Bacille Calmette Guerin Vaccination in Early Childhood and Risk of Allergic Disease: A Systematic Review and Meta-analysis of data from 13 large scale studies

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Abstract

Background and objectives Several large scale cohort studies suggest that BCG vaccination in early childhood may reduce the risk of allergic disease, but the consequences remain controversial. The objective of this study was to investigate the associations between early childhood BCG vaccination and the risk of developing allergic disease. Methods Eligible studies published on PubMed, EMBASE and Cochrane Central Register of Controlled Trials were systematically sourced from inception to April 2020. Large-scale cohort or cross-sectional studies with 100 participants or more, focusing on the association between BCG vaccine and allergic disease including eczema, asthma and, rhinitis were included. An assessment was undertaken by two independent investigators looking at methods, interventions, outcomes, and study quality. Odds Ratio (OR) with 95% confidence interval (CI) were calculated. Results Our study included 13 large-scale studies involving a total of 260,029 participants. Our quantitative analysis found that administering BCG vaccine in early childhood significantly reduced the risk of developing asthma (OR 0.74, 95%CI 0.61 to 0.91), but there was no association between early childhood BCG vaccination and the risk of developing eczema (OR 0.87, 95%CI 0.68 to 1.11) or rhinitis. (OR 1.03, 95%CI 0.87 to 1.22). The effect of BCG vaccination with asthma was evident especially in European countries (OR 0.59, 95%CI 0.40 to 0.88) and American countries (OR 0.90, 95%CI 0.82 to 0.98) Conclusions Use of BCG vaccination in early childhood may be associated with a reduced risk of allergic disease, especially in European and American countries.

1 | Introduction

Allergy is defined by an inappropriate immune response to one or more foreign antigens. This response can give rise to conditions such as allergic asthma, atopic dermatitis (eczema), allergic rhinitis (hay fever) and anaphylaxis.[1]Allergic diseases are characterized by a latency period between primary exposure (sensitization) and symptoms (elicitation) that develop upon subsequent exposures, and may involve Ig-E and/or non-Ig-E-mediated responses. An Ig-E-mediated allergic reaction (sometimes called immediate-type hypersensitivity (Type I)) involves the production of Th2 cytokines, which initiate Ig-E production by B cells[2]. Allergic and autoimmune diseases seem to have increased in prevalence in many countries. In recent decades the

prevalence of allergic disorders, including hay fever and bronchial asthma, has increased worldwide. This has mostly occurred in western countries where up to 20% of the population[3] and one in three children in economically developed countries[4]are affected by allergic diseases. Furthermore, allergic diseases, are also leading common chronic diseases; they may have great social and economic impact on both individuals and their families. They are leading causes of chronic illness in young people, having a negative impact on the quality of life and school performance[5], for which the reasons are not fully clear. A recent register-based study showed that the lifetime prevalence of asthma and allergic rhinitis at age 10 was 15.6% and 20.4% respectively.[6]

Vaccination is used worldwide for preventing infectious diseases[7]. Childhood vaccination plays an important role in the early development of the immune system[8]. Furthermore, most children with allergic diseases start to have symptoms early in life; these early childhood influences are crucial in the development of allergic diseases.[9] The link between vaccination and the risk of allergy was first published in 1994 by Odent et al.[10] Since then, numerous publications have investigated this hypothesis[11-15]. However, most commonly researched is the relationship between Bacille Calmette Guerin (BCG) vaccine and allergic disease, but the consequences remain controversial. The BCG vaccine has been used for almost 100 years to prevent tuberculosis[16] and is standard in childhood immunization programs of many countries. Since BCG has been demonstrated to inhibit TH2 immunologic response and antagonize atopy in both human and animal models, it is also a therapeutic model to investigate the effect of early-life stimulation of TH1 cells.[17] A recent study showed that BCG may have non-specific beneficial effects on the infant immune system, reducing early atopic diseases.[18] The association between BCG and childhood atopic disease has been studied with conflicting results.[19] Given the relationship between sample size and statistical power, we conducted a meta-analysis of studies with sample size >100 and assessed as high-quality. We examined the association between BCG vaccine and allergic disease and explored the implications of evidence from existing trials for clinical practice and future research.

2 | Material and Methods

2.1 | Searches strategy and selection criteria

Our systematic review was performed and reported in accordance with Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[20] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[21]guidelines

We performed a systematic search in PubMed/Medline (1950 to Apr 2020), EMBASE (1980 to Apr 2020), and Cochrane Central Register of Controlled Trials (1950 to Apr 2020) for association between BCG vaccination and Allergic disease by using relevant keywords including asthma, eczema, rhinitis, BCG vaccines and other synonyms. The search method is provided in appendix 1. We restricted the search to studies published in English language and we screened bibliographies of relevant review articles to ensure that all relevant studies were included.

Studies were first selected on the basis of their titles and abstracts by two independent investigators. Then they retrieved full texts and performed further screening when studies were deemed eligible. Studies had to be either cohort or cross-sectional with participants data included. Disagreements were resolved by discussion and, if necessary, in consultation with a third, senior investigator.

