BCG REVACCINATION TO COMBAT TUBERCULOSIS INFECTION: AN EVIDENCE BASED CASE REPORT

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Abstract

An elderly man came to the Emergency Room with labored breathing with a history of prior tuberculosis infection and BCG vaccination when he was an infant. He was diagnosed with tuberculosis reinfection with negative microbiology result. This study aims to see whether revaccination of BCG vaccination will positively impact suppressing the rate of tuberculosis infection. A literature search was conducted on three databases: PubMed, Cochrane, and EBSCOhost. Of the searches, three articles were selected for further critical appraisal using the criteria provided by the University of Oxford Centre of Evidence-Based Medicine. The first study shows that BCG Revaccination does not become a protective factor against tuberculosis reinfection with OR 0.92 (0.80 – 1.05) in all populations yet interestingly yielded OR 0.77 (0.59-1.00) in HIV-negative patients, while the second study shows that BCG Revaccination can prevent conversion of QFT with the study showing p <0.05, thus believed to lower tuberculosis infection rates, the third study shows that BCG revaccination yield modest protection against TB infection after 15 years (Hazard Ratio 0.64 95% CI 0.46-0.89). The main difference between the studies is the main population, which the first study also includes HIV-positive patients. In conclusion, BCG Revaccination may be considered to be given and be considered as protective factor against tuberculosis reinfection in HIV-negative patients.

Keywords

BCG Revaccination, Tuberculosis infection, Tuberculosis prevention, Evidence based case report

Introduction

Indonesia ranks second worldwide in terms of annual tuberculosis (TB) cases, and this issue has evolved into a national concern over the past decade. To achieve the goal of eradicating TB by 2035, the government initiated a national TB control program back in 1995.[1] However, despite efforts, the annual incidence of new TB cases rose to 25.40 per 1 million population in 2017, with a treatment success rate of 88%.[2] Unfortunately, the TB incidence in Indonesia continues to exceed the desired target, standing at 316 cases per 100,000 people. The TB fatality rate remained at 12% in 2017.1 In 2016; the Indonesian government devised a national program to combat TB, encompassing various strategies such as health promotion, TB surveillance, risk factor control, case detection and treatment, expanded vaccinations, and prophylactic treatment of latent TB.[3] As part of these overarching efforts, Bacillus Calmette–Guerin (BCG) vaccination has been administered since 1956.[4] BCG vaccination is obligatory for children in TB-endemic countries like Indonesia and is administered to infants up to 12 weeks old. Efficacy studies on BCG vaccination have reported a range of effectiveness from 0 to 80%.[5]

The development of vaccines that can prevent pulmonary tuberculosis infections in young adults holds significant promise in controlling drug-sensitive and multidrug-resistant TB strains by breaking the chain of transmission.[6] Unfortunately, the process in creating new vaccines is hindered by the lack of validated preclinical models and established human immune factors that indicate protection. Exposure to M. tuberculosis can lead to either the early elimination of the bacteria through innate or adaptive immunity or the establishment of an infection, which can remain asymptomatic (latent) in most individuals or progress to active disease.[7]

Many countries have historically implemented repeated BCG vaccination as a policy, and some continue to do so despite limited solid evidence supporting its effectiveness. The World Health Organization's (WHO) BCG policy guidelines do not endorse this practice.[8] Nevertheless, the interest in using repeat BCG vaccination as a means of protection against tuberculosis has been rekindled following a trial involving South African adolescents. This trial suggested that BCG revaccination might contribute to a reduction in sustained Mycobacterium tuberculosis infection.[9]

Without alternative strategies, the potential value of repeating BCG vaccination remains a significant question. Furthermore, a thorough analysis of long-term outcomes after repeat BCG vaccination may unveil patterns crucial for developing and assessing other vaccines aimed at combating mycobacterial infections. Preventing M. tuberculosis infection through vaccination could serve as a critical indicator of efficacy in the fight against tuberculosis.

Case Report

A 60-year-old elderly man came to the Emergency Room with labored breathing. The patient experienced shortness of breath unaffected by activity or position. When the patient was sitting or at rest, there was no improvement in the shortness of breath. The shortness of breath was not accompanied by chest pain radiating to the back or jaw. The patient did not feel chest pain when taking deep breaths. There were no complaints of swollen legs or hands. The shortness of breath did not occur suddenly but gradually worsened over the past week. The patient had a history of night fevers for the past two weeks. Coughing for more than three weeks with yellowish sputum was also noted. The patient denied any history of trauma or accident.

