Meta-analysis Article | Iran J Med Microbiol. 2025; 19(2): 83-95

Category: Microbial Immunology | Peer Reviewed | Open Access

10.30699/ijmm.19.2.83

Iranian Journal of Medical Microbiology | ISSN:2345-4342

Protective Effect of Bacillus-Calmette Guerin (BCG) Vaccination in 21st Century: A Systematic Review and Meta-Analysis

Alivery Raihanada Armando[1*], Sulistiawati Sulistiawati [1,2], Muhammad Fadhil Kamaruddin[1], I Made Agus Dwipayana[1], Hammam Izza Rofiqi[1], Dini Zulfatus Saniyah[1], Tamma Nisrina Lutfi[1], Maftuhatur Rizkiyah Putri[1], Achmad Iqbal Uswanas[1], Fasha Rudilla Putri[1], Nathania Nathania[1], Muhammad Zulfikar Salim[1]

1. *Faculty of Medicine, Airlangga University, Surabaya, Indonesia*
2. *Department of Public Health Science-Preventive Medicine, Faculty of Medicine, Airlangga University, Surabaya, Indonesia*

ABSTRACT

Background and Aim: Tuberculosis remains a global leading cause of death. Tuberculous meningitis (TBM), a severe extrapulmonary manifestation caused by *Mycobacterium tuberculosis* infection, represents 1–2% of pediatric TB cases. Despite widespread Bacillus-Calmette Guerin (BCG) vaccination, its protective efficacy against TBM remains controversial. This meta-analysis evaluates the association between BCG vaccination and TBM incidence in pediatric populations.

Materials and Methods: A systematic review and meta-analysis was conducted across PubMed Central, ScienceDirect, and Google Scholar for the studies published during January 2014–June 2024. Inclusion criteria followed a predefined PICO framework. A fixed-effect model was employed due to minimal heterogeneity (I^2 = 0.00%).

Results: In total of 7 studies, 344 children with BCG vaccination history (20.28%) developed TBM, while 1352 (79.72%) did not. In the control group, 281 children (32.01%) developed TBM, and 597 (67.99%) did not. The overall incidence of TBM in the studied population was 24.28%. The pooled odds ratio (OR) for BCG vaccination and TBM incidence was 0.47 (95% CI: 0.38–0.57), suggesting a statistically significant inverse association. Cochran's Q test (Q=3.37, df=6, *P*=0.76) indicated no significant heterogeneity across studies.

Conclusion: This meta-analysis found a significant inverse association between BCG vaccination and the incidence of TBM in children. These findings support the continued execution of BCG vaccination programs as a potential public health strategy for reducing severe forms of TB.

Keywords: Children, Meningitis, Meta-analysis, Tuberculosis, Vaccines

Received: 2025/02/27; **Accepted**: 2025/06/01; **Published Online:** 2025/06/06;

Corresponding Information: **Alivery Raihanada Armando**, *Faculty of Medicine, Airlangga University, Surabaya, Indonesia* & Email: aliveryraihanadaarmando@gmail.com

Use a device to scan and read the article online

Armando AR, Sulistiawati S, Kamaruddin MF, Dwipayana IMA, Rofiqi HI, Saniyah DZ, et al . Evaluating the Protective Effect of Bacillus-Calmette Guerin Vaccination in 21st Century : A Systematic Review and Meta-Analysis. Iran J Med Microbiol. 2025;19(2):83-95.

Download citation: BibTeX | RIS | EndNote | Medlars | ProCite | Reference Manager | RefWorks

Send citation to: Mendeley Zotero RefWorks

1. Introduction

Tuberculosis meningitis (TBM) is the most serious form of tuberculosis infection (1). A study in Germany from 2002-2009 documented the population-based incidences of Tuberculosis (TB), capturing approximately 1% TB infection from a randomly selected cohort (2).

Children younger than 5 years of age are at greatest risk of TBM **(3)**. An estimated 15% of meningitis cases in Africa, were due to TBM **(4)**. This number is also linked with the global mortality rate of TBM, which was 22.8%.

Mycobacterium tuberculosis is known to be the most common etiology in central nervous system (CNS) infection (48.8%) as seen in a cohort study by Lee et al **(5)** in Malaysia, where 29% of TBM cases were seen in the acute phase. Age, co-infection with Human Immunodeficiency Virus (HIV), Bacillus-Calmette Guerin (BCG) vaccine, worm infection, and nutritional status are some of the risk factors that have been associated with TBM infection **(6, 7)**.

Mycobactorium tuberculosis from inhalants will undergo a hematogenic dissemination process that will deposit at oxygen-rich tissues like brain. Subsequently, the infection will lead to ischemia, hydrocephalus, and also increased intracranial pressure resulting in neurodisability **(6, 7)**. A study performed by Anderson et al **(8)** on 104 patients with TBM (81%) presented complications, of which the most frequent in long-term evaluations were cognitive impairment (12%) and epilepsy (11%) **(8)**.

Following exposure to tuberculosis (TB) bacteria, four potential scenario could occur: 1) no infection occurs as evidenced by a negative tuberculin skin test, 2) infection that progresses to active TB, 3) development of latent TB, where the immune system prevents the disease from advancing to an active state, and 4) latent TB that later reactivates, potentially developing into active TB months or years after initial infection **(9)**. In cases of latent TB, individuals typically remain asymptomatic and are not contagious. In contrast, active TB is characterized by symptoms such as a persistent cough with sputum (sometimes including blood), chest pain, fatigue, weight loss, prolonged fever, night sweats, and other symptoms, which vary depending on the location of the TB infection **(10)**. Current diagnostic methods for tuberculosis (TB), which rely on detecting immune responses to mycobacterial antigens through skin tests or interferon-gamma (IFN-γ) release assays in vitro, exhibit low sensitivity. These limitations make it difficult to differentiate between latent tuberculosis infections (LTBI) and active TB, posing a significant challenge in diagnosing latent and active infections **(11)**.

BCG is a live attenuated vaccine in which *Mycobacterium bovis* is cultured under nonpathogenic conditions for 1 until 3 years to obtain the essential virulence and immunogenicity **(12)**. The vaccine was created by Calmette and Guérin and first given to humans in 1921. BCG is the sole vaccine against tuberculosis. It is also the most commonly administered vaccine and is typically included in the newborn immunization schedule **(13)**. BCG vaccination is an immunization performed to protect against severe *mycobacterium tuberculosis* infection, as in spite of BCG vaccination primary or slight tuberculosis infection could still happen.

