

Bacille Calmette-Guerin (BCG) Revaccination: Is it Beneficial for Tuberculosis Control?

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Abstract

Background: The duration of the protective efficacy of BCG vaccine plays an important role in the establishment of vaccination policies particularly for tuberculosis endemic countries. The effectiveness of revaccination with two or more doses is still a controversial issue. In this systematic review, we qualitatively appraised available epidemiological evidence.

Method: A search strategy using both PubMed and Embase databases and manual search was done up to January 2013. The main search terms used include BCG, revaccination, tuberculosis, mortality and adverse reaction. The studies were grouped by designs; randomized-control trials, cohort and case-control studies. Outcomes were categories into primary outcomes (tuberculosis and mortality from tuberculosis) and secondary outcomes (vaccine efficacy, immunity and adverse reaction from BCG revaccination).

Results: Nine articles were selected and data on the primary and secondary outcomes were extracted. The review noted no significant difference in the incidence rate ratio (range 0.57-1.74), relative risk [0.39 (0.31-0.49)] and hazard ratio [1.20 (0.77-1.89)] from tuberculosis in the BCG revaccinated group compared to BCG non-revaccinated group. Comparison between the two groups also noted no significant difference in the relative risk of adverse reaction [2.3 (0.67-7.80)] and vaccine efficacy [8 (-77-52)], but a significant increase in immune response in revaccinated group.

Conclusion: In summary, our review demonstrated the available evidences do not support BCG revaccination as a strategy to reduce tuberculosis.

Keywords: Bacille calmette-guerin (BCG); Revaccin; Tuberculosis; Adverse reaction; Immunity

Background

Tuberculosis (TB) is a recognized public health problem worldwide. In 2011, there were an estimated 8.7 million new cases of TB and 1.4 million deaths from TB with 990,000 of those deaths occurred among HIV-negative individuals and 430 000 deaths among HIV-positive. The burden of TB is highest in Asia and Africa. About 60% of TB cases are in the South-East Asia and Western Pacific regions [1].

Immunisation with bacilli Calmette-Guerin (BCG) is thought to reduce hematogenous spread of *Mycobacterium tuberculosis* (Mtb) from the site of primary infection which may result in serious disease, such as miliary TB and TB meningitis [2]. Its efficacy varies, ranged from zero to 80% against pulmonary TB [3-5], and over 70% against TB meningitis [6-8].

Several studies indicated that immune response conferred by BCG vaccination decline by age [9-12] and revaccination with two or more doses is proposed to boost immunity [5,13,14]. Routine revaccination is practiced in some TB endemic countries, to individuals who are tuberculin negative or to those without a visible BCG scar after the first dose [15,16]. However, the effectiveness of BCG revaccination has been questioned [16-18]. In 1995, World Health Organization (WHO) Global Programmes on Tuberculosis and on Vaccines recommended that for persons who have received BCG vaccination, repeat vaccination is not recommended as no scientific evidence for its protection [19]. However with the on-going threat of tuberculosis particularly to Asia and Africa, a systematic review is important to identify any new evidence on the beneficial effect or otherwise, of BCG revaccination. This systematic review aims to assess the protective effect of BCG revaccination against outcomes measured; tuberculosis, mortality from tuberculosis, adverse reaction, vaccine efficacy and immune response.

Methods

Study selection

The criteria for study selection were based on its design and scope. For the study design, we selected case-control and cohort studies, and randomized controlled trials. We included studies that compared outcomes of single vaccination at birth or infancy with revaccination at a later age. Studies were selected if involved general population of any age, who had received primary BCG vaccination, irrespective of proof of previous vaccinations.

The intervention, i.e. BCG revaccination was defined as either (i) routine revaccination irrespective of TB immune status; or (ii) revaccination given for either absence or presence of visible scar following primary vaccination; or (iii) revaccination given following negative tuberculin test in patients who had received primary vaccination.

Outcomes measured were defined as either primary or secondary outcomes. The primary outcome measured either (i) the incidence or prevalence of pulmonary tuberculosis within ten year vaccination; (ii) the incidence or prevalence of non-pulmonary tuberculosis within ten

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year vaccination; (iii) the mortality rate due to tuberculosis within ten year vaccination; or (iv) all causes of mortality from revaccination. Secondary outcome measured was either measures of immunity for example by tuberculin skin test or any adverse reactions (mild or severe) following revaccination.