The patient had a previous history of tuberculosis infection and completed anti-tuberculosis treatment in 2014. Microbiological sputum examination yielded negative results. The patient had a 20-year history of smoking, consuming 2-3 packs of cigarettes per day, but quit smoking ten years ago when diagnosed with pulmonary tuberculosis. HIV status was checked, with negative results. Currently, the patient is on pulmonary tuberculosis treatment for one month.

Based on these findings, the patient was diagnosed with recurrent TB on anti-tuberculosis treatment. The patient had a history of receiving BCG vaccination during infancy, and a BCG scar was also found on the right deltoid. The patient was then asked about the history of receiving BCG vaccination as a child and whether revaccination would affect his immunity against TB.

The physician then ponders whether BCG revaccination is useful in combating tuberculosis. The clinical question for this study is, "Is there a difference between patients that received BCG revaccination after its initial one to his/her tuberculosis infection rate?" The type of this evidence-based case report is prognostic.

The PICO for this study is as follows

Patient (P)	Patient with history of BCG Vaccination
Intervention (I)	BCG Revaccination
Comparison (C)	No comparison
Outcome (O)	Tuberculosis Infection Rates

Results and Discussion

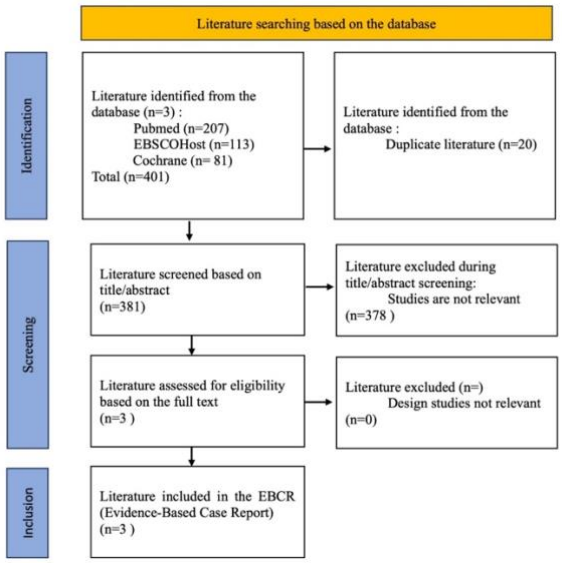
Literature searches were conducted on the 28th of September 2023, using three databases, including Pubmed, EBCSOHost, and Cochrane Library. The keywords and search results are provided in the table below (Table 1).

Table 1. Literature Searching

Database	Keywords	Articles Found	Articles Selected
Pubmed	((("tuberculosis, pulmonary"[MeSH Terms] OR "TB"[All Fields] OR ("tuberculosi"[All Fields] OR "tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR "tuberculoses"[All Fields] OR "tuberculosis"[All Fields])) AND "BCG"[All Fields] AND ("repeat"[All Fields] OR "repeating"[All Fields] OR "repeats"[All Fields] OR ("immunization, secondary"[MeSH Terms] OR ("immunization"[All Fields] AND "secondary"[All Fields]) OR "secondary immunization"[All Fields] OR "revaccination"[All Fields] OR "revaccinations"[All Fields] OR "revaccinate"[All Fields] OR "revaccinated"[All Fields] OR "revaccinating"[All Fields])))) AND (y_10[Filter])	207	2
EBSCOHost	(pulmonary tuberculosis OR TB OR tuberculosis) AND BCG AND (repeat OR revaccination)	113	1
Cochrane Library	(pulmonary tuberculosis OR TB OR tuberculosis) AND BCG AND (repeat OR revaccination)	81	0

Articles obtained from literature searching then undergo a selection process. First, the article goes through a duplicate selection process and is excluded if one is a duplicate. Then, the titles and abstracts are screened, and relevant articles are selected. In the end, three studies undergo a critical review. These articles consist of two prospective cohort studies and one retrospective cohort study—the selection process is illustrated below (Figure 1).

Figure 1. Selection Process



The three selected articles were then assessed for validity based on the criteria provided by the Oxford Centre for Evidence-Based Medicine in 2010, which includes standards for intervention research (validity), the importance of the research (importance), and the applicability of various studies (applicability). In this evidence-based case report, only three articles with a cohort study design were found. The following are the results of the critical appraisal of the articles (Table 2).