The immune response induced by BCG vaccination starts in the site of intradermal injection, where resident neutrophils, macrophages, and dendritic cells engage with bacilli and specific constituents of bacterial peptidoglycan **(14)**. Vaccines are intended to provide body with its first exposure with the pathogenic microorganism, so the body responds to the microorganism as foreign objects and produces antibodies and T-lymphocytes for the incoming antigens **(15, 16)**. For decades, BCG vaccination has been incorporated into childhood immunization programs in nations where the incidence of tuberculosis is high. Several alternative route to BCG vaccination are being studied, i.e mucosal route, which consist of intranasal and intrapulmonary route, in animal model show increase immune activation, since both routes mimic the natural infection route, hence increasing immune system provoked by the vaccine showing reduced bacterial counts in mice compared to intradermal injection **(17–19)**.

Based from the samples collected, children with vaccinated history of BCG dominated the study, with a total of 1701 patients (65, 32%), compared to 903 control patients (34, 68%). The incidence of TB in samples with BCG vaccination history in Liao et al **(20)** study was high due to the fact that TB incidence was high in population-based national epidemiology study between 1979 and 2010 in the study location. This resulted in new policy of the government for BCG vaccination of all newborns to enhance the neonatal immunization program, decrease the dangers of TB, and also ensure the follow up vaccination for children who were not vaccinated at an early age.

The BCG vaccine provides partial protection against TBM in children, with varying effectiveness depending on the context. Considering only the deposited cases that would be prevented in the first 5 years of life, Trunz et al **(21)** estimated that 100.5 million doses of BCG vaccine delivered to children in 2002 that have modeled prevention of 29,729 cases of TBM, the highest in Southeast Asia (46%), Sub-Saharan Africa (27%) and the Western Pacific (15%) **(21)**. A meta-analysis by Roy et al **(22)** Showed that children received BCG vaccine had 19% lower risk of TBM than children with no vaccination **(22)**.

The aim of this study was to investigate the effect of BCG vaccination on incidence of TBM in children. This is a systematic review article focused on providing evidence for the status of BCG vaccines in pediatric

populations and assessing the potential of BCG to protect children against one of the severest forms of tuberculosis—TBM. Understanding the relationship between BCG vaccination and the incidence of TBM in children can be elucidated by a detailed examination of BCG vaccination program among populations that report further cases of TBM in children. Evidence generated through this study would be beneficial for reducing the burden of TBM among at-risk populations.

2. Materials and Methods

A systematic literature search was conducted following the Preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to evaluate the association between BCG vaccination and incidence of tuberculous meningitis (TBM) in children. The search covered publications from January 2014 to June 2024, across 3 major databases including PubMed, ScienceDirect, and Google Scholar.

2.1 Search Strategy and Boolean Operators

The search strategy employed combinations of Medical Subject Headings (MeSH) terms and free-text keywords. Boolean operators were used as follows: ("BCG" OR "Bacillus Calmette–Guérin") AND ("vaccine" OR "vaccination") AND ("tuberculous meningitis" OR "TB meningitis") AND ("child" OR "pediatric" OR "infant" OR "neonate"). No language filters were initially applied during the search.

2.2 Study Selection and Automation Tools

All identified citations were imported into Rayyan.ai, a web-based tool that allows collaborative systematic review screening. Rayyan was used specifically to automatically detect and remove duplicates prior to the initial screening phase. Title and abstract screening were then conducted independently by six authors (T.N.L, D.Z.S, M.Z.S, M.F.K, I.M.A, and H.I.R). Full-text screening was performed by four authors (M.R.P, A.I.U, F.R, N). Any disagreement or unclear inclusion were resolved via consensus discussions led by a senior reviewer (S).

2.3 Eligibility Criteria

The inclusion criteria for this review encompassed peer-reviewed quantitative studies, including observational studies, cross-sectional surveys, cohort studies, and experimental designs written in English or Indonesian. Eligible studies were required to involve pediatric and/or neonatal populations, with clearly defined groups of both BCG-vaccinated and controls individuals. Additionally, only studies that reported data on BCG vaccination status in relation to the incidence of TBM were considered. Conversely, exclusion criteria were applied to filter out articles published before January 2014, and publications for which the full text was not accessible.

2.4 Data Extraction

A standardized data extraction form was employed to systematically collect relevant variables from each included study. The extracted information included the first author's name and the year of publication, the country or region where the study was conducted, and the study design. Additionally, the form recorded the number of children who received BCG vaccine and those who were controls. Diagnostic criteria used to confirm cases of TBM were also documented, along with the outcome measures specifically related to the incidence of TBM. Data were extracted using Microsoft Excel.

2.5 Risk of Bias Assessment

The RoB 2.0 tool was used to assess the risk of bias for randomized studies and an adapted version for observational studies. Two reviewers (N and M.F.K) assessed each study independently. Conflicts were resolved through discussion with a third reviewer (A.R.A). Risk of bias visualization was generated using RobVis.

2.6 Meta-Analysis and Heterogeneity

The meta-analysis was conducted using R-studio version 4.5.0. Heterogeneity assessment was conducted using both the I^2 statistic and Cochran's Q test. The I^2 statistic was used to quantify the percentage of variation across studies due to heterogeneity rather than chance, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Cochran's Q test was performed to test the null hypothesis that all studies share a common effect size, with statistical significance set at $P<0.10$. Between-study variance was estimated using tau² (τ^2). Due to no observed heterogeneity across studies ($I^2 = 0.0\%$), a fixed-effect model was used to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs). Forest plots were provided in supplementary material (Appendix 1).

2.7 Publication Bias

Publication bias was assessed through funnel plot analysis, which showed relative symmetry, suggesting a low likelihood of reporting bias. However, to increase robustness, Egger's test was also performed using R (Meta package), and results showed no statistically significant asymmetry ($P>0.05$). These findings are presented in Appendix 2.

2.8 Confounding Factors and Sources of Bias

We explored sources of conflicting results across studies. For instance, Al Yazidi et al **(23)** had a relatively small sample size, limiting generalizability. Mazhar et al **(24)** relied on scar presence for BCG status verification, potentially underestimating vaccination coverage. Furthermore, most studies lacked control for the socioeconomic status, co-infections, nutritional status, and access to healthcare, which may confound the association between BCG vaccination and TBM incidence. These issues are discussed further in the Limitations section.

2.9 Risk of Bias

The risk of bias assessment across seven studies reveals a mixed methodological quality profile as shown in Figure 1, with bias due to confounding (D1) emerging as the most problematic domain, where six of seven studies demonstrated moderate risk primarily due to inadequate control for the potential confounders in observational study designs. Most studies were performed well in domains related to intervention classification (D3), deviations from intended interventions (D4), and missing data handling (D5), suggesting robust study execution and data management practices. However, notable heterogeneity was observed in participant selection bias (D2) and outcome measurement bias (D6), indicating variability in recruitment strategies and outcome assessment methods across studies. Al Yazidi et al **(23)** showed the most concerning bias profile with moderate risk across four domains (D1, D2, D5, D6), while Mazhar et al **(24)** and Morris et al **(25)** demonstrated the strongest methodological rigor with low overall risk of bias. The predominance of moderate overall risk ratings (5 of 7 studies) suggests that while the included evidence provides valuable insights, the conclusions should be interpreted with appropriate caution due to potential residual confounding and methodological limitations that may affect the reliability and generalizability of the findings.

