacteria. One of them is the Bacillus Calmette-Guerin (BCG) vaccine. The BCG vaccination was created to prevent TB, however other studies show that the vaccine may provide general protection against a variety of tiny organisms that cause infection called pantogens. These non-specific effects include providing positive benefits to fight viral infections [1]–[5]. Other studies suggest that BCG vaccines also protect themselves through epigenetic reprogramming of monocytes [2], and provide protection through immunological effects of non-specific protection [6], [7]. The BCG vaccine provides an innate and adaptive immune response to a variety of internal and external factors, despite the fact that the protective mechanism is not completely understood.

Several studies support the non-specific protective effect of BCG in substantially reducing mortality, which involves immune responses that are both innate and adaptive, involving multiple factors. Biering-Sørensen conducted a randomized clinical trial and found that administering the BCG-Danish vaccine to infants who have a birth weight of <2500 g can reduce neonatal mortality [8]. Stensballe also conducted a multicenter clinical trial and showed that BCG vaccine at birth can reduce

hospitalization rates in early childhood [9]. Another study by Leentjens showed that BCG vaccination improved influenza vaccine immunogenicity in healthy volunteers [10].

In addition, a number of epidemiological studies demonstrate the non-specific antimicrobial properties of BCG. Roth discovered that previous BCG vaccinations were associated with higher child survival rates in Guinea-Bissau [11]. Overall, the BCG vaccine exhibits promise for lowering mortality and offering broad-spectrum prevention of a variety of infections. Although some studies support the non-specific protective effect of the BCG vaccine, findings are still inconsistent.

In the context of the COVID-19 pandemic, research on the BCG vaccine's general protective effect against COVID-19 is still ongoing. Recent BCG vaccinations are associated with reduced COVID-19 symptoms, according to research. [12]–[18]. Additional research suggests that BCG vaccinations may be associated with a reduction in COVID-19 disease severity [12]. These findings support the idea that non-specific innate immune system-related processes may underlie the increased protection against viral infections, particularly COVID-19, that BCG vaccinations may provide.

On the other hand, some studies did not find sufficient evidence to support the vaccine's effectiveness against COVID-19 infection [19]–[26]. Gong also concluded that there is insufficient evidence to support the BCG vaccine's ability to prevent COVID-19 infection [27]. It is crucial to remember that research is underway to learn more about the COVID-19 effects of the BCG vaccination and to see whether it can offer meaningful non-specific protection. Consistent results point to the necessity for more research using bigger samples and more meticulous observation in order to understand the BCG vaccine's function against COVID-19.

To determine the effects of BCG vaccination on COVID-19, we conducted a meta-analysis and systematic review of prior randomized controlled trials for this study. We anticipate that the findings of this study will cast more light on how BCG vaccines contribute to non-specific protection against COVID-19 and lay the groundwork for the development of effective anti-pandemic vaccination strategies.

## 2. Data Collection and Selection of Studies

A literature search begins with a search in electronic databases, including PubMed, Google Scholar, Crossref, OpenAlex, and Scopus. Keywords used include “BCG”, “COVID”, “randomized controlled trials”, “RCT”, and “cohort”. We are limiting the search for published articles to April 2023. The titles and abstracts of articles generated from subsequent literature searches were selected to match the inclusion criteria. The inclusion criteria include studies involving randomized controlled trials (RCTs) evaluating the BCG vaccine's effect on COVID-19. Relevant articles are selected for further analysis.

Relevant data include study design, number of participants, population characteristics, BCG vaccination interventions, measured outcomes (e.g. infection rates, mortality rates), and statistical outcomes. This data was extracted independently by researchers and verified to ensure consistency. Data extracted from studies that meet inclusion criteria were analyzed using meta-analysis methods.

For the study, we selected journals with the criteria described in the following table:

| Criteria | Description |
|---|---|

| | |
|---|---|
| Population (P) | Participants were individuals who were at least 17 years old. Participants who have undergone COVID-19 testing by PCR or antigen are considered to be positive for the virus. Gender, race, ethnicity, or geographic distribution are all unrestricted. |
| Intervention (I) | Participants were given BCG vaccine with any dose. |
| Control/Placebo (C) | Participants who were not given any treatment or empty injections. |
| Outcome (O) | The success rate of the BCG vaccine is determined by (a) the number of patients affected by COVID-19, (b) the number of COVID-19 patients admitted to the hospital, (c) the number of COVID-19 patients admitted to the intensive care unit, and (d) the number of COVID-19 patients who perished. |