Table 2. Critical Appraisal

Criteria	Nemes et Al [9]	Glynn et al[10]	Velayutham et al[11]
	Validity		
1. Was the defined representative sample of patients assembled at a common (usually early) point in the course of their disease?	Yes Patient assembled are between 12 – 17 years old who had received BCG vaccine in infancy	Yes A retrospective study using The Karonga Prevention Trial data. The entire population of Karonga District was surveyed	Yes A retrospective study using the Chingleput BCG Vaccination trial data, taking subjects that have prior BCG Vaccination
2. Was patient follow-up sufficiently long and complete?	Yes There are 330 subject that received BCG Revaccination and 329 subject that received placebo, was then followed up on day 0, 56, 70, 3 months, 6 months, 12 months, 18 months, and lastly 24 months.	Yes Follow up was done using house to house surveys, demographic surveillance for 30 years	Yes Continuous follow up with period repeat surveys every 2.5 years, selective case finding every 10 months, and passive case detection over 15 years period

3. Were outcome criteria either objective or applied in a 'blind' fashion?	Yes Outcome was measured as a QuantiFERON-TB In-tube Assay (QFT) conversion as a way to test tuberculosis infection	Yes Outcome were objective using the diagnosis of pulmonary tuberculosis based on culture, geneXpert, and genotyping. Blinding were applied	Yes Outcome was measured by the incidence of tuberculosis based on at least one positive sputum culture and or abnormal chest x ray
4. If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?	Yes Yes, there are adjustment being made like excluding patients with known tuberculosis history	Yes There are adjustments being made for any subject with self-reported diagnosed tuberculosis before vaccination	Yes Subject with known tuberculosis history were excluded
Importance			
1. How likely are the outcomes over time?	There are graphics that shows how likely are the outcomes over time Data shows that 41 out of 312 subject that received BCG revaccination got infected with TB (13.1%) BCG Vaccine reduced sustained QFT conversion with 45.4% efficacy (p=0.03)	There are no graphics that shows how likely are the outcomes over time The BCG group results in 1.6% (397/23502) of them contracting tuberculosis Whereas the placebo group results in 427 out of 23330 contracting tuberculosis OR 0.92 (0.82-1.05)	There are graphics that shows how likely are the outcomes over time. 15 years after post vaccination showing a 36% protection rate for subject that get revaccination Hazard Ratio 0.64 95%CI 0.46-0.89
2. How precise are the prognostic estimates?	The study uses 95% confidence interval	The study uses 95% confidence interval	The study uses 95% confidence interval
Applicability			
1. Can I apply this valid, important evidence about prognosis to my patient?	Yes	Yes	Yes
2. Were the study patients similar to your own?	Yes	Yes	Yes
3. Can you apply this valid, important evidence about prognosis in caring for your patient?	Yes	Yes	Yes

Bacillus Calmette-Guérin (BCG), an attenuated strain of Mycobacterium Bovis, is the only approved vaccine against tuberculosis since 1921.[12] Countries with high tuberculosis incidences apply universal BCG vaccination strategies. In contrast, remaining countries with low-to-moderate incidence consider selective vaccination strategies. Repeated BCG

vaccination or BCG revaccination used to be standard practice. Due to a lack of evidence and effectiveness, the WHO does not recommend it. A previous study in 2005 by Rodrigues *et al.* reinforced the WHO's statement when they found that there was no significant difference in the crude incidence of tuberculosis between the group that received a second BCG vaccination and the control group (crude rate ratio 0.97; 95% CI 0.76 – 1.28).[13] But after the study by Nemes *et al.* that showed some evidence that BCG revaccination may reduce sustained Mycobacterium Tuberculosis infection, interest in said topic experienced a resurgence.[9]

Nemes *et al.*, in their study, found that although there were no significant differences in QFT conversion occurring in BCG revaccination subjects and placebo subjects (41 out of 312 and 49 out of 310, respectively), the subjects that received BCG revaccination showed that it reduced the rate of sustained QFT conversion (45.5%, p=0.03). It concludes that sustained QFT conversion, synonymous with sustained M. tuberculosis infection, was reduced by revaccination in a high transmission setting.[9]

Glynn *et al.* found that after a 30-year follow-up after BCG revaccination, there was virtually no effect of a second BCG (OR 0.92 95% CI 0.80-1.05). When those with known HIV were removed, the OR became lower (OR 0.77 95% CI 0.59-1.00). They concluded that in the population with high prevalence of HIV, a second BCG vaccination provides no appreciable protection against tuberculosis.[10]

A third study by Velayutham *et al.* found that after a 15-year follow-up, they concluded that the incidence of TB disease was significantly lower after BCG vaccination (Hazard Ratio 0.64 95% CI 0.46-0.89). It revealed that BCG revaccination offered modest protection against the development of TB disease after 15 years.[11]

Out of all the studies, it was found that BCG revaccination reduces the sustained QFT conversion rate, thus offering modest protection against the development of tuberculosis in high transmission settings in HIV-negative patients. There is still room for revaccination of BCG vaccines in Indonesia, considering Indonesia is a high transmission nation for tuberculosis.

Competing Interests

Authors (AR, JQ) declare no conflict of interest

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