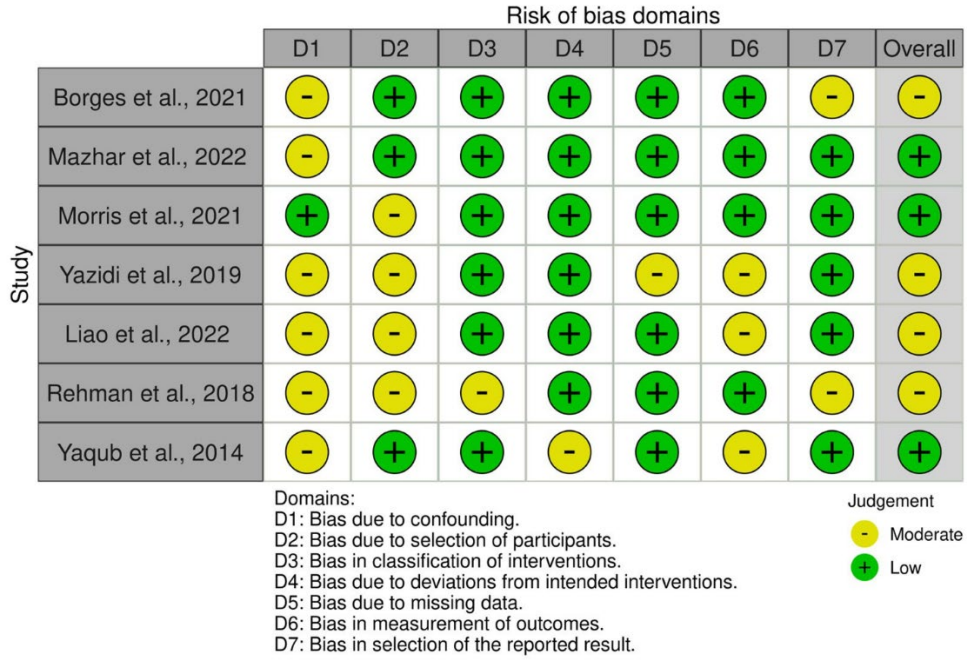

Figure 1. Risk of bias assessment with RobVis2.0 tool

3. Results

The search and selection of included studies following the PRISMA guidelines are highlighted in Figure 2. A total of 4,133 records were retrieved from various databases and registers during the identification stage, with the following contributions: Scopus (3,813), PubMed **(32)**, Cochrane **(45)**, and Springer (209). After exclusion of duplicate records (n = 2,934), 199 unique records were retained for full evaluation. Notably, no records were filtered out by automation tools or for other reasons at this stage. The screening step was performed: 199 identified records were assessed against the inclusion criteria based on the title and abstract, leading to the exclusion of 158 records. Forty full-text reports were requested for retrieval and all were retrieved and assessed for eligibility.

Table 1. The characteristics of each included study

Authors	Title	Study design	Sample	Result
Liao et al (20), China	*Effectiveness of Bacillus Calmette Guérin vaccination against severe childhood tuberculosis in China: a case-based, multicenter retrospective study*	*Analytic cross-sectional*	The study was conducted at 3 Children's Hospitals in China, between January 1, 2002 and December 31, 2018. The study included 1701 children with active TB (mean age 7.63 years; SD 5.14 years).	A total of 1701 children with active TB were registered. 1171 children were vaccinated with BCG and 369 children were not vaccinated. The incidence of TBM was 412 children, while the incidence of non-meningitis was 1128 children.
Al Yazidi et al (23), Australia	*Overview of pediatric tuberculosis cases treated in the Sydney Children's Hospitals Network, Australia*	Analytic *cross-sectional*	Pediatric patients in New South Wales, Australia. This study involved 921 patients diagnosed with TB between January 2014 and December 2015, with 26 pediatric TB patients.	Of the 23 patients, 3 patients suffered from TBM and none of those suffering from tuberculosis meningitis received the vaccine. In the non-meningitis population, the number of patients vaccinated was 9 people (56.3%)
Mazhar et al (24), Pakistan	*Incidence of Several Forms of Tuberculosis (TB) and Their Bacillus Calamette Guerin (BCG) Vaccination Status among Children*	analytic *cross-sectional*	Pediatric patients at Jinnah Hospital, Lahore, aged 2 - 14 years who were diagnosed with Tuberculosis between January 2021 and December 2021, numbered 200 children	From 200 samples, 50 patients were diagnosed with TBM. Of the 50 TBM patients, 15 patients received BCG vaccination. While in non TBM patients, there were 70 patients who received BCG vaccine.
Morris et al (25), Canada	*Epidemiologic clinical features and outcomes of incident tuberculosis in children in Canada in 2013– 2016: results of a national surveillance study*	*Case control*	Prospective surveillance from 2013 to 2016 of over 2700 pediatricians plus TB program verticals for incident tuberculosis disease in children under 15 years in Canada	Of the 16 patients with TBM, 7 patients received BCG vaccination. It was found that 81 non TBM patients did not receive BCG vaccination.
Rehman et al (26), Pakistan	*Role of Tuberculin test as a Diagnostic tool for tuberculosis*	Analytic *crosssectional*	Patients aged 1-15 years diagnosed with Tuberculosis at Ayub Pediatric Teaching Hospital, Pakistan	150 sample patients, 65 patients were diagnosed with tuberculosis meningitis with 23 vaccinated and 42 controls. While non TBM patients were 85 patients, 52 vaccinated and 33 controls.
Borges et al (27), Portugal	*Pediatric Tuberculosis: 12 Years of Experience in Tertiary Referral Center in Portugal*	Analytic *crosssectional*	Patients aged <18 years diagnosed with TB in a tertiary Pediatric Hospital from 2008-2019 in Portugal.	Of the 145 total samples, 7 patients were diagnosed with TBM and 138 were non TBM. 5 TBM patients were recorded as having been vaccinated and 2 were not vaccinated, while in non-TBM patients, 103 patients had been vaccinated with BCG and 35 patients had not been vaccinated with BCG.
Rashid et al (28), India	Frequency of Various Forms of Tuberculosis (TB) and their Bacillus Calamette Guerin	Cross sectional	350 patients of various forms of tuberculosis visiting the outpatient department (TB clinic) of Children's Hospital, fulfilling the inclusion and	Among 350 patients enrolled 168 patients (48.0%) were vaccinated (having BCG scar) and 182 patients (52%) were controls. 72 cases (20.6%) were of TBM

Authors	Title	Study design	Sample	Result
	(BCG) Vaccination Status in Children		exclusion criteria were enrolled.	