## 3. Methodology

Using "Publish or Perish version 8", a total of 1389 publications that may correspond to the provided keywords were discovered. There were 89 duplicate publications according to the titles and DOIs obtained. Using the programming language R, all duplicated data is retrieved from one of the datasets and then returned to the dataset. 1300 is the condition of duplicate-free paper. After that, the publication is double-checked by examining the abstract for the search term. The search criteria were applied to abstracts and titles to narrow down 50 publications to 50. In the end, the content of filtered publications is examined by perusing each one individually. For this investigation, a total of 13 sources were utilised. Here is a PRISMA flowchart for conducting a literature search.

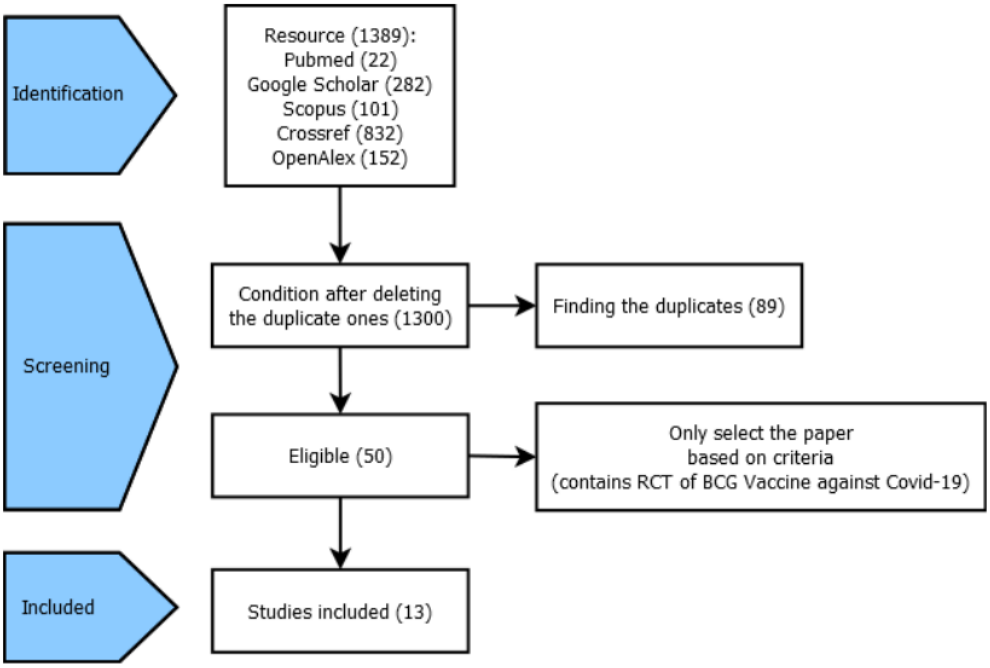


*Figure 1. Extracting eligible criteria using PRISMA 2020 flow diagram*

The characteristics of each obtained publication are summarised in the following table. There are 14 publications, including 8 RCT MultiCentre studies and 5 RCT SingleCentre studies, and 1 Cohort study. In addition, there are 10 healthy adult patients and patients with a disease history who have up to four publications. Patients who tested positive for Covid-19 up to ten publications and patients with symptoms up to four publications were given the diagnosis.

