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Impact of BCG Vaccination on Morbidity and Mortality among Adult Patients with Tuberculous Meningitis: A Prospective Cohort Analysis

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Abstract

Background: Tuberculous Meningitis is a severe form of Tuberculosis with high morbidity and mortality. BCG has long been employed to prevent severe forms of tuberculosis, particularly useful in the paediatric population, as suggested by multiple studies. However, there is scarcity of research concerning its efficacy in the adult age group. Consequently, this study was conducted to investigate the impact of BCG vaccination status on Tuberculous Meningitis (TBM) outcomes using the modified Rankin Scale.

Methods: A prospective cohort study was conducted from September 2022 to February 2024, involving adult patients with TBM. Participants were divided into two groups based on BCG vaccination status and followed-up for six months. Morbidity and mortality were assessed using the modified Rankin Scale (mRS). Data were analysed using SPSS, with a Chi-square test to compare outcomes, considering a p-value <0.05 as significant. Nutritional status and BCG vaccination were key factors in the analysis.

Results: In a study of 65 participants with TBM, the mean age was similar between BCG-vaccinated and unvaccinated groups, with more females than males. Clinical symptoms included fever, headache, and seizures, with some participants also having pulmonary TB. Nutritional status varied, with 29% being underweight. Over a six-month follow-up, no significant differences were found between vaccinated and unvaccinated groups or between different BMI categories in terms of functional dependence and mortality. Statistical analysis showed no significant correlation between BCG vaccination or BMI and clinical outcomes.

Conclusion: The findings indicate that morbidity and mortality outcomes in adult and adolescent patients with TBM are similar regardless of BCG vaccination status. Additionally, no significant correlation was found between malnutrition and severe disease or increased mortality. This lack of association may be due to the dominant influence of TBM, which appears to have a consistent impact on all study participants.

Key words: Tuberculous Meningitis (TBM), BCG, adult age group, adolescent age group.

Introduction

Tuberculous meningitis (TBM) occurs when *M. tuberculosis* spreads to the cerebrospinal fluid and meninges, leading to conditions such as ischaemia, hydrocephalus, and increased intracranial pressure, which cause significant brain injury and neurodisability. Key risk factors for TBM include young age and HIV infection. The BCG (Bacillus Calmette-Guérin) vaccine, used for over five decades to prevent tuberculosis (TB), is particularly effective in young children. According to a meta-analysis by Fine[1], the BCG vaccine offers moderate protection - 50% against any form of TB, 64% against TBM, and 71% against TB-related deaths – with greater efficacy against miliary TB and TBM compared to pulmonary TB. While numerous studies confirm the BCG vaccine's effectiveness in reducing morbidity and mortality in children with severe forms of TB, such as miliary tuberculosis and TBM, research on its impact in adults is limited. This study aimed to assess the relationship between BCG vaccination status and the morbidity and mortality outcomes in non-HIV adolescents and adults with TBM, as well as to explore the influence of nutritional status on these outcomes. The primary objective was to compare the morbidity and mortality of TBM based on BCG vaccination status, while the secondary objective was to examine the outcomes in relation to nutritional status.

Material and Methods

An observational prospective cohort study was conducted between September 2022 and August 2023. Patients with TBM were divided into two groups based on their BCG vaccination status and were followed-up over time. Eligible patients, who were newly diagnosed with TBM, over 12 years of age, and HIV-negative, were selected from the wards and ICU of the hospital after meeting the inclusion criteria. Follow-up occurred in person at OPDs or via telephone, weekly for the first two months and biweekly

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for the next four months. Morbidity and mortality were assessed at each follow-up stage using the modified Rankin Scale (mRS), where a score of 0 - 2 indicated functional independence, and a score of 3 - 6 indicated functional dependence, with 6 signifying death.