Search strategy

We used a four-part search strategy: Firstly, we searched electronic bibliographic databases (PubMed and EMBASE) for published work. Secondly, we searched grey literature from local universities for unpublished work. Thirdly, we searched trial registers for ongoing and recently completed trials. Finally, we searched reference lists of eligible studies for other related articles. We reviewed all abstracts irrespective of journal languages and full texts of the eligible article were searched.

For the first part of the search strategy, a systematic and comprehensive bibliographic search for all available evidence up to January 2013 was performed. Publications were retrieved from PubMed from 1969 onwards, from EMBASE from 1967 onwards and from the Cochrane Central Register of Controlled Trials. In order to capture studies on BCG revaccination in PubMed, either one of the following medical subject heading terms and keywords was used: 'tuberculosis', 'tuberculosis [MeSH]', 'Mycobacterium infection' 'BCG', 'Bacillus Calmette Guerin', 'tuberculosis vaccin*', 'Calmettevaccin*', 'revaccin', 'tuberculin test', 'revaccination [MeSH]', 'secondary vaccination', 'reimmunis*', 'catch-up', 'repeated', 'mortality', 'mortality"[MeSH]', 'drug resistance', 'adverse reaction', 'adverse effect', and 'side effect'. We then combined our searches to include results for any of the BCG revaccination keywords and any of the tuberculosis keywords. We further limit our search to study on humans and Randomized Controlled Trial and Comparative Study. For EMBASE database search strategy, we combined all terms: 'tuberculosis', 'BCG' and 'revaccination' before filtered for human study only.

The titles and abstracts of each identified articles were reviewed to exclude those which were unrelated including review papers, animal-based studies, studies pertaining to effect of primary vaccination alone and cost-effectiveness and cost-benefit analysis studies. Local university libraries were then checked for relevant unpublished studies and dissertations. Cochrane Central Register of Controlled Trials was also searched for ongoing for completed trials on BCG revaccination. Manual searching was also done using google scholar based on the reference lists of accepted articles.

Screening and review process

All articles identified from the search process were exported to a bibliographic database (EndNote version X4) for duplication and screening. Two review authors (NHS and HAAH) independently examined the titles, abstracts, and keywords of electronic records for eligibility according to the identified inclusion criteria [20]. All abstract reviewed were in English even though from non-English journals. Results of this initial screening were then compared between the two review authors, and full-texts obtained for all potentially relevant topics. Secondary screening were then done by each reviewer using a screening form based on the inclusion criteria for final inclusion in the review, with disagreements resolved by discussion with a third author (NAA). The screening form assessed whether the articles discussed on general population or specific group who received primary vaccination and also BCG revaccination irrespective of its reason. The articles were rejected if these two criteria were not fulfilled. Reference lists of all eligible trials were then searched for further eligible trials.

Data extraction

Two authors (BMH and MFMY) independently extracted out characteristics of each trial using a standardized, pre-piloted, data extraction form and eligibility of candidate studies [20]. Data extracted to this form include first author's name, research question, study design, inclusion and exclusion criteria for study participants, trial methods including method of allocation generation and allocation concealment, blinding methods (participants, trial administer, outcome assessor and data analyser), intention to treat, loss to follow-up, baseline characteristics of intervention and control groups, outcomes including primary outcomes (incidence of tuberculosis or mortality) and secondary outcomes (measures of immunity or adverse reaction).

Analysis

The characteristics of the selected studies were described based on their study design, intervention and control groups, and the outcomes assessed.

The findings from the association between BCG revaccination and various outcome categories were explained in detail. Wherever possible, objective findings such as incidence rate ratio and hazard ratio were mentioned.