*Table 1. Study Characteristics*

| Study Design | Study | Year Published | Participant Characteristics | | | | | Study Characteristics | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Characteristics | Age | Sex (%) | | Total | Group | | Diagnosis | Timing of follow-up |
| | | | | | Male | Female | | Intervention (BCG Vaccinated) | Control (Placebo) | | |
| -3 | -1 | -2 | -4 | -5 | -7 | -8 | -6 | -9 | -10 | -12 | -11 |
| RCT multi center | Claus [28] | 2023 | Adults (Health Care Workers) | 42.49 (mean) | 25,6 | 74,41 | 1309 | Danish Strain | Placebo | Based on participant self-reports (serologic test) | 90 days |
| RCT multi center | Koekenbier [21] | 2023 | Adults | 69 (median) | 62,8 | 37,22 | 6112 | Danish Strain | Placebo | Participant self-reports + hospital records (if relevant) | 180 days |
| RCT multi center | Pittet [30] | 2023 | Healthcare workers | 42.8 (mean) | 25,4 | 74,6 | 3386 | BCG Denmark | Placebo | SARS-CoV-2 infection (PCR / rapid antigen / | 6 months |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | serologic test) + death / hospitalization / severe disease (≥3 consecutive days unable to work) | |
| RCT multi center | Santos [31] | 2023 | Adults (Health Care Workers) | 18 to 60+ | 20,5 | 79,55 | 264 | BCG Moreau or BCG Moscow | Placebo | PCR (Positive) | 180 days |
| RCT multi center | Blossey [18] | 2022 | Adults | 67,3 (mean) | 52,9 | 47,1 | 2025 | VPM1002 | Placebo | PCR (Positive) | 240 days |
| RCT multi center | Czajka [20] | 2022 | Healthcare workers | 45 (mean) | 19,3 | 80,7 | 342 | BCG Moreau | Placebo | PCR (Positive) | 3 months |
| RCT multi center | Doesschate [22] | 2022 | Healthcare workers | 42 (mean) | 25,7 | 74,3 | 1511 | Danish Strain | Placebo | PCR (Positive) | 26 weeks |
| RCT single center | Dos Anjos [15] | 2022 | Healthcare workers | 43 (mean) | 23,7 | 76,3 | 131 | BCG Moscow | Unvaccinated | PCR or rapid antigen test (Positive) | 180 days |
| RCT single center | Faustman [26] | 2022 | Patients with type 1 diabetes | 43,8 (mean) | 58,3 | 41,7 | 144 | Multiple Tokyo 172 strain | Placebo | Symptoms and PCR (Positive) | 15 months |
| RCT single center | Moorlag [29] | 2022 | Adults | 67 (mean) | 52,5 | 47,5 | 2014 | Danish Strain | Placebo | PCR (Positive) | 12 months |
| RCT multi center | Sinha [16] | 2022 | Adults' underlying medical conditions | 43 (mean) | 52,1 | 47,9 | 495 | BCG Moscow | Placebo | PCR (Positive) | 9 months |
| RCT single center | Tsilika [14] | 2022 | Adults at risk | 69 (mean) | 67,8 | 32,2 | 301 | BCG Moscow | Placebo | PCR (Positive) | 6 months |
| RCT multi center | Upton [25] | 2022 | Healthcare workers | 39 (mean) | 29,6 | 70,4 | 1000 | Danish Strain | Placebo | PCR (Positive) | 52 weeks |
| Cohort Study | Weng [32] | 2020 | Adults | 39,5 (median) | 25 | 75 | 120 | Unknown | Placebo | Obtain to Hospital | Unknown |

The table summarizes the characteristics of studies conducted to assess the effectiveness of the Bacillus Calmette-Guerin (BCG) vaccine against COVID-19. In this study, various study designs were used involving diverse populations of participants, including adults and health workers. The BCG vaccine used also varies, be it BCG Moreau, BCG Moscow, or the Danish Strain. Control groups in these studies received either a placebo or were unvaccinated. A positive PCR test result or a positive rapid antigen test is used to diagnose COVID-19, with a monitoring period ranging from a few weeks to several months. The information contained in this table provides valuable insights in understanding the effect of BCG vaccines on COVID-19, especially in the context of diverse populations.

For the result, we use a statistical method to combine the findings of the analyses' included research. Continuous variables will be represented by mean and standard deviation (SD), whereas dichotomous variables will be represented by frequency and percentage. The magnitude of the effect will be described by odd ratio (OR) with confidence intervals (CI) displayed as a forest plot. Using the chi-square Q test and statistical I2, heterogeneity between studies was determined, with I2 > 50% indicating statistical significance. The cut-off values for low, medium, and high inconsistencies are 25%, 50%, and 75%, respectively. If I2 is more than 50% or less than 50%, a fixed-effect model will be used to produce results with a 95% confidence interval.

To determine the reliability of aggregate data, a sensitivity analysis is performed by deleting studies in order. Moreover, a subgroup analysis was intended based on the vaccine strains. Each BCG strain is a member of a subgroup comprised of at least two separate investigations. We also use funnel plots and Egger's test to look for any bias. The trim-and-fill strategy is used to fill in any gaps in possible research if publication bias is detected (p 0.05).

