

QUESTION 2

Does neonatal BCG vaccination prevent allergic disease in later life?

CLINICAL SCENARIO

You are working on the postnatal ward of a busy maternity hospital. While doing a routine discharge check of a newborn baby, the mother asks you about the availability of BCG vaccination. Her two older children have severe eczema, asthma and food allergies, and she has read on the internet that BCG may reduce the risk of allergic disease.

STRUCTURED CLINICAL QUESTION

In a newborn infant (patient), does BCG vaccination (intervention) prevent the development of allergic disease in later life (outcome)?

SEARCH STRATEGY AND OUTCOME

Medline and Embase were searched (1946 to current date) using the keywords ((bacille Calmette-Guérin) OR (BCG)) AND (allergy OR asthma). Restrictions were human subjects, randomised controlled trials, systematic reviews and meta-analyses. This search yielded 64 articles. A search of the Cochrane Library revealed a further five articles. Of these 69 articles, one randomised controlled trial and four systematic reviews (three with meta-analyses) of observational studies were relevant and selected for full text review. Excluded articles included 10 randomised controlled trials of BCG as an immune therapy for asthma and allergic rhinitis in childhood as they did not relate to the question of prevention.

COMMENTARY

The hygiene hypothesis proposes that diminished microbial exposure in early life prevents the switch from the T helper 2 (Th2) immune response that predominates in neonates to a T helper 1 (Th1) response.¹ A persistent Th 2-dominant immune response is associated with the development of allergic disease. BCG has strong immunomodulatory properties that include the induction of Th1 cytokines,^{2 3} as well as significant effects on innate immunity.⁴ BCG is the most widely administered neonatal vaccine worldwide and has a well-documented safety profile. It is an attractive potential intervention for the prevention of allergic disease.

We found only one randomised controlled trial of neonatal BCG vaccination as a preventive intervention for allergic disease (table 1).⁵ In this study, neonates with a family history

of allergic disease were vaccinated with BCG or saline placebo at 6 weeks of age. At 18 months of age, there was significantly less use of eczema medication in the BCG-vaccinated group and a trend towards less eczema. However, the study population was small and powered only to detect a 50% difference in prevalence of allergic disease between the two groups. Although there was no difference between the groups in respiratory symptoms, the trial was too short to provide a definitive assessment of asthma. The results also need to be interpreted in light of the selection of infants at high risk of allergic disease.

There have been a large number of observational studies addressing the influence of BCG vaccination on allergic disease. These have been qualitatively evaluated in no less than four systematic reviews, each of which highlights the clinical and methodological heterogeneity of the available evidence. The search strategy varied between reviews depending on the research question. Two early reviews included studies of the potential positive and negative effects of all childhood vaccines on the development of allergic disease.^{6 7} However, two more recent systematic reviews of observational studies were relevant as they focused solely on the potential protective effect of BCG vaccination.^{8 9}

El-Zein *et al*⁸ examined the effect of BCG vaccination on the development of asthma (23 studies) while Arnoldussen *et al*⁹ looked at multiple allergic outcomes (17 studies) (table 1). There are important differences in the 28 individual studies included in the two reviews. A key difference is the age at

which BCG vaccine was administered. To exert a protective immunomodulatory effect, it is likely that BCG vaccination would have to be administered in the early neonatal period. However, BCG was given in the studies up to 12 years of age. BCG was described as 'neonatal' in only 11 of the 28 studies, the age at vaccination varying between 1 day and 3 months. Revaccination at up to 12 years of age occurred in two studies. There were also differences in the reliability of the method used to assess BCG vaccination status, which varied between health records (15 studies), scar (7 studies), and positive tuberculin skin test (4 studies). The method used was not mentioned in two studies. There was also considerable heterogeneity between the included studies in the duration of follow-up. El-Zein *et al* pooled their asthma data in a random effects model ($I^2=39\%$) to give an OR of 0.82 (95% CI 0.72 to 0.92) for the protective effect of BCG vaccination on asthma. For the six studies of children vaccinated at less than 1 year of age, the OR was 0.86 (95% CI 0.79 to 0.94). The more homogenous data, from the 16 studies in which vaccination was confirmed by health records, were combined in a fixed effects model to give an OR of 0.86 (95% CI 0.79 to 0.93). In contrast, Arnoldussen *et al* did meta-analyses for multiple outcomes without any stratification by age at vaccination (table 1). Both reviews highlighted the limitations of the data but concluded that a protective effect of BCG was likely for the outcome of asthma.