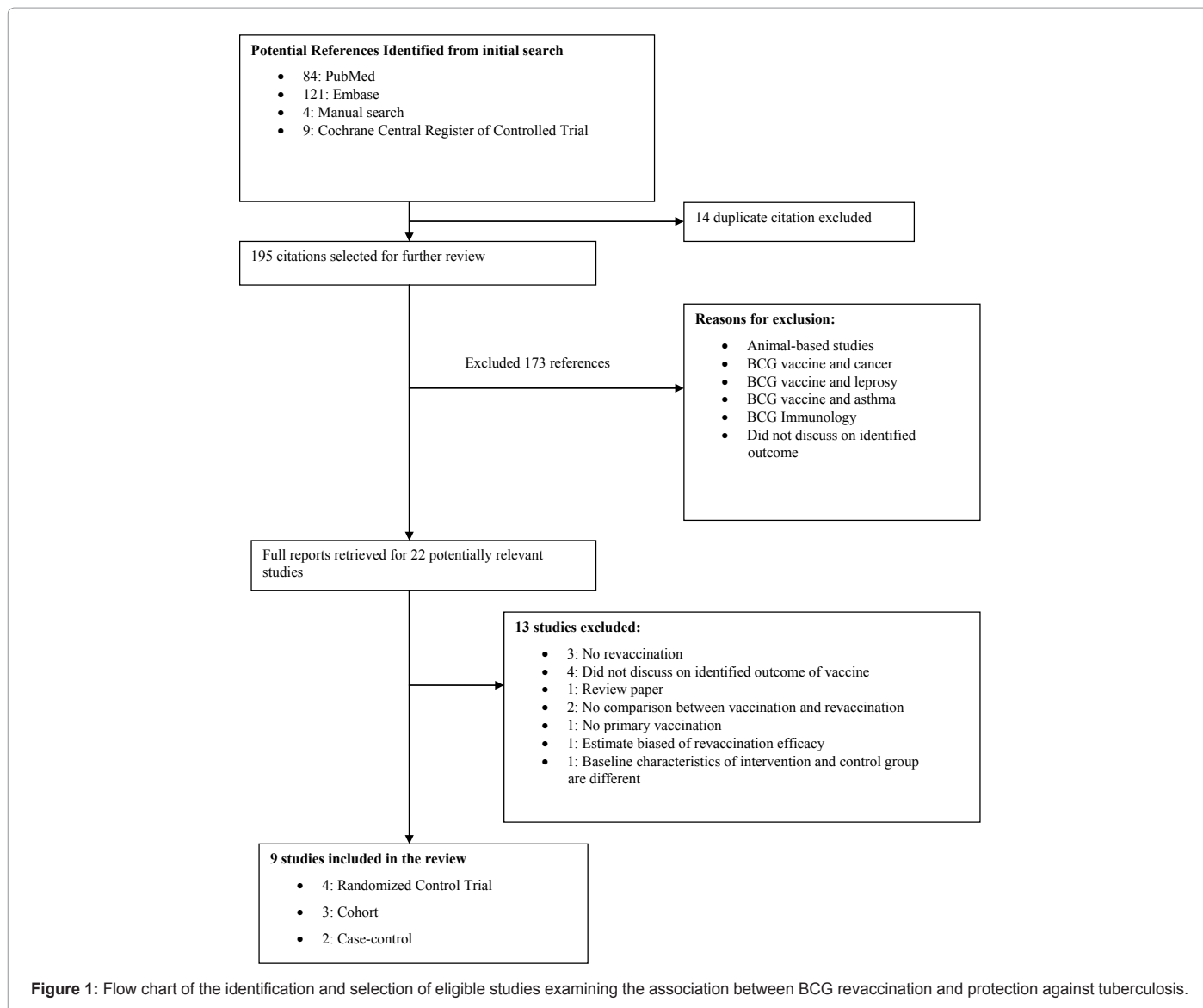
Results

Figure 1 summarized the process involved in the identification and selection of studies for this systematic review. Search strategy using PubMed and EMBASE resulting in 205 citations with another nine articles from Cochrane Central Register of Controlled Trials. A total of 14 duplicate studies were excluded. Based on the predetermined screening form, 173 studies were excluded mainly due to the absence of the outcomes of interest; i.e., TB. Full reports were retrieved from 22 potentially relevant studies. Based on the set criteria, 13 studies were excluded; three studies only discussed the effect of single dose of BCG vaccine, another four studies did not focus on the identified primary and secondary outcomes, two studies had no comparison between the outcome of primary vaccination alone and revaccination, one study had no information on primary BCG vaccination, one study discussed on the bias found in the study comparing primary vaccination and revaccination, one study has different baseline characteristic in the two comparison groups, and another one study is a review paper.

Study characteristics

Table 1 provided description of studies and the association between BCG revaccination with primary outcomes and secondary outcomes. The description of the studies was organized by study design and listed by year of publication. The studies were published between 1996 to 2011. Of these nine studies, four were randomized-controlled trials, three were cohort studies and two were case-control in design. The studies were conducted in various countries: four were conducted in Brazil, each one study was conducted in Malawi [21], Guinea-Bissau [22], Finland [23], Hong Kong [24] and Sweden [25]. The minimum age at BCG revaccination was 18-19 months [22] and the maximum age was less than 80 years old [21].