Participants who met the inclusion criteria and provided informed consent were enrolled in the study. Their demographic and clinical profiles were recorded, including a comprehensive clinical examination within 24 hours of admission, which covered history-taking, examination of BCG scars, and assessment of nutritional status. BCG vaccination was verified by examining for a scar on the upper arms, historical recollection, or available documentation, such as a vaccine card. In the absence of a scar or documentation, patients were classified as unvaccinated. Participants' height and weight were measured at recruitment to calculate their BMI. The sample size was determined using Epi Info 7 software, requiring a minimum of 30 participants per group. Participants were categorised into BCG vaccinated and unvaccinated groups and further divided into underweight and normal/overweight groups based on their nutritional status. Those lost to follow-up were excluded from the final analysis.

Data was entered into an MS Excel sheet and analysed using SPSS 20.0 software. Categorical variables were presented as proportions, and continuous variables as means with Standard Deviation (SD). A Chi-square test was employed to compare morbidity and mortality outcomes between the groups, with a p-value of <0.05 considered statistically significant.

Results

The study included 65 adult and adolescent participants, as shown in Fig. 1. The mean age was 27.5 (± 15.5) years in the unvaccinated group and 29.4 (± 14.7) years in the vaccinated group. Of the participants, 25 (38.4%) were male and 40 (61.6%) were female, with 12 unvaccinated males and 15 unvaccinated females.

Clinical Profile: Participants presented with symptoms including fever, headache, altered sensorium, nausea, vomiting, and seizures. Some also had co-morbidities, with pulmonary TB being the most common. The distribution of symptoms and co-morbidities between the two groups is summarised in Table I.

Nutritional Profile: Based on Asian BMI criteria, 29% of participants were underweight (BMI <18.5), 51% had normal weight (BMI 18.5 - 22.9), and 20% were overweight (BMI ≥23).

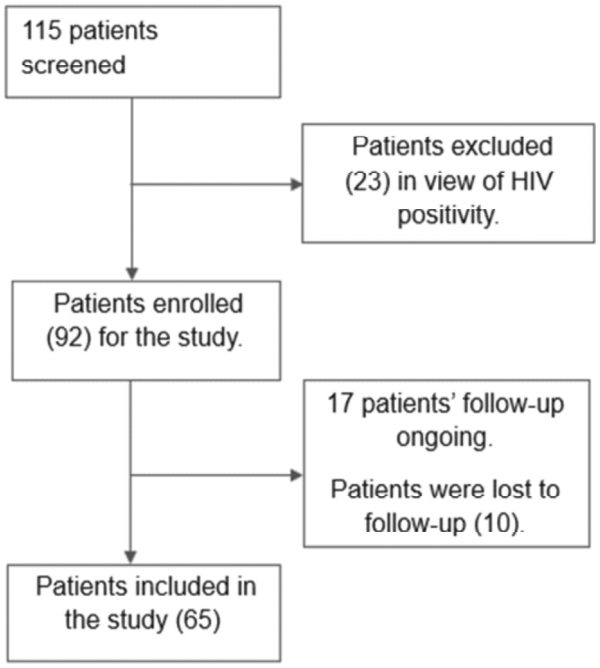

Fig. 1: *Flow diagram for the study.*

Table I: Table depicting the presenting symptoms and comorbidity profile of the participants.

	Unvaccinated Group (n = 30); (Number of participants, percentage)	Vaccinated group (n = 35); (Number of participants, percentage)
Symptom		
Fever ≥30 Days	14 (46.6%)	12 (34.2%)
Headache	28 (93.3%)	34 (97.1%)
Altered Sensorium	30 (100%)	30(85.7%)
Altered Sensorium ≥3 days	13 (43.3%)	13 (37%)
Seizures	9 (30%)	10 (28.5%)
Nausea and Vomiting	26 (86.6%)	31 (88.5%)
Co-morbidity		
Extra Neural TB	15 (50%)	20 (57.1%)
Pulmonary TB	15 (50%)	16 (45.7%)
Past History of TB	5 (16.6%)	7 (20%)
Hypertension	1 (3%)	3 (8.5%)
Diabetes	0 (0%)	2 (5.7%)

Follow-up: Participants were followed for six months. Functional dependency and mortality rates were analysed based on vaccination status (Table II) and nutritional status (Table III) using Chi-square analysis. Initially, 100% of

Table II: Table depicting the follow-up of participants and fraction of participants who were functionally dependent at follow-up and overall mortality according to vaccination status.