In summary, only eight studies addressed BCG administered in the neonatal period confirmed by the medical record or a

Table 1 Does neonatal BCG vaccination prevent allergic disease in later life?

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Steenhuis <i>et al</i> , 2008 ⁵	121 infants in Denmark with a first-degree relative with previous or present allergic disease. BCG-vaccinated at 6 weeks of age, n=62; Non-BCG-vaccinated, n=59	Prospective single blind, randomised placebo-controlled trial (Level 2)	Validated questionnaires for symptoms of allergic disease at 6 weeks (baseline), 4 months and 18 months of age	<i>Eczema (ever)</i> 44% vs 61% RR 0.72 (0.5–1.0) p=0.07 NNT=5.6* <i>Medication use for eczema</i> 25% vs 43% RR 0.58 (0.3–1.0) p=0.04 NNT=5.9*	Study was only powered to detect a reduction of greater than 50% in the prevalence of allergic disease in the intervention group. 18 month follow-up inadequate to assess asthma
El-Zein <i>et al</i> , 2010 ⁸	23 studies: 10 cohort 5 case control 8 cross-sectional Total vaccinated, n=41 003	Systematic review and meta-analysis of observational studies (Level 3)	Asthma diagnosis or presence of wheeze	<i>Asthma/wheeze</i> BCG confirmed by scar or positive TST or vaccine record (23 studies) REM OR 0.82 (0.72 to 0.92). BCG confirmed by vaccine record (16 studies) FEM OR 0.86 (0.79 to 0.93)	Marked heterogeneity between studies. Significant protective effect; confirmed in subset of 16 homogenous studies ($I^2=0$) with documented BCG vaccination
Arnoldussen <i>et al</i> , 2011 ⁹	17 studies: 1 randomised controlled trial ⁵ 7 cohort 2 case control 7 cross-sectional Total vaccinated, n=39 403	Systematic review and meta-analysis of observational studies (Level 3)	Sensitisation (IgE/SPT), eczema, allergic rhino-conjunctivitis, asthma	<i>IgE</i> (5 studies; $I^2=0\%$) FEM OR 1.31 (1.07 to 1.60) <i>SPT</i> (5 studies; $I^2=57\%$) REM OR 0.87 (0.67 to 1.13) <i>Atopic dermatitis/eczema</i> (7 studies; $I^2=89\%$) REM OR 0.84 (0.64 to 1.09) <i>Allergic rhino-conjunctivitis</i> (9 studies; $I^2=67\%$) REM OR 1.07 (0.89 to 1.28) <i>Asthma</i> (12 studies; $I^2=91\%$) REM OR 0.73 (0.56 to 0.95)	Modest protective effect only for asthma. Results include a sensitivity analysis to reduce identified publication bias

*Calculated from the data provided.

FEM, fixed effects model; NNT, number needed to treat; REM, random effects model; RR, relative risk; SPT, skin prick test; TST, tuberculin skin test.

scar and had adequate follow-up to detect relevant clinical outcomes. Methodological differences preclude pooling of the data from these studies and the results are conflicting, including one retrospective cohort study of 20 383 participants that found an association between BCG vaccination and increased eczema.

In summary, there is some evidence that BCG vaccination at birth protects against allergic disease. However, this is based on only one randomised controlled trial and the conclusions of systematic reviews of observational studies that have significant methodological weaknesses, heterogeneity and conflicting results. While BCG vaccination is generally safe, adverse effects can occasionally occur. Therefore, in the absence of an adequately-powered, randomised controlled trial of BCG vaccination at birth for the prevention of allergic disease is completed, there is insufficient evidence to recommend this intervention.

Clinical bottom lines

- One randomised controlled trial suggests that neonatal BCG vaccination in those with a family history of allergic disease reduces the development and severity of eczema measured up to 18 months of age (Level 2).
- Two meta-analyses of observational studies found a protective effect of BCG vaccination on the development of asthma (Level 3).
- In the absence of adequately powered randomised controlled trials, there is insufficient evidence to recommend routine BCG vaccination for the prevention of allergy.

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