Seven of the studies [8,21-24,26,27] have similar characteristics at the start of the studies; i.e., given BCG vaccination at birth, and were then revaccinated with BCG (intervention). Remainder two studies [25,28] have different baseline characteristics. In one study [28], one group without BCG scar assumed as did not receive neonatal BCG vaccination and another group with scar assumed as received BCG vaccination followed by the intervention; i.e., BCG vaccination at 7-14



years. In another study [25], one group never been vaccinated with the comparison group received BCG vaccination at birth, followed by BCG vaccination as intervention for both group.

The participants of each study were assessed by the outcomes in the intervention and control groups. The outcomes from eight studies [8,21,22,24-28] were assessed in the BCG revaccinated group as the intervention group, except one study [23] where the outcome was assessed in the group who received single dose of BCG (as intervention).

The outcomes from studies were assessed differently based on the study design and the type of outcome. Several studies [21,26] used incidence rate ratio and crude incidence rate ratio [29], while one study [22-24,26-28,30,31] used hazard ratio. Two studies [24,28] used relative risk for assessment, while another two studies [25,27] compared the effect in the two groups.

In six studies [8,21-24,26], the effect of BCG revaccination was assessed using primary outcomes; either pulmonary tuberculosis alone [4,23] or both pulmonary tuberculosis and extra-pulmonary

tuberculosis [8,21,24], with one study [22] assessed the mortality after revaccination. Another two studies [27,28] assessed the effect of BCG revaccination against secondary outcomes; adverse reaction [28], vaccine efficacy [27] and the immune response [25] after BCG revaccination.

The outcome assessment was done based on the study design and also the outcome assessed. The outcome of two studies [21,25] were assessed based on laboratory procedures, four studies were assessed based on records [8,23, 24,26] and the remaining three studies [22,27,28] were assessed based on home visits and parental information.

Outcomes of BCG revaccination

Effects of BCG revaccination against pulmonary tuberculosis:

The randomized controlled trial [26] reported no significant difference between the intervention and control group [rate ratio of 0.91 (0.79-1.05)], while the cohort study [23] also reported no significance difference between the intervention and control group [relative risk 0.59 (0.14-2.47)].

Author	Participants characteristics	Exposure indicator	Age at exposure	Intervention group	Control group	Incidence rate ratio	Primary Outcome measures	Secondary outcomes	Outcome assessment
Randomised Controlled Trials									
Karonga prevention trial group [21] Malawi	All participant given primary vaccination at birth. Recruited Jan 1986-Nov 1989. Exclusion criteria: <3 months, born before 1914, evidence of past or current tuberculosis, severe malnutrition or severe illness.	BCG revaccination	Non-specific (less than 80 years)	14742 [1.74 (1.00-3.03)]	14501	0.51 (0.26-0.99)	Pulmonary tuberculosis (positive sputum culture and at least one other sputum specimen positive on either culture or microscopy) Extra-pulmonary TB: clinical signs, biopsy samples, and bacteriological results.	Laboratory diagnosis	
Rodrigues et al. [8] Brazil	All participant given primary vaccination at birth. Children age 7-14 years in two cities in Brazil; Manaus and Salvador	BCG revaccination	Children aged 7-14 years	Pulmonary TB: 117 Non-pulmonary TB: 27 (29.3/100,000 person years)	Pulmonary TB: 98 Non-pulmonary TB: 37 (30.2/100,000 person years)	0.97 (0.76-1.28) *crude rate ratio	Incidence of Tuberculosis. Pulmonary tuberculosis and non-pulmonary tuberculosis.	Record of TB link to The Tuberculosis Control Programme	
Roth et al. [22] Guinea-Bissau	All participant given primary vaccination at birth. Inclusion: Mantoux Test reaction < 15 mm and sufficiently health.	BCG revaccination	18-19 months	1437 Mortality rate: 1.2/100 person years	1434 Mortality rate: 1.0/100 person years	Hazard ratio: 1.20 (0.77-1.89)	Any cause of death from 18 months old until 5 years old.	Observation of deaths obtained from the pediatric ward and through 3 monthly home visits	
Barreto et al. [4] Brazil	All participant given primary vaccination at birth. Children aged 7-14 years with one BCG scar only before. revaccination	BCG revaccination	7-14 years	103718 Crude incidence: 41.6/100,000 person years	97087 Crude incidence: 45.5/100,000 person years	Rate ratio: 0.91 (0.79-1.05)	Incidence of Tuberculosis.	Cases were identified from Brazilian Tuberculosis Control Programme	
Cohort studies									
Tala-Heikkila et al. [23] Finland	All participant given primary vaccination at birth. Age cohorts born in 1969-1974 and covered by BCG revaccination programme. Age cohorts born 1979-1984 and no longer covered by BCG revaccination programme.	BCG revaccination	School children aged 11-13 years if they were tuberculin-negative (induration <5mm) after two step Mantoux testing.	388089 (no revaccination) 2.23 (0.72-6.90)	371199 (revaccination) 3.78 (1.57-9.07)	Relative Risk: 0.59 (95% CI: 0.14-2.47)	Tuberculosis confirmed bacteriologically or histologically or if the clinical evaluation of symptoms and sign indicate full course of tuberculosis chemotherapy.	Cases were identified from The National Tuberculosis Register.	
Leung et al. [24] Hong Kong	All participant given primary vaccination at birth. Cohort of children born between 1 July 1978 and 30 June 1982	BCG revaccination	Children in primary school at age 6-9 years, between 1984 and 1991	183 Incidence: 12.5/100,000 person-years	119 Incidence: 32.0/100,000 person-years	Relative Risk: 0.39 (0.31-0.49)	Pulmonary tuberculosis (two or more positive sputum cultures for <i>M. tuberculosis</i> ; or one positive sputum culture for <i>M. tuberculosis</i> plus compatible clinical history & radiological picture; or one or more positive sputum smears for acid-fast bacilli plus compatible clinical history and radiological picture; or a clinical compatible clinical history and radiological picture plus clinical and radiological improvement after anti-tuberculosis treatment). Extra pulmonary TB: histological or bacteriological confirmation. Compatible clinical history and/or radiological features of TB with clinical and/or radiological improvement after anti-TB treatment (absence of histological or bacteriological confirmation).	Active cases was carried out by a search of Tuberculosis Notification List in Hong Kong Government Department of Health.	