	Total Participants (n = 65)		
Follow-up Duration	Unvaccinated Participants (N = 30) Functionally Dependent*	Vaccianted Participants (N=35) Functionally Dependent*	p-Value
Week 4	29 (96.7%)	35 (100%)	0.462
Week 5	26 (86.7%)	31 (88.6%)	1.00
Week 6	26 (86.7%)	28 (80%)	0.475
Week 7	23 (76.7%)	25 (71.4%)	0.63
Week 8	20 (66.7%)	22 (62.9%)	0.74
Week 10	16 (53.3%)	18 (51.4%)	0.87
Week 12	14 (46.7%)	17 (48.6%)	0.87
Week 14	14 (46.7%)	16 (45.7%)	0.93
Week 16	14 (46.7%)	15 (42.9%)	0.758
Week 18	14 (46.7%)	15 (42.9%)	0.758
Week 20	13 (43.3%)	15 (42.9%)	0.96
Week 22	13 (43.3%)	15 (42.9%)	0.96
Week 24	13 (43.3%)	15 (42.9%)	0.96
Overall Mortality	12 (40.0%)	13 (37.1%)	0.81

**During follow-up in case of the death of a participant the mRS(score-6) of that participant is carried forward.*

Table III: Table depicting the follow-up of participants and fraction of participants who were functionally dependent at follow-up and overall mortality according to nutrition status.

	Total Participants (n = 65)		
Follow-up Duration	Unvaccinated Participants (N = 30) Functionally Dependent*	Vaccianted Participants (N=35) Functionally Dependent*	p-Value
Week 4	19 (100%)	45 (97.8%)	1.00
Week 5	17 (89.5%)	40 (87.0%)	1.00
Week 6	16 (84.2%)	38 (82.6%)	1.00
Week 7	16 (84.2%)	32 (69.6%)	0.353
Week 8	14 (73.7%)	28 (60.9%)	0.326
Week 10	10 (52.6%)	24 (52.2%)	0.973
Week 12	8 (42.1%)	23 (50.0%)	0.562
Week 14	8 (42.1%)	22 (47.8%)	0.674
Week 16	8 (42.1%)	21 (45.7%)	0.794
Week 18	8 (42.1%)	21 (45.7%)	0.794
Week 20	8 (42.1%)	20 (43.5%)	0.919
Week 22	8 (42.1%)	20 (43.5%)	0.919
Week 24	8 (42.1%)	20 (43.5%)	0.919
Overall Mortality	7 (36.8%)	18 (39.1%)	0.863

**During follow-up in case of the death of a participant the mRS (score-6) of that participant is carried forward.*

participants were functionally dependent in both vaccinated and unvaccinated groups. Over time, this proportion decreased, with similar percentages of functional dependency at the end of six months in both unvaccinated and vaccinated groups (43.3% vs. 42.9%; p = 0.96). Mortality rates were also comparable (40.0% vs. 37.1%; p = 0.81). Additionally, of the 65 participants, 19 (29.2%) were underweight (BMI <18.5 kg/m^2), and the rest had normal or overweight BMI. The proportion of functionally dependent patients decreased gradually in both groups during the follow-up. By the end of 24 weeks, the proportion of functionally dependent participants was similar between underweight and normal/overweight participants (42.1% vs. 43.5%; p = 0.919), with comparable overall mortality rates (36.8% vs. 39.1%; p = 0.863).

Discussion

This study aimed to evaluate the morbidity and mortality outcomes of TBM in relation to BCG vaccination and nutritional status in non-HIV adolescents and adults. The findings showed that morbidity and mortality rates were similar across both vaccinated and unvaccinated groups, as well as across different nutritional status groups, indicating a consistent and uniform impact on the participants.

While BCG vaccination is known to offer substantial protection against severe TB forms, including TBM, especially in children, evidence regarding its efficacy in adults is less conclusive[2]. The decline in BCG efficacy with age might be due to waning immunity or misclassification. A case-control study by Thilothammal *et al*[3] showed that BCG efficacy was high (79% - 82%) in children under 8 years but dropped to 19% in older children, highlighting diminished immunity with age.