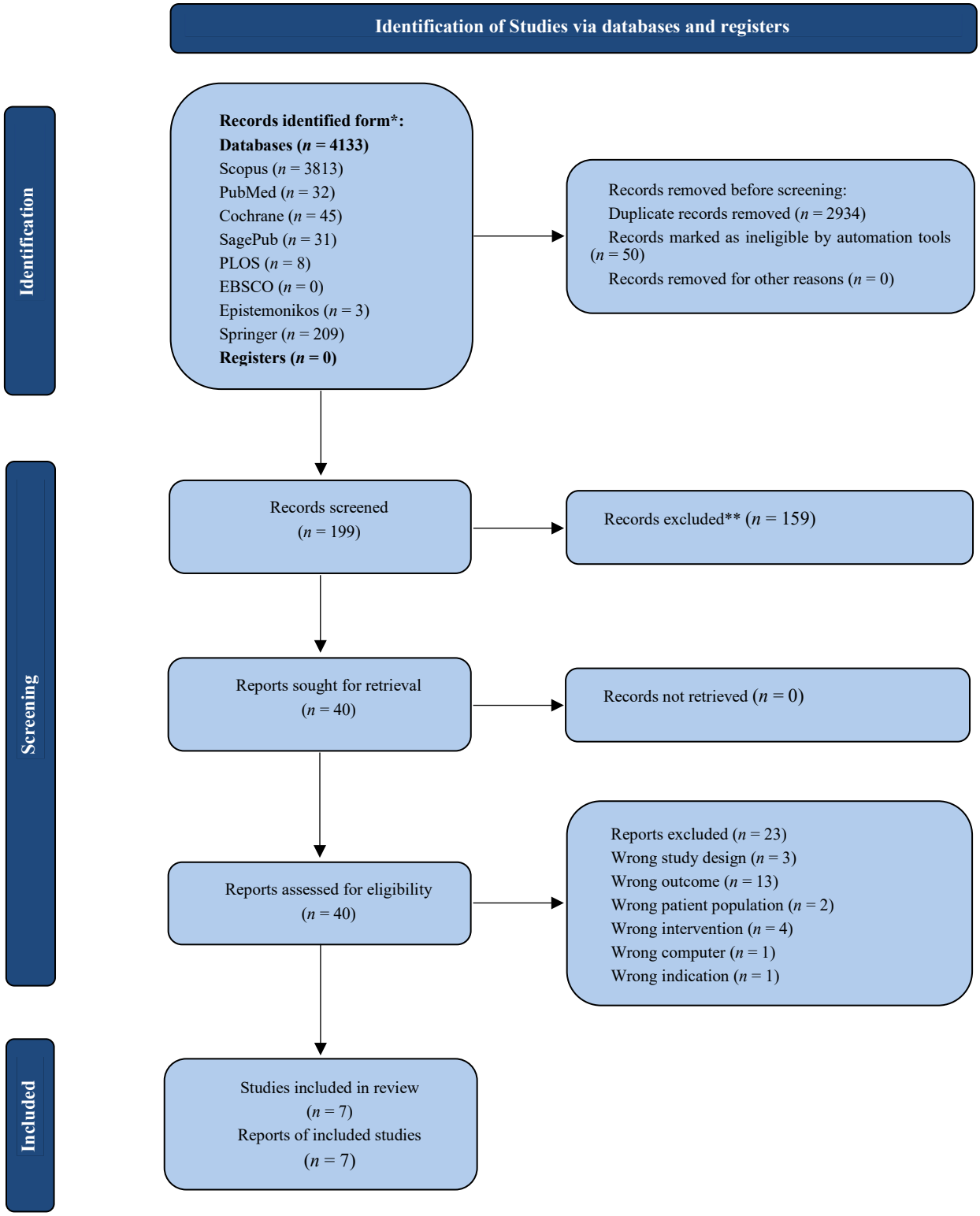

Figure 2. PRISMA flowchart demonstrating literature search and selection process

The meta-analysis in this study includes literatures published from January 2014 till June 2024 with study design of cross sectional, cohort, and case control studies, comparing the relationship of BCG vaccination and TBM. As shown in Table 1, it computed the distribution of each article on TB vaccinated and not vaccinated patients. The numbers of BCG vaccinated pediatric patients were 1171 in the study of Liao et al **(20)**, 9 children in the study performed by Al Yazidi et al **(23)**, 85 children according to the study done by Mazhar et al **(24)**, 85 children in the study done by Morris et al **(25)**, 75 children based on the study of Rehman et al **(26)**, and 108 children in the study of Borges et al **(27)**. Rashid et al **(28)** noted that 168 of their samples had vaccination history while the other 182 lacked history of vaccination.

The frequencies of Tuberculosis (TB) cases by TBM and non-TBM in the vaccinated and control groups across seven studies from various countries are shown in Table 2. The outcomes are categorized into two groups (vaccinated and control group). According to data, the proportion of TBM cases among vaccinated cases (20.28%), was lower than the cases of non-TBM (79.72%). According to the data, the proportion of TB meningitis cases among those vaccinated (20.28%), was lower than that of the control (32.01%). The number of non-TB meningitis cases was 1352 (79.72%) and 597 (67.99%) in the vaccinated and control groups, respectively. The total number of TB meningitis cases in the entire group was 625 (24.28%), while the number of non-TB meningitis cases was 1949 (75.72%).

Table 2. Frequency of vaccinated and unvaccinated populations with meningitis in each study

No	Author	Intervention	TBM N(%)	Non-TBM N(%)
1	Liao et al **(20)**, China	Vaccinated	273 (23,32)	898 (76,69)
		Control	139 (37,67)	230 (62,33)
2	Al Yazidi et al **(23)**, Australia	Vaccinated	0 (0)	9 (100)
		control	3 (30)	7 (70)
3	Mazhar et al **(24)**, Pakistan	Vaccinated	15 (17,65)	70 (82,35)
		control	35 (30,43)	80 (69,57)
4	Morris et al **(25)**, Canada	Vaccinated	7 (6,36)	103 (93,64)
		control	9 (10)	81 (90)
5	Rehman et al **(26)**, Pakistan	Vaccinated	23 (30,67)	23 (30,67)
		control	42 (56)	42 (56)
6	Borges et al **(27)**, Portugal	Vaccinated	5 (4,63)	103 (95,37)
		control	2 (5,41)	35 (94,59)
7	Rashid et al **(28)**, Pakistan	Vaccinated	21 (12,5)	147 (87,5)
		control	51 (28,02)	131 (71,98)
Total		Vaccinated	344 (20,28)	1352 (79,72)
		Control	281 (32,01)	597 (67,99)

The meta-analysis (Figure 3) demonstrated excellent homogeneity across the included studies. The I^2 statistic was 0% (95% CI: 0%-75%), indicating no observed heterogeneity between studies (Figure 4). This finding was corroborated by Cochran's Q test (Q=3.37, df=6, *P*=0.76), which showed no statistically significant heterogeneity. The between-study variance (τ^2) was 0.00, confirming minimal variance between studies. The overall test for the effect showed Z=7.38 (*P*<0.00001), indicating a highly significant inverse effect of BCG vaccination.