2.2 | Data extraction and quality assessment

Two authors extracted data independently using a standard data extraction form. The following baseline characteristics were extracted from the included studies: first author, year of publication, study design, location in which the study was performed, number of included participants and allergic disease. Studies were excluded when participant data was not integrated.

Quality of all included trials was assessed by two authors independently by using the Cochrane Collaboration risk of bias tool.[22] This tool evaluated biases from seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and others. The risk of bias in each domain was judged as low, high, or unclear. The overall risk of bias in a study was classified as low if all domains had low risk; as high if one or more domains had high risk, or as unclear otherwise.[12] Based on these standards, we classified the studies into the following three grades: A, high quality and low risk of bias; B, moderate quality and moderate risk of bias and C, low quality and high risk of bias. Disagreements between the reviewers were resolved by discussion with involvement from a third senior investigator if necessary.

2.3 | Data analysis

We used STATA (version 12.0) to perform the data analysis, Odds ratios (ORs) and their associated 95% confidence intervals (CI) were used to assess the strength of association between BCG vaccination in early life and the risk of getting allergic disease. Statistical tests were judged statistically significant if the two-side P value was less than 0.05[23]. $\mathbf{I^2}$ statistic were used for investigating heterogeneity and if $\mathbf{I^2}$ value was greater than 50%, it implied statistical heterogeneity. We used random-effects modeling to perform the meta-analysis if significant heterogeneity were performed and if not, we used fixed-effects modeling.

If heterogeneity existed, we performed a subgroup analysis to investigate whether the heterogeneity was related to the participant's race. Different ethnic background in different continents may be considered potentially important to heterogeneity because of living habit diversity. Funnel plots were used for displaying the publication bias graphically, both specifically and officially with Egger's test.

3 | Results

Our search strategy generated 3949 citations from 2 databases. 3773 articles were removed after exclusion of duplicates and screening of titles and abstracts. Of the remaining 176 studies, 163 studies were excluded after reviewing the full text. In total, 13 articles including 260,029 participants met the inclusion criteria and were included in the meta-analysis.[11,24-35] The flow diagram of trial identification and selection is shown in fig 1. Descriptions and baseline characteristics of included studies are detailed in Table 1. No problems were encountered with participant data deficiency during the data integrity check.

Two cohorts were conducted in Americas, five in Europe and two in Asia. Two Cross-sectional studies were conducted in Europe, one was in Asia and one in America. One cohort study was conducted in Africa. None of the included studies were at low risk of bias (rated A) as all trials had an element of pragmatism in using different methods. Nine included studies, including 87% participants, were deemed to be at moderate risk of bias (rated B). We judged four studies including only 13% participants to have high risk of bias (rated C) in the field of study participation or statistical reporting.

3.1 | Association of BCG Vaccination in Childhood with Incidence of Allergic Disease

In the pooled analysis, we found that participants received BCG in childhood associated with a lower risk of allergic disease than that of non-BCG group (OR=0.86, 95%CI 0.75 to 0.97; fig 2).

12 studies involving 139035 participants reported the relationship between BCG vaccination and the risk of asthma. Compared with non-BCG group, received BCG in early childhood was associated with a significantly reduced risk of asthma (OR=0.74, 95%CI 0.61 to 0.91; fig 2).

8 studies including 58,825 participants reported the association between rhinitis and BCG vaccine and 9 studies including 61,109 participants studied eczema and BCG vaccine. Compared with the control group,

use of BCG vaccine showed no significant effect in preventing eczema and rhinitis (OR=0.87 and 1.03, 95%CI 0.68 to 1.11 and 0.87 to1.22, respectively; fig 2).

3.2 | Association between BCG Vaccination and Demographics Factors on the Risk of Allergic Disease

We evaluated the association between BCG vaccination and participants demographics on the preventative effect of allergic disease. Participants from Europe and America were associated with a significantly lower risk of developing asthma when administered BCG vaccine in early childhood (pooled OR=0.59 and 0.90, 95%CI 0.40 to 0.88 and 0.82 to 0.98, respectively; fig 3). However, in Asia and Africa, participants who received BCG vaccine in early childhood were not associated with a significant reduced risk of allergic disease (pooled OR=0.97 and 1.16, 95%CI 0.51 to 1.87 and 0.68 to 1.97, respectively; fig 3).

Use of BCG vaccine was not associated with the risk of eczema in the subgroup analysis of different continents (fig 4). Similar results were obtained in participants with rhinitis (fig 5). The results from our study did not observe an association of BCG vaccination with reduction in risk of eczema or rhinitis in Europe, America, Asia or Africa.

3.3 | Publication Bias

The total publication bias is outlined in the funnel plot (fig 6). From visual inspections of the funnel plots and by Egger's test[36], it is suggested that publication bias did not impact our estimates. (bias coefficient for the main analysis 1.18, 95%CI 0.38 to 2.75, P=0.13)

4 | Discussion

4.1 | Main findings

In this systematic review and meta-analysis of data from large scale participants-based studies, there is ample epidemiologic evidence to show that BCG vaccine might be effective in preventing allergic disease, especially asthma among European and American countries. However, compared with asthma, the risk of developing allergic disease was not reduced for both eczema and rhinitis. In both Asia and Africa, there was no association between BCG vaccine and allergic disease. To the best of our knowledge, this systematic review and meta-analysis is the most comprehensive and latest study between BCG vaccination and allergic disease.

