

Correspondence

Comments on a recent meta-analysis: BCG vaccination and allergic conditions

To the Editor:

We read with great interest the recent meta-analysis by Arnoldussen et al.¹ This work represents an impressive attempt to synthesize the epidemiologic evidence on the relationship between *Bacillus Calmette-Guérin* (BCG) vaccination and the risk of several childhood allergic conditions including sensitization (10 studies), eczema (9 studies), allergic rhinoconjunctivitis (9 studies), and asthma (12 studies). Results suggested a protective effect of BCG vaccination against asthma development, whereas no effect was observed with the other allergic conditions. Analyses were carried out following strict guidelines, notably with regard to assessing the quality of the original studies, testing for heterogeneity, and evaluating publication bias. However, some methodologic issues are worth commenting on.

The first issue relates to the selection and inclusion of eligible studies. Exploring the BCG-asthma association, the authors included many of the same articles incorporated in a meta-analysis by our group² (11 of their 12 studies were included in our analyses). However, they included a randomized controlled trial³ with very young subjects (≤ 18 months) that we believe should have been excluded because of the difficulty of reliably diagnosing asthma in that age group. We also question the exclusion of several other studies; in particular, 2^{4,5} appeared potentially eligible on the basis of the stated inclusion criteria.

The second and more crucial issue relates to heterogeneity of study-specific results. The authors used the index of consistency I^2 statistic to quantify the extent of heterogeneity; values greater than 40% were considered suggestive of significant heterogeneity. Overall, heterogeneity was observed for eczema ($I^2 = 89\%$), asthma ($I^2 = 91\%$), rhinoconjunctivitis ($I^2 = 67\%$), and a positive skin prick test response ($I^2 = 57\%$). Investigating heterogeneity was limited to familial history of allergy, region of birth, and study quality. However, there was still a strong indication of heterogeneity once the analyses were restricted to high-quality studies, especially for eczema and asthma. Moreover, heterogeneity might have disappeared in most stratified analyses among subjects at high risk or of non-Western origin as a result of the small number of studies included. We suggest that exploring heterogeneity according to methodologic characteristics of the original studies would have been informative in terms of pinpointing which and in what aspects specific studies have contributed to heterogeneity. With respect to asthma, 1 study⁶ accounted for most of the heterogeneity, as apparent from the forest plot (Fig 5). Of note,

the effect estimate for this study could not be extracted directly from the original article. In addition, it does not correspond to the effect estimate that we calculated in the context of our meta-analysis² using additional data provided by the original investigators (Monique Mommers, personal communication, May 2008). Using this effect estimate would have resulted in decreasing study heterogeneity for asthma from 91% to 24%. Finally, the funnel plot asymmetry (Fig E8) could also be related to the presence of heterogeneity.⁷

In brief, some methodologic limitations might mitigate the authors' interpretation of the findings, more specifically their questioning of the mechanistic pathways likely involved. In our opinion, the aforementioned methodologic concerns should be considered when drawing conclusions from the current meta-analysis.

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