This Begg's test analysis (Figure 5) reveals minimal evidence of publication bias in the systematic review. The rank correlation plot shows studies scattered around the horizontal reference line with no clear pattern (Kendall's τ=0.048, *P*=0.881), indicating no significant correlation between the effect sizes and their variances. The funnel plot (Figure 5) displays relatively symmetric distribution of studies around the overall effect estimate, with Egger's test confirming this symmetry (*P*=0.248). Both statistical tests suggest publication bias is unlikely to substantially affect the meta-analysis results, supporting the validity of the pooled effect estimates.

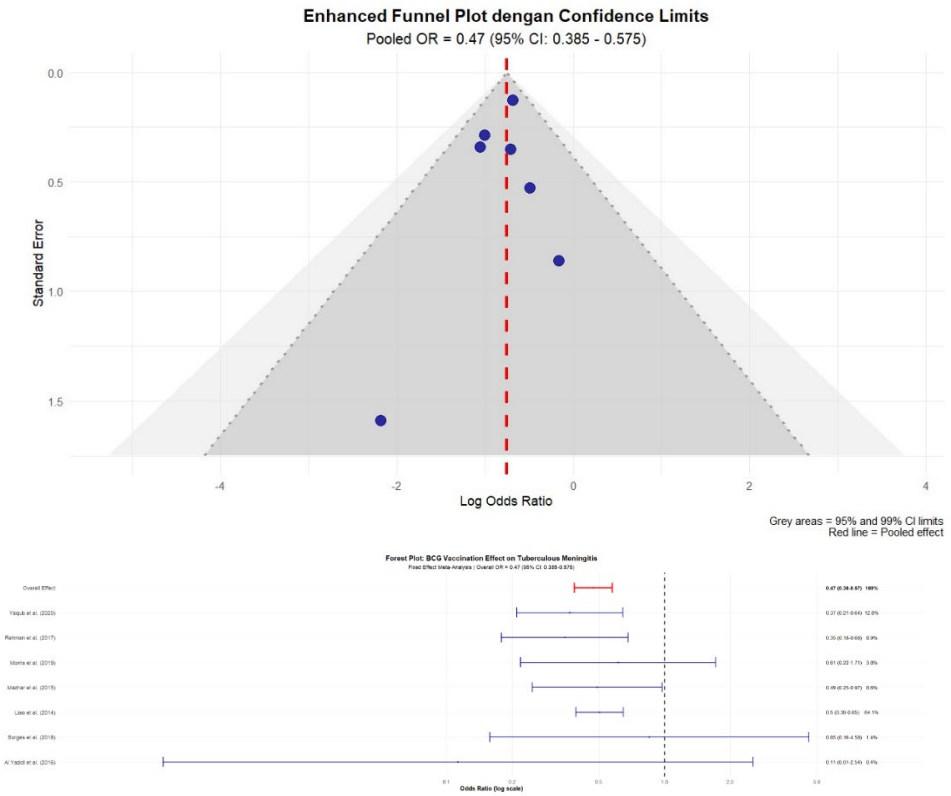

Figure 3. Funnel and Forest plot of the meta-analysis

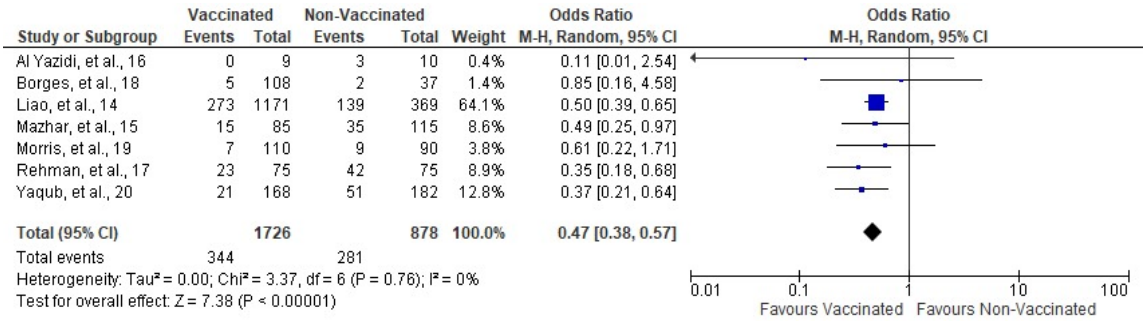

Figure 4. Statistical analysis of included studies

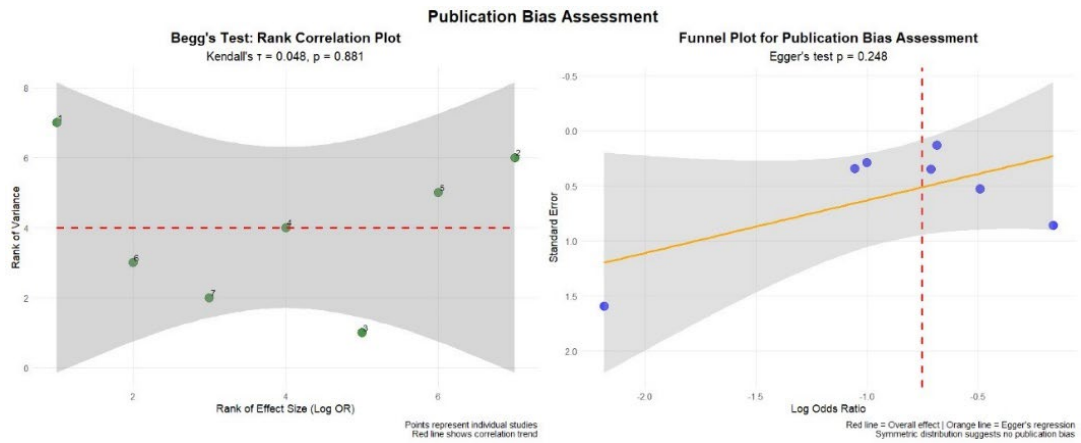

Figure 5. Begg's test and Funnel plot for publication bias assessment

4. Discussion

Our meta-analysis demonstrates a significant inverse association of BCG vaccination against TBM in children, with a pooled OR of 0.47 (95% CI 0.38-0.57). This finding indicates that control group children are approximately twice as likely to develop TBM compared to those who received BCG vaccination (1/OR: 1/0.47 = 2.13). Given the severe clinical consequences of TBM, including mortality rates reaching 42.12% in hospitalized pediatric patients and neurological sequelae affecting nearly half of survivors **(4, 29, 30)**, this finding effect carries substantial clinical significance. The consistent significant association across our analyzed studies reinforces BCG vaccination as a critical public health intervention for preventing severe forms of tuberculosis in children.