In this study, we found that receiving a BCG vaccine in early childhood reduced the risk of allergic disease, especially asthma. According to other studies on BCG vaccination and asthma, the anti-inflammatory properties of BCG has been tested in murine models of atopic asthma where the mycobacteria were shown to inhibit allergen-induced airway inflammation[37]. BCG altered the immune balance towards Th1-like activity by decreasing the IL-4 and IL-10 production. The mechanism of IFN-γ-induced inhibition of Th2 responses is not fully understood, but could involve activation of macrophages, direct suppression of developing Th2 lymphocytes, or altered antigen presentation[38]. The mechanism responsible for the effect of BCG on asthma is more complex than simple changes in the Th1/Th2 balance[39] and we hypothesized that early childhood mycobacterial infection promotes the switch from a Th2 to a Th1 profile, therefore inhibiting the expression of atopy.

In European and American countries, the performance of BCG vaccination in preventing asthma is highly significant. This could be attributable to the fact that children born into these regions of the world in which helminth infections and tuberculosis are endemic might derive particular benefits from BCG vaccine[40]. The protection level of BCG vaccination appear to follow a gradient from poor protection in countries close to the equator towards higher protection with increasing distance from the equator, a gradient that

overlaps with exposure to environmental mycobacteria[41]. Early-life events or diseases, such as perinatal circumstances or early allergen exposure are also reported to increase the prevalence of allergic diseases[42]. However, heterogeneity might not be present in most stratified analyses among subjects at high risk or of non-Western origin as a result of the small number of studies included. Based on this meta- analysis, the positive protective role of BCG vaccine in allergic disease requires further investigation, especially more cohort studies on children from high risk areas.

As for rhinitis and eczema, there is significant association, even though they may share the same genetic architecture with asthma[43]. That is likely because some methodologic limitations may have impacted limit our interpretation of the findings. We expected that exploring heterogeneity according to methodologic characteristics of the original studies may have been informative in terms of pinpointing which and in what aspects specific studies have contributed to heterogeneity. As these participants lacked information on the severity of allergic disease especially eczema in the included studies, the applicability of findings to children with varying degrees of severity is therefore uncertain. This may have influenced the resulting protective effective of BCG vaccination in eczema and rhinitis.

4.2 | Strengths and limitations of study

Our meta-analysis has several strengths. Compared with a similar meta-analysis[19], 5 new articles were included in this paper. Each study sample size in this meta-analysis was larger than 100 participants and with high quality so the result can be more accurate than others with low quality and smaller sample size[44]. Furthermore, we followed the recommendations of the Cochrane Collaboration and PRISMA statement, including a priori protocol. Comprehensive assessment of the study quality was achieved by using GRADE approach.

As with all systematic reviews, we may have failed to identify some studies, especially those with negative results, therefore, this may have influenced our findings. Finally, the length of time that the early effective protection from BCG vaccination lasts remains unanswered. The age of participants in this review may partially explain the result of the protective effect of BCG vaccination. In Linehan's study, it was shown that any benefits of BCG vaccine are likely to be transient.[45] Therefore, a large proportion of the protection from BCG vaccination may not be attribute to a reduction in the risk of atopy. Nonetheless, it can be confirmed that BCG vaccination in early childhood does reduce the risk of developing asthma in early life.

5 | Conclusion

Use of BCG vaccine in early childhood can provide benefits by reducing risk of allergic disease, especially asthma. This finding supports the hypothesis that BCG vaccine should be encouraged as prevention in asthma. However, the findings from this study did not suggest that use of BCG vaccine in early childhood can reduce the risk of developing allergic disease among all races, significant effect of BCG vaccination is currently only evident among European countries and American countries.

Supplementary Material:

Refer to Web version on PubMed Central for supplementary material.

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Author contribution:

All the authors conceived and designed the study project. Keyu Zhao and Phoebe Miles performed literature research, assessed study details and evaluated the study quality supported by Chao Cao and Suling Xu. Qiongyan Zhou and Wei Lin performed the statistical analyses. Keyu Zhao wrote the first draft of the paper with the support of Richard Hubbard, which was critically revised by all the other authors. All the authors gave final approval of the version to be submitted and agreed to be accountable for the whole paper.

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Table 1. Characteristics of 13 studies included in the present study:

Figure 1 . Flowchart summarizing evidence search and study selection

Figure 2. Forest plot showing ORs and 95% CIs for the association between BCG vaccination and total allergic disease.

Figure 3. Forest plot showing ORs and 95% CIs for the association between BCG vaccination and asthma.

Figure 4. Forest plot showing ORs and 95% CIs for the association between BCG vaccination and rhinitis.

Figure 5. Forest plot showing ORs and 95% CIs for the association between BCG vaccination and eczema.

Figure 6. Funnel plot for the association between BCG vaccination and total allergic disease with pseudo 95% confidence intervals (se=standard error).

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