Author	Study Design	Population	Intervention	Comparison	Outcome	Adverse reactions defined	Validity of scar based on vaccination card and parental information
Dourado et al. [28] Brazil	Case-control studies	Children aged 7-14 years. Children with absence of neonatal BCG scar assumed to have no previous BCG revaccination.	BCG revaccination	Children 7-14 years	23 1 in 2580 (1/1692-1/3984)	Ascertained by project nurse through enhanced routine passive surveillance using standardized form.	Validity of scar based on vaccination card and parental information
Dantas et al. [27] Brazil	Case-control studies	All participant given primary vaccination at birth. Children aged 7-19 years with at least one BCG scar, residing in Recife	BCG revaccination	7-14 years	169	Adverse reactions defined based local dissemination to deltoid area or tuberculous-like cutaneous lesions around BCG vaccine area.	Validity of scar based on vaccination card and parental information
Fjallbrant et al. [25] Sweden	Case-control studies	TST negative healthcare students. 15 subjects never been BCG-vaccinated vs 16 subjects vaccinated as newborns.	BCG revaccination	Young adults students	15 1) LT response x3.3 increase of median 2) IFN-γ level median 2700 pg/ml	Adverse reactions defined based local dissemination to deltoid area or tuberculous-like cutaneous lesions around BCG vaccine area.	Validity of scar based on vaccination card and parental information
					477	Adverse reactions defined based local dissemination to deltoid area or tuberculous-like cutaneous lesions around BCG vaccine area.	Validity of scar based on vaccination card and parental information
					15 1) LT response x1.9 increase of median 2) IFN-γ level median 2200 pg/ml.	Adverse reactions defined based local dissemination to deltoid area or tuberculous-like cutaneous lesions around BCG vaccine area.	Validity of scar based on vaccination card and parental information
					8 (95%CI: -77-52)	Adverse reactions defined based local dissemination to deltoid area or tuberculous-like cutaneous lesions around BCG vaccine area.	Validity of scar based on vaccination card and parental information
					RR: 2.3 (95%CI: 0.67-7.80)	Adverse reactions defined based local dissemination to deltoid area or tuberculous-like cutaneous lesions around BCG vaccine area.	Validity of scar based on vaccination card and parental information

Table 1: Summary of 9 studies included in the systematic review of the BCG revaccination and protection against tuberculosis.