## 4. Results

### 4.1. Number of Respondents affected by COVID-19

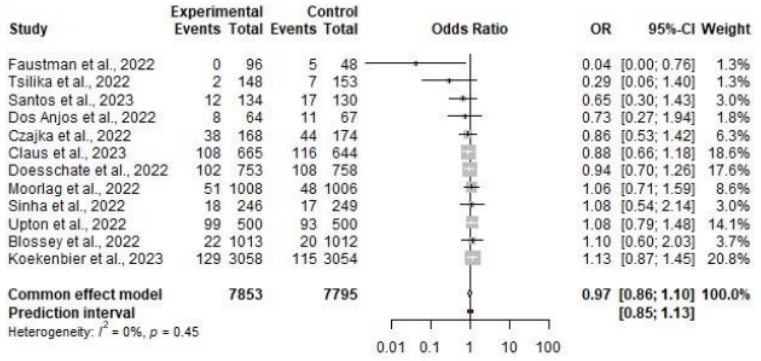


*Figure 2. The odds ratio of respondents being infected with COVID-19 (Forest Plot)*

This meta-analysis consisted of 12 studies with 15,648 total observations. There were a total of 1,190 identified cases of infection. The results of the meta-analysis employing a fixed effects model revealed an odds ratio (OR) of 0.9716, with a 95% confidence interval ranging from 0.8606 to 1.0916. With an I2 value of 0%, the analysis of heterogeneity revealed that there was no significant heterogeneity among the included studies. The Q test for heterogeneity yielded no statistically significant differences (p-value = 0.4494). The results of this meta-analysis indicate that there is no link between BCG vaccination and COVID-19 infection.

### 4.2. COVID-19 Respondens Admitted to Hospital

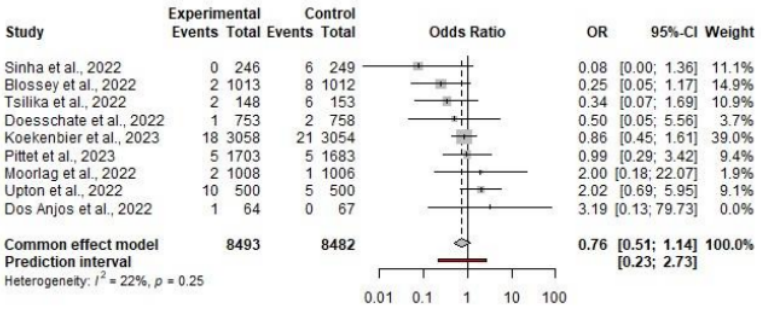

*Figure 3. The odds ratio of respondents being admitted to hospital with COVID-19 (Forest Plot)*

This meta-analysis consisted of 12 investigations with 15,648 observations in total. There were a total of 1,190 infections identified. The 95% confidence interval for the estimated odds ratio (OR) from the meta-analysis employing a fixed effects model ranged from 0.8606 to 1.0916. Analysis of heterogeneity revealed no significant heterogeneity between the included studies, with an I2 value of 0%. The Q test for heterogeneity revealed no statistically significant difference (p-value = 0.4494). The results of this meta-analysis indicate that there is no association between BCG vaccination alongside COVID-19 infection.

### 4.3. COVID-19 Respondents Admitted to the ICU

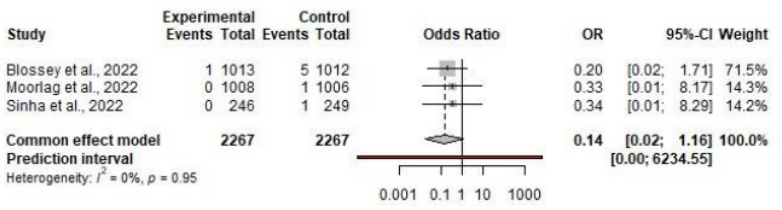


*Figure 4. The odds ratio of respondents being admitted to ICU with COVID-19 (Forest Plot)*

This meta-analysis aims to assess the effectiveness of the BCG vaccine regarding COVID-19 infections that necessitate intensive care unit (ICU) treatment. This analysis included 3 studies with a total of 4,534 observations, including 8 cases that required ICU treatment. The estimated odds ratio (OR) using a fixed effects model was 0.1422, with a 95% CI of 0.0175 to 1.1542. Although a p-value of 0.0684 indicates a protective trend against COVID-19 infection necessitating ICU treatment, this result is not statistically significant (p 0.05). I2 = 0% indicates that there was no significant heterogeneity between the included studies. In addition, the heterogeneity test revealed no significant differences (p-value = 0.9484). This meta-analysis did not provide conclusive evidence that the BCG vaccine provides significant protection against COVID-19 infections requiring intensive care unit (ICU) treatment. To fully comprehend the function of the BCG vaccine in preventing severe COVID-19 infection, however, additional research is necessary due to the limited data and close p-values to thresholds.