The results of this study are in contrast with the results of the studies of Al Yazidi et al **(23)**, Mazhar et al **(24)**, Morris et al **(25)**, and Rehman et al **(26)**, which indicated that not vaccinated cases were more prevalent than samples with BCG vaccination history. This might be due to conducting the study in a country with low incidence of meningitis tuberculosis infection. Another reason mentioned in the study of Mazhar et al **(24)** was that the criteria for BCG vaccination was based on the presence or absence of scar on deltoid, whereas the history of BCG vaccination does not necessarily leaves scars.

TBM is a leading cause of morbidity and mortality associated with tuberculosis in children, mainly due to unspecific clinical manifestiations compared to other bacterial meningitis, as well as inadequate and time-consuming microbiological tests to confirm the diagnosis **(31, 32)**. Non-specific nature of TBM symptoms & poor, limited or in the majority of cases, inadequate diagnostics mechanisms, children suffering from TBM are often prone to delay in diagnosis and management. Almost half of TBM patients continue to have neurological sequelae later on, and mortality reaches 42.12% among hospitalized patients **(4, 30, 31)**.

Mycobacterium tuberculosis causes TBM, which gain access via inhalation droplets leading to local infection in the lungs. It will proliferate along vascular and lymphatic routes to the system organs such as CNS **(33)**.

Risk factors for TBM are similar to those of pulmonary tuberculosis like socioeconomic, malnutrition, density, immune factors, and endemic areas **(34, 35)**. By reviewing 7 articles, it was estimated that about 32.06% of the samples were that of TBM. In Liao et al **(20)**, the population of TBM were as many as 412 (36.52%) out of 1,540. The lowest incidence of TBM was reported in Borges et al **(27)** which was 7 (0.05%) among total of 145 samples. Out of TB cases, there were 1 million children, and it was estimated for more than 100 000 TBM cases annually and it is estimated that the number will always increase **(36)**.

BCG vaccination is not primarily or necessarily for the prevention of primary infection, the goal is that TB does not progress to reach severe infection stage. BCG has low efficacy against primary TB infection for a number of reasons including human and mycobacterial genetics, environmental mycobacterial exposure, viral and/or parasitic co-infection, geographic location, and socioeconomic and nutritional status **(37)**. The meta-analysis results of this study conducted with the inclusion and exclusion of the articles obtained odd ratio of 0.47 (95% CI 0.38 - 0.57), explaining a protective effect between BCG vaccination and incidence of TBM in children. BCG vaccination can prevent children from having the risk of TBM according to the results of analyzed data.

Our findings align with previous systematic reviews and meta-analyses examining BCG significant association against severe tuberculosis. Roy et al **(22)** reported a risk ratio of 0.81 (95% CI 0.71-0.92) across 14 studies, indicating 19% greater protection against TBM with BCG vaccination compared to non-vaccination. Similarly, Thilothammal et al **(38)** found BCG vaccine effectiveness of 52-84% against TBM in a study of 406 patients, while Rofiq et al **(39)** demonstrated a 0.72-fold decrease in TBM risk among BCG-vaccinated children. These consistent findings across different populations and time periods support the robustness of BCG protective effect against TBM. Additionally, the large-scale retrospective study by Teo and Shingadia **(40)** on over 50,000 children aged 14-15 years showed 78.4% protective efficacy (99% CI 69%-86%) against miliary TB and meningitis, with all severe cases occurring in control individuals.

BCG vaccination primary mechanism against TBM operates through prevention of disease progression rather than initial infection. The vaccine enhances immune responses by promoting CD4+ and CD8+ T cell activation, which prevents tuberculosis from progressing to severe forms such as miliary TB and TBM **(37)**. This mechanism is particularly relevant given that TBM develops when *Mycobacterium tuberculosis* gains access through inhalation, establishes local pulmonary infection, and subsequently disseminates via vascular and lymphatic routes to the central nervous system **(33)**. The clinical importance of this protection is underscored by real-world evidence, such as increased TBM incidence observed in Bosnia and Herzegovina following decreased BCG vaccination program coverage in 2003 **(41)**. The analysis of six studies showed data in 3 articles with significant results that BCG vaccination

prevented TBM in children. Some studies with the highest weighting were researches by Rashid et al **(28)** with an OR= 0.39 (95% CI=0.21 - 0.64), Liao et al **(20)**, with an OR of 0.5 (CI 95%, 0.39 – 0.65), Mazhar et al **(24)**, with an OR of 0.49 (CI 95%, 0.25-0.98), and Rehman et al **(26)**, with an OR of 0.35 (CI 95%, 0.18-0.68). However, BCG protective efficacy can be influenced by various factors including human and mycobacterial genetics, environmental mycobacterial exposure, co-infections, geographic location, and socioeconomic status **(37)**.

The contents of the other three results of the analysis yielded differing outcomes. Al Yazidi et al **(23)**, Morris et al **(25)**, and Borges et al **(27)** yielded insignificant data outcomes not supporting the role of BCG vaccination in TBM among children significantly. The limitations in Al Yazidi et al **(23)** were the small number of the population, and the absent of pediatric TB patients group who received outpatient care that could cause bias. Morris et al **(25)** limitation was human error because the doctor who treated the patient was not contacted when the data were collected, thus the TB cases were not reported.

No evidence of publication bias was observed from the funnel plot. The funnel plot points are remote with 1 small size study. To reduce the likelihood of heterogeneity of other infections, researchers restricted the analysis to extrapulmonary tuberculosis, specifically TBM. The observed homogeneity (I^2 = 0%, *P*=0.75) across studies strengthens the confidence in our findings, suggesting consistent significant inverse association of BCG vaccination across different populations and settings. However, this apparent homogeneity should be interpreted cautiously given the relatively small number of included studies (n = 7). While Cochran's Q test showed no significant heterogeneity, the limited number of studies may reduce the statistical power to detect meaningful differences between studies. The consistent direction and magnitude of effect across studies from diverse geographical regions (China, Pakistan, Australia, Portugal, Canada, and India) support the generalizability of our findings.

Several limitations must be acknowledged in this meta-analysis. First, heterogeneity in population age across included studies may influence the generalizability of findings across different pediatric age groups. Second, we were unable to analyze the variable levels of tuberculosis exposure or other risk factors, as not all included studies compared these factors between BCG-vaccinated and control populations. Third, the limited number of available studies meeting inclusion criteria restricts the statistical power for the subgroup analyses and limits our ability to detect publication bias. Fourth, differences in BCG vaccination confirmation methods across studies (clinical history versus scar presence) may introduce misclassification bias, as vaccination history does not necessarily result in visible scarring **(24)**. Finally, variations in TBM diagnostic criteria and case definitions across studies may contribute to heterogeneity outcome despite the apparent statistical homogeneity observed.