Effects of BCG revaccination against both pulmonary tuberculosis and extrapulmonary tuberculosis: Randomized control trial by Karonga prevention trial group in Malawi reported higher rate of pulmonary disease among revaccinated group [1.74 (1.00-3.03)] in comparison with control, due to excess of pulmonary TB among HIV-positive individuals who were revaccinated. However, this trial reported lower incidence of glandular TB among revaccinated group [0.57 (0.17-1.93)] compared to control group. In general, this trial concluded that second BCG vaccination did not give any protection against tuberculosis [21].

Another randomized control trial in Brazil [8] reported no significance difference in the incidence of any type of tuberculosis; crude incidence of 29.3 per 100,000 person years in intervention group vs 30.2 per 100,000 person years in control group [crude rate ratio: 0.97 (0.76-1.28)].

A cohort study in Hong Kong among children who were vaccinated at birth, reported no significant difference in the proportion of patients with extra-pulmonary TB between the revaccinated group and non-vaccinated group (p=0.44). In addition, there is no significant difference in the proportion of patients with positive bacteriology between revaccinated group and non-revaccinated group (p=0.19). In general, revaccinated group had a relative risk of 0.39 (0.31-0.49) in comparison with non-revaccinated group [24].

Effect of BCG revaccination against mortality: A randomized control trial in Guinea-Bissau reported that BCG revaccination had no overall effect on mortality where hazard ratio for BCG revaccination children compared to non-revaccinated children of 1.20 (0.77-1.89). The mortality rate among BCG revaccinated group was 1.2 per 100 person years, compared to 1.0 per 100 person years among the non-revaccinated group [22].

Effect of BCG revaccination against secondary outcomes: A retrospective cohort study in Brazil [25] reported a relative risk of adverse reaction from BCG revaccination of 2.3 (0.67-7.80) comparing revaccinated group with those received single dose of BCG vaccine.

A case-control study in Brazil [28] reported no difference in the efficacy of BCG revaccination [8 (-77-52)]. Another case-control study [25] in Sweden reported significant increase in LT response after 2 months in the primary-vaccinated group compared to the re-vaccinated group (x1.9 and x3.3 increase of median value, p<0.05), with higher IFN-γ level after 1 year in revaccinated group (median 2700 pg/ml) compared to primary vaccinated group (median 2200 pg/ml), but it was not significant (p=0.07).

Discussion

Our systematic review of nine studies demonstrated no significant difference in the incidence rate ratio (range 0.57-1.74), relative risk [range 0.39-0.59] and hazard ratio [1.20 (0.77-1.89)] from tuberculosis. In addition, there was no significant difference in the relative risk of adverse reaction [2.3 (0.67-7.80)] and vaccine efficacy [8 (-77-52)] but a significant increase in immune response in revaccinated group.

In general, our review concluded that BCG revaccination does not provided additional significant protective effect based on the outcomes measured; tuberculosis, mortality from tuberculosis, adverse reaction and vaccine efficacy. However, our review noted one article on BCG revaccination that resulted in significant increase in immune response, suggesting a protective effect. Similar finding was mentioned by a study in Brazil which demonstrated *in vitro* increase of IFN-γ response to

mycobacterial antigen that postulated revaccination boost the immune response [30].

We were unable to proceed with meta-analysis due to the heterogeneity of the outcomes, and limited eligible studies. Findings from our systematic review support WHO recommendation in 1995 against BCG revaccination.

Even though revaccination does not confer additional protection against tuberculosis, BCG vaccination provides protection against the severe form of tuberculosis and childhood TB. Meta-analyses on the protective effect of a single dose of BCG vaccination observed the effect from 73% to 86% [31,32]. A study in Brazil among adolescents 15 to 20 years who received BCG vaccination at birth, noted the prolonged protective effect of the first dose ranging from 9% to 58% [33,34].

The way forward in the control of tuberculosis is through development of new vaccine which should be superior to the current BCG vaccine. The new vaccine should be able to act as booster to the BCG or capable of replacing BCG vaccine [34].

The strength of this review include clear definitions and inclusion criteria, and a systematic approach to searching, screening and reviewing studies and extracting data using standardized forms by at least two researchers at all stages. We used multiple databases in our search using a search strategy that emphasizes on sensitivity to capture all possible types of studies that fulfill our criteria. Although every effort has been made to locate unpublished trials, our findings are still vulnerable to selective reporting. Despite a pre-defined and systematic approach to screening and reviewing, this report still involve judgments made by review authors, either of which may lead to biases.

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