### 4.4. Respondents Who Died Due to COVID-19

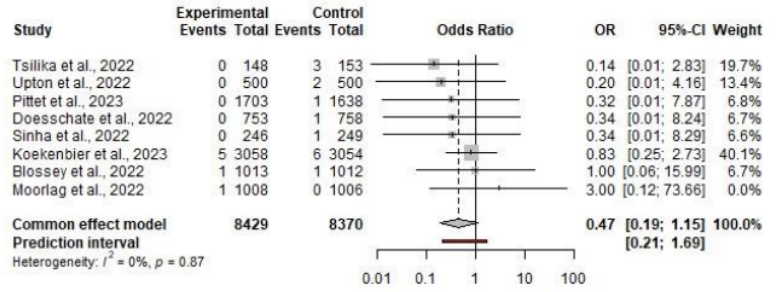


*Figure 5. The odds ratio of respondents who died due to COVID-19 (Forest Plot)*

The purpose of this meta-analysis is to assess the impact of BCG vaccination on COVID-19 mortality rates. This analysis included eight studies with a total of 16,799 observations, which included 22 cases of mortality. The estimated odds ratio (OR) using a fixed effects model was 0.4671, with a 95% confidence interval of 0.1903 to 1.1465. Despite the p-value of 0.0966 was below the generally acknowledged level of significance (p-value of 0.05), the BCG vaccine exhibited a tendency to protect against COVID-19-related mortality. I2 = 0% represents the absence of significant heterogeneity between the included studies. In addition, the test for heterogeneity revealed no differences of statistical significance (p-value = 0.8683). Due to the minimal amount of fatalities and the wide confidence interval, however, these results must be interpreted with caution. Additional research is required to obtain an improved comprehension of the BCG vaccine's role in reducing the risk of mortality from COVID-19.

### 4.5. Publication Bias

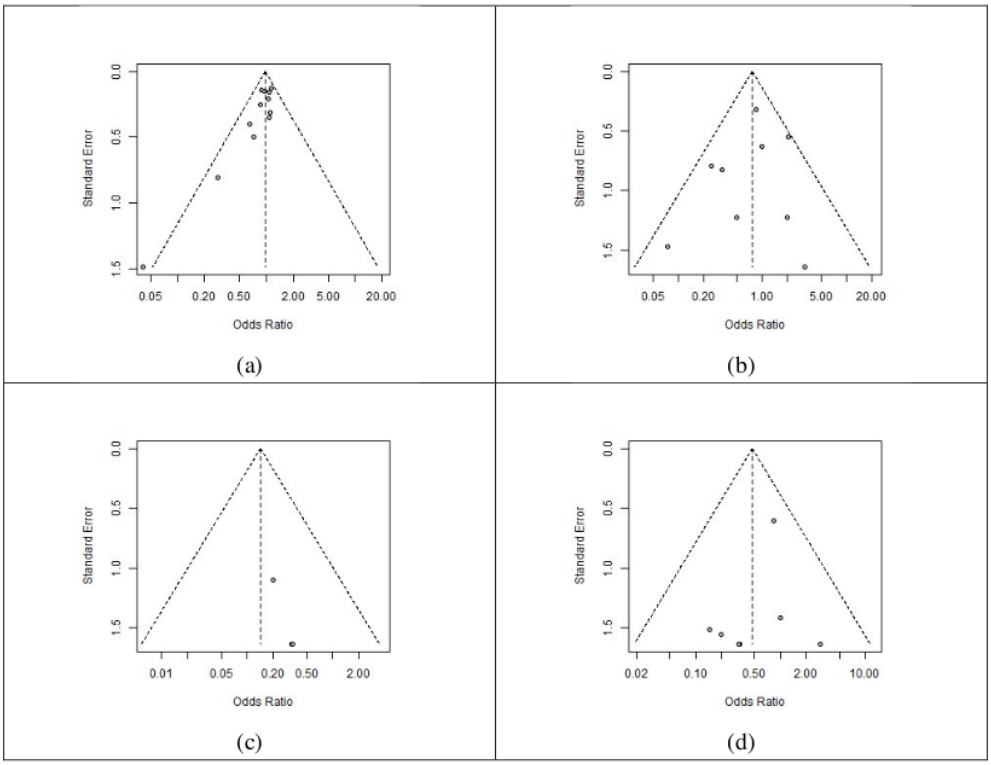


*Figure 6. Funnel plot with (a) Number of Respondents affected by COVID-19, (b) COVID-19 Respondens Admitted to Hospital, (c) COVID-19 Respondents Admitted to the ICU, and (d) Respondents Who Died Due to COVID-19*