Despite extensive research indicating a significant protective effect of BCG against TBM, our study did not find a significant correlation between malnutrition and severe disease or increased mortality. This discrepancy may be due to the overwhelming impact of TBM, which seems to exert a uniform effect across all participants.

Rodrigues *et al* conducted a meta-analysis demonstrating BCG's strong protective effect against TBM and miliary TB, with 86% protection in randomised trials and 75% in other

studies. However, the protection against pulmonary TB varied, likely due to factors such as patient age, waning BCG effectiveness, and the diverse mechanisms of pulmonary TB[4]. Colditz *et al* in a meta-analysis of 1,264 abstracts confirmed a 64% protective effect of BCG against TBM across various study designs and populations[5].

A cross-sectional study by Kumar *et al* suggested that BCG's protective effect may be influenced by factors such as high infection doses from household contacts, severe malnutrition, and declining immunity over time. In their study of 150 children, vaccinated and unvaccinated groups showed notable differences, particularly in the duration of altered sensorium, which was significantly longer in the unvaccinated group[6].

A case-control study by Kumar *et al* also found that the absence of a BCG scar in TBM cases yielded a crude odds ratio of 2.28. Factors like higher TB contact rates, longer time since BCG vaccination, and older age were observed in some cases, although BCG's protective effect persisted after accounting for these variables[7].

In an observational study by Kelekçi, BCG positivity was a protective factor against mortality, with zero mortality in the vaccinated group, underscoring BCG's protective role in the first two years of life[8]. Barday *et al* in a cohort study spanning 1985 - 2020 found that unvaccinated children with TBM exhibited more severe disease, emphasizing the impact of the global BCG shortage in 2015 on TBM severity in the subsequent years[9].

Zachariah's observational study of 1,181 TB patients found that those with severe malnutrition, age >35 years, and HIV seropositivity had a higher risk of early mortality[10]. Similarly, Kumar *et al* in a case-control study showed significant differences in average weight and height among TBM patients, highlighting the importance of nutritional status on TBM outcomes[7].

In a retrospective cohort study by Bhargava *et al*, lower pre-treatment weight was significantly associated with TB death in men but not in women. They concluded that nutritional support should be provided to severely underweight TB patients to reduce mortality risk[11].

Feleke *et al* in a cross-sectional study found that malnutrition odds were 47% higher in extra-pulmonary TB patients compared to pulmonary TB patients, with a high prevalence of underweight individuals among TB patients[12].

Ren M *et al* in a case-control study on nutritional risk in TBM children found that those at nutritional risk had higher rates of complications, cranial nerve damage, and drug-induced liver injury, highlighting the economic burden and health challenges associated with nutritional deficiencies in TBM patients[13].

Our study has limitations, including being a single-center study in the national capital, which may limit generalisability. The six-month follow-up period, while informative, may be insufficient for a comprehensive understanding of TBM outcomes. Accurately determining BCG vaccination status was challenging, particularly among older participants, leading to potential misclassification and impacting the study's precision regarding BCG vaccination and TBM outcomes.

Exploring BCG's potential protective efficacy in adults against TBM remains relatively underexplored. Conducting a multicentric study with an extended follow-up period could provide a more robust understanding, allowing for broader generalisation and extrapolation of findings.

Conclusion

This prospective cohort study examined TBM outcomes in relation to BCG vaccination and nutritional status. Sixty-five newly diagnosed TBM patients were divided into groups based on vaccination status (unvaccinated vs. vaccinated) and nutritional status (underweight vs. normal/overweight). The overall morbidity and mortality were similar across both vaccination and nutritional status groups. No substantial difference in outcomes was observed among adult TBM patients based on BCG vaccination or nutritional status.

Tuberculosis and its complications have had a significant and enduring impact on global health. Despite medical advancements, TB remains a formidable challenge, emphasizing the need for ongoing research, prevention, and treatment efforts to alleviate its global burden.

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