This meta-analysis provides robust evidence supporting BCG vaccination protective effect against TBM in children, with control group having approximately twice the risk of developing this severe form of tuberculosis. The consistency of findings across diverse geographical settings supports the continued inclusion of BCG vaccination in pediatric immunization programs, particularly in regions with high tuberculosis burden. Future research should focus on conducting larger prospective studies with standardized diagnostic criteria and comprehensive assessment of confounding factors. Investigation of optimal vaccination timing, alternative delivery routes (such as mucosal administration), and strategies to enhance vaccine efficacy in different populations would further strengthen evidence-based tuberculosis prevention strategies. Given the estimated 100,000 annual cases of pediatric TBM globally **(36)**, maintaining and strengthening BCG vaccination programs remains a critical public health priority for preventing severe tuberculosis outcomes in children.

5. Conclusion

This meta-analysis highlights the higher number of children vaccinated with BCG, exceeding the number of children who have not received the vaccine represented in different countries. Furthermore, among vaccinated children, the incidence of TBM is significantly lower compared to the control group children. This highlights a significant inverse association between BCG vaccination and reduced incidence of TBM in children, underscoring the vaccine efficacy in mitigating the risk of TBM as one of the severe manifestations of tuberculosis.

6. Declarations

6.1 Acknowledgment

We would like to extend our sincere thanks to Atika, Department of Public Health Science-Preventive Medicine, Faculty of Medicine, Universitas Airlangga, for their invaluable support in performing the statistical analysis. Their expertise and assistance were crucial in ensuring the accuracy and rigor of our data analysis process.

6.2 Ethical Considerations

This review was prepared based on previously published studies and did not involve any human subject; thus, ethics board approval was not required.

6.3 Authors' Contributions

Initial screening was done by six authors (T.N.L, D.Z.S, M.Z.S, M.F.K, I.M.A, and H.I.R). Remaining studies were screened with full-text by four authors (M.R.P, A.I.U, F.R, N). Doubtful decisions, disagreement, and further discussions related to unclear paper were done and settled with discussions led by senior author (S). Two authors (N and M.F.K) evaluated the bias risk. Any conflicts or discrepancies in the assessments were discussed with a third author (A.R.A). Data analysis was done by N, M.F.K, and T.N.L. Manuscript was written by A.R.A and H.I.R and consulted by senior author (S). All authors have reviewed the manuscript and given their approval for publication.

6.4 Conflict of Interests

The authors state no conflict of interest or personal relationship that might influence the research presented in this paper.

6.5 Financial Support and Sponsorship

This research was conducted independently without any external funding or sponsorship from any organization or institution.

6.6 Using Artificial Intelligence Tools (AI Tools)

Rayyan.ai was used to input the collected studies, followed with duplicate removal and screening process.

References

1. Bourgi K, Fiske C, Sterling TR. Tuberculosis meningitis. Curr Infect Dis Rep. 2017;19(11):39. [DOI:10.1007/s11908-017-0595-4] [PMID]
2. Ducomble T, Tolksdorf K, Karagiannis I, Hauer B, Brodhun B, Haas W, et al. The burden of extrapulmonary and meningitis tuberculosis: an investigation of national surveillance data, Germany, 2002 to 2009. Euro Surveill. 2013; 18(12):20436. [PMID] [DOI:10.2807/ese.18.12.20436-en]
3. Sandgren A, Hollo V, Van der Werf MJ. Extrapulmonary tuberculosis in the European Union and European Economic Area, 2002 to 2011. Euro Surveill. 2013;18(12):20431. [DOI:10.2807/ese.18.12.20431-en] [PMID]
4. Navarro-Flores A, Fernandez-Chinguel JE, Pacheco-Barrios N, Soriano-Moreno DR, Pacheco-Barrios K. Global morbidity and mortality of central nervous system tuberculosis: a systematic review and meta-analysis. J Neurol. 2022;269(7):3482-94. [PMID] [DOI:10.1007/s00415-022-11052-8] [PMCID]
5. Lee HG, William T, Menon J, Ralph AP, Ooi EE, Hou YA, et al. Tuberculous meningitis is a major cause of mortality and morbidity in adults with central nervous system infections in Kota Kinabalu, Sabah, Malaysia. BMC Infect Dis. 2016;16(1):1640. [PMID] [PMCID] [DOI:10.1186/s12879-016-1640-x]
6. Dodd PJ, Prendergast AJ, Beecroft C, Kampmann B, Seddon JA. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. Thorax. 2017;72(6):559-75. [PMID] [PMCID] [DOI:10.1136/thoraxjnl-2016-209421]
7. Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: a mathematical modelling study. Lancet Glob Health. 2017;5(9):e898-906. [DOI:10.1016/S2214-109X(17)30289-9] [PMID]
8. Anderson NE, Somaratne J, Mason DF, Holland D, Thomas MG. Neurological and systemic complications of tuberculous meningitis and its treatment at Auckland City Hospital, New Zealand. J Clin Neurosci. 2010;17(9):1114-8. [DOI:10.1016/j.jocn.2010.01.006] [PMID]
9. Martin U. Prevalensi TB laten pada petugas kesehatan di RSUP H. Adam Malik (Doctoral dissertation, Universitas Sumatera Utara, Indonesia). Repository USU. 2008. [cited 2025 Jul 7]; Available from: [https://repositori.usu.ac.id/handle/123456789/45540]
10. World Health Organization. Tuberculosis: Fact sheets. 2025. [cited 2025 Jul 7]; Available from: [https://www.who.int/news-room/fact-sheets/detail/tuberculosis]

11. Jomehpour N, Soleimanpour S, Sankian M. Diagnosis of latent tuberculosis infection: promising antigens corresponding information. Iran J Med Microbiol. 2023;17(5):505-19. [DOI:10.30699/ijmm.17.5.505]

12. Jafri YS. Status imunisasi BCG dengan kejadian tuberkulosis paru pada anak usia balita. Pros Sem Kesehat Perintis. 2018;1(2):54. [DOI:10.35473/ijnr.v2i1.228]

13. Okafor CN, Rewane A, Momodu II. Bacillus Calmette Guerin. [Updated 2025 Jul 07]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: [https://www.ncbi.nlm.nih.gov/books/NBK538185/]

14. Covián C, Fernández-Fierro A, Retamal-Díaz A, Díaz FE, Vasquez AE, Lay MK, et al. BCG-induced cross-protection and development of trained immunity: implication for vaccine design. Front Immunol. 2019;10:2806. [PMID] [PMCID] [DOI:10.3389/fimmu.2019.02806]