Funnel Plot

This asymmetry in the funnel plot may indicate publication bias, where studies with small sample sizes that have larger effects tend to be more likely to be published than studies with large sample sizes that have smaller effects.

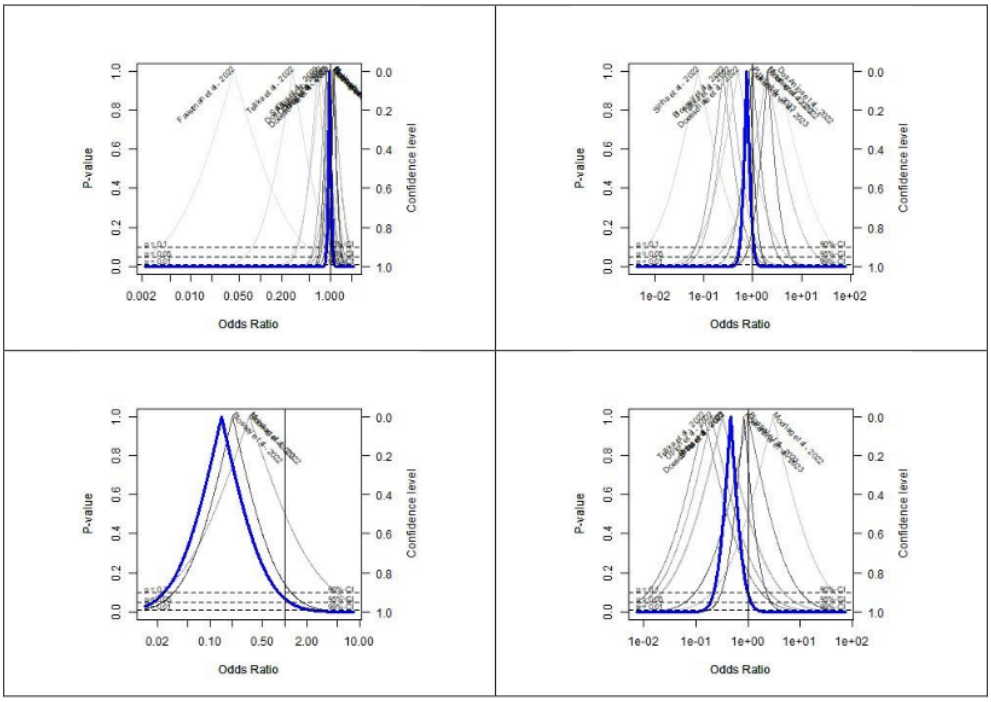


*Figure 7. Drapery plot with (a) Number of Respondents affected by COVID-19, (b) COVID-19 Respondens Admitted to Hospital, (c) COVID-19 Respondents Admitted to the ICU, and (d) Respondents Who Died Due to COVID-19*

*Table 2. Study Characteristics*

| Study | interception | 95% CI | t | p |
|---|---|---|---|---|
| (a) By infection rate | -1.429 | -2.26 - -0.6 | -3.362 | 0.007221623 |
| (b) Based on patients admitted to the hospital | -0.54 | -2.1 - 1.02 | -0.676 | 0.5204804 |
| (c) Based on patients admitted to the ICU | 0.963 | 0.94 - 0.99 | 81.185 | 0.007841193 |
| (d) Based on mortality | -0.661 | -1.79 - 0.47 | -1.144 | 0.2963708 |

The purpose of Egger's analysis was to evaluate the presence of publication bias in each studied aspect. The analysis produced distinct outcomes for each of the observed variables. First, for the variable infection rate, an intercept of -1.429 with a 95% confidence interval of -2.26 to -0.6 was determined. These findings reveal a statistically significant publication bias (t = -3.362, p = 0.007221623). However, no significant evidence of publication bias was found in the hospitalized patient variable (intercept = -0.54, 95% confidence interval: -2.1 to 1.02, t = -0.676, p = 0.5204804). In addition, for the variable ICU patients, an intercept of 0.963 with a 95% confidence interval of 0.94 to 0.99 was found. These outcomes suggested a modest publication bias (t = 81.185, p = 0.007841193). No significant publication bias was found in the mortality rate variable (intercept = -0.661, 95% confidence interval: -1.79 to 0.47, t = -1.144, p = 0.2963708). These results indicate that the presence of publication bias varies depending on the variables observed.

In order to comprehend the factors that influence the existence of publication bias in this context, additional research is required.

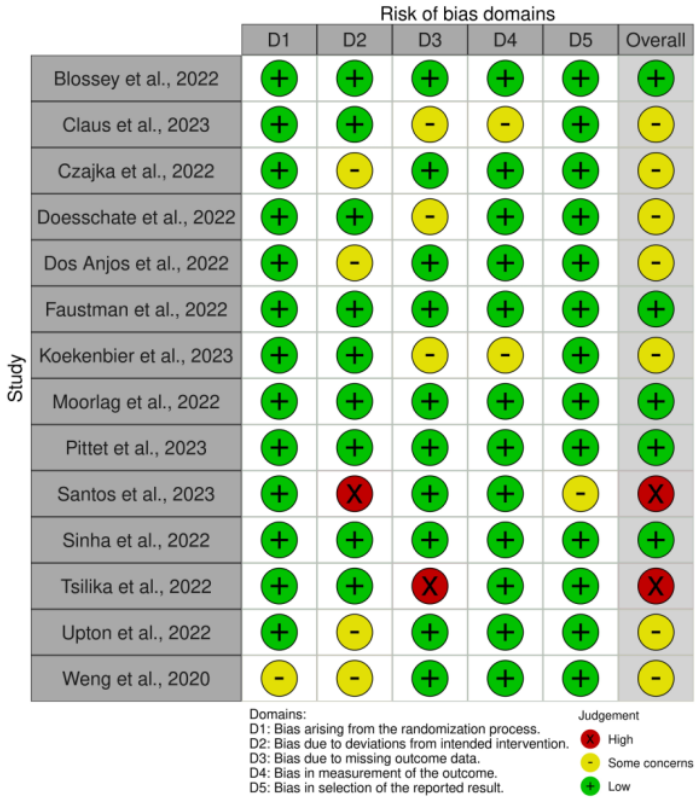


*Figure 8. Evaluation of the studies' bias risk in terms of quality*

As shown in the image above, there are a number of publications that have been identified as being biased. There are a total of 5 publications rated as having low bias, 2 publications rated as having high bias, and 7 publications that remain of concern.

## 5. Conclusion

Based on the results of the meta-analysis, we can draw multiple conclusions about this investigation. First, in the general analysis of COVID-19 infection, there was no significant relationship between BCG vaccine and COVID-19 infection was found. These findings suggest that the BCG vaccine provides minimal protection against COVID-19 infection. Keep in mind, still that these results are based on analyses of a substantial number of studies and cases.

In the analysis of COVID-19 patients who required hospitalization, the BCG vaccine tended to protect against infections requiring hospitalization. Despite the fact that the difference was not statistically significant, these results suggest that the BCG vaccine may provide protection against more severe cases. However, additional research with larger samples is required to confirm these findings.

Thirdly, there was insufficient evidence in the analysis of COVID-19 patients requiring ICU care to support the BCG vaccine's ability to prevent infections requiring ICU care. Despite the protective trend, these results did not reach the statistical significance level typically accepted by the scientific community. On the basis of the meager evidence available, additional research is necessary to fathom the function of the BCG vaccine in reducing the risk of severe infection.

A protective effect of the BCG vaccine against death was discovered in a final analysis of the COVID-19 mortality rate. Nonetheless, these results also fall short of the statistical significance threshold typically accepted in the field. Small sample size and vast confidence intervals may have impacted these results. To gain a clearer understanding of how the BCG vaccine reduces the risk of death from COVID-19, additional research with a larger sample size is necessary.

Despite some protective tendencies, this meta-analysis does not provide sufficient evidence to conclude that the BCG vaccine has a substantial impact on COVID-19 infection or its complications. To gain a more complete and accurate understanding of the protective potential of the BCG vaccine against COVID-19, however, additional studies with enhanced designs and more representative populations are required.

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