15. Patel VB, Theron G, Lenders L, Matinyena B, Connolly C, Singh R, et al. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous meningitis in a high-burden setting: a prospective study. PLoS Med. 2013; 10(10):e1001536. [PMID] [PMCID] [DOI:10.1371/journal.pmed.1001536]

16. Tobin EH, Tristram D. Tuberculosis Overview. [Updated 2025 Jul 07]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: [https://www.ncbi.nlm.nih.gov/sites/books/NBK441916/]

17. Uranga S, Marinova D, Martin C, Aguilo N. Protective efficacy and pulmonary immune response following subcutaneous and intranasal BCG administration in mice. J Vis Exp. 2016;(115):e54443. [DOI:10.3791/54440-v] [PMID] [PMCID]

18. Perdomo C, Zedler U, Kühl AA, Lozza L, Saikali P, Sander LE, et al. Mucosal BCG vaccination induces protective lung-resident memory T cell populations against tuberculosis. MBio. 2016; 7(6):10-128. [DOI:10.1128/mBio.01686-16] [PMID] [PMCID]

19. Manjaly Thomas ZR, McShane H. Aerosol immunisation for TB: matching route of vaccination to route of infection. Trans R Soc Trop Med Hyg. 2015;109(3):175-81. [DOI:10.1093/trstmh/tru206] [PMID] [PMCID]

20. Liao Q, Zheng Y, Wang Y, Ye L, Liu X, Jiao W, et al. Effectiveness of Bacillus Calmette-Guérin vaccination against severe childhood tuberculosis in China: a case-based, multicenter retrospective study. Int J Infect Dis. 2022;121: 113-9. [DOI:10.1016/j.ijid.2022.04.023] [PMID]

21. Trunz BB, Fine PE, Dye CJ. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. The Lancet. 2006;367(9517): 1173-80. [DOI:10.1016/S0140-6736(06)68507-3] [PMID]

22. Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. BMJ. 2014;349: g4643. [DOI:10.1136/bmj.g4643] [PMID] [PMCID]

23. Al Yazidi LS, Marais BJ, Wickens M, Palasanthiran P, Isaacs D, Outhred A, et al. Overview of paediatric tuberculosis cases treated in the Sydney Children's Hospitals Network, Australia. Public Health Res Pract. 2019;29(2). [DOI:10.17061/phrp28231807] [PMID]

24. Mazhar O, Khan SA, Qaisar MA, Bhatti ZI, Qureshi MA. Incidence of Several Forms of Tuberculosis (TB) and Their Bacillus Calamette Guerin (BCG) Vaccination Status among Children. Pak J Med Health Sci. 2022;16(6): 1071. [DOI:10.53350/pjmhs221661071]

25. Morris SK, Giroux RJ, Consunji-Araneta R, Stewart K, Baikie M, Kakkar F, et al. Epidemiology, clinical features and outcomes of incident tuberculosis in children in Canada in 2013-2016: Results of a national surveillance study. Arch Dis Child. 2021;106(12):1165-70. [DOI:10.1136/archdischild-2021-322092] [PMID]

26. Rehman MU, Bibi S, Imran I, Khan Z, Khan AS, Gilani SY. Role of tuberculin test as a diagnostic tool for tuberculosis. J Ayub Med Coll Abbottabad. 2018;30(4):529-33.

27. Borges M, Rocha AP, Veiga de Macedo C, Gouveia C, Candeias F, Brito MJ. Pediatric Tuberculosis: 12 Years of Experience in a Tertiary Referral Center in Portugal. Acta Medica Portuguesa. 2022;35(5):367-75. [DOI:10.20344/amp.16474] [PMID]

28. Rashid U, Yaqub U, Kasif A, Bari A. Frequency of various forms of tuberculosis (TB) and their Bacillus Calamette Guerin (BCG) vaccination

status in children. Pak Pediatr J. 2014;38(3): 173-8.

29. Chiang SS, Khan FA, Milstein MB, Tolman AW, Benedetti A, Starke JR, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2014;14(10):947-57. [DOI:10.1016/S1473-3099(14)70852-7] [PMID]

30. du Preez K, Jenkins HE, Donald PR, Solomons RS, Graham SM, Schaaf HS, et al. Tuberculous meningitis in children: a forgotten public health emergency. Front Neurol. 2022;13:751133. [DOI:10.3389/fneur.2022.751133] [PMID] [PMCID]

31. Méchaï F, Bouchaud O. Tuberculous meningitis: challenges in diagnosis and management. Rev Neurol (Paris). 2019;175(7-8):451-7. [DOI:10.1016/j.neurol.2019.07.007] [PMID]

32. Sagarzazu AS, Llanos EG, Radigales JR, Cano NR, Torre PP, Gutierrez HU, et al. Meningitis tuberkulosoa, ezohikoa baina posiblea. Osagaiz J Health Sci. 2024;8:5133.

33. Slane VH, Unakal CG. Tuberculous Meningitis. [Updated 2022 Nov 18]. StatPearls [Internet]. 2023.

34. Khanna SR, Kralovic SM, Prakash R. Tuberculous meningitis in an immunocompetent host: A case report. Am J Case Rep. 2016;17:977-81. [DOI:10.12659/AJCR.900762] [PMID] [PMCID]

35. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. Pulm Med. 2013; 2013(1):828939. [DOI:10.1155/2013/828939] [PMID] [PMCID]

36. Seddon JA, Tugume L, Solomons R, Prasad K, Bahr NC. Tuberculous Meningitis International Research Consortium. The current global situation for tuberculous meningitis: epidemiology, diagnostics, treatment and outcomes. Wellcome Open Res. 2019;4:167. [DOI:10.12688/wellcomeopenres.15535.1] [PMID] [PMCID]

37. Moliva JI, Turner J, Torrelles JB. Immune responses to Bacillus Calmette-Guérin vaccination: why do they fail to protect against Mycobacterium tuberculosis?. Front Immunol. 2017;8:407. [DOI:10.3389/fimmu.2017.00407] [PMID] [PMCID]

38. Thilothammal N, Krishnamurthy PV, Runyan DK, Banu K. Does BCG vaccine prevent tuberculous meningitis?. Arch Dis Child. 1996;74(2):144-7. [DOI:10.1136/adc.74.2.144] [PMID] [PMCID]

39. Rofiq A. Daya lindung vaksin BCG terhadap meningitis tuberkulosis anak di beberapa RS di Jakarta. 2000.

40. Teo SS, Shingadia DV. Does BCG have a role in tuberculosis control and prevention in the United Kingdom?. Arch Dis Child. 2006;91(6): 529-31. [DOI:10.1136/adc.2005.085043] [PMID] [PMCID]

41. Puvacic S, Dizdarevic J, Santic Z, Mulaomerovic M. Protective effect of neonatal BCG vaccines against tuberculous meningitis. Bosn J Basic Med Sci. 2004;4(1):46-9. [PMID] [PMCID] [DOI:10.17305/bjbms.2004.3460]