Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis

Mary F. Linehan, PhD,[a] Ulugbek Nurmatov, PhD,[b] Timothy L. Frank, MD,[a] Robert M. Niven, MD,[a] David N. Baxter, PhD,[c] and Aziz Sheikh, MD[b,d] *Manchester and Edinburgh, United Kingdom, and Boston, Mass*

Background: The Manchester Community Asthma Study (MANCAS) found a protective effect against the risk of wheeze at age 6 to 11 years for children given neonatal BCG vaccination. Our subsequent systematic review and meta-analysis suggested that BCG vaccination did not protect against allergic sensitization but might have exerted a protective effect against nonatopic asthma.

Objectives: We sought to assess whether the protective effect of BCG vaccination on wheeze observed in the MANCAS cohort was maintained at age 13 to 17 years and to incorporate the findings from this final MANCAS analysis into an updated systematic review and meta-analysis.

Methods: BCG vaccination status was determined from health records and respiratory outcomes from questionnaire responses. We updated the systematic review and used fixed-effects and random-effects modeling to undertake meta-analyses.

Results: There were 1608 participants in the final MANCAS analysis. The 12-month prevalence of wheeze was 15.1%. There was no difference in prevalence between those who were and were not BCG vaccinated (15.8% vs 14.3%; relative risk, 1.05; 95% CI, 0.94-1.19). The updated meta-analysis incorporated 4 new studies: this showed that the protective effect of BCG vaccination against the development of asthma identified in our previous meta-analysis was attenuated (odds ratio, 0.95; 95% CI, 0.89-1.00). No protective effect of BCG was seen for sensitization, eczema/atopic dermatitis, rhinoconjunctivitis, or allergy in general.

Conclusions: Taken together, the final results of the MANCAS cohort and the updated systematic review and meta-analysis provide clearer evidence that any protective effect of BCG vaccination on childhood asthma is likely to be transient. (J Allergy Clin Immunol 2014;133:688-95.)

Key words: *Wheeze, asthma, atopy, allergy, BCG, children, systematic review, meta-analysis*

Asthma is a chronic childhood disease with many different phenotypes.[1] Atopic asthma is principally an immunologic disease with T_H2-biased immune pathways that is believed to occur as a consequence of a failure of the immature immune system to adapt its cytokine response to a T_H1-dominant environment.

BCG is a potent immune modulator capable of deviating the immune system toward T_H1 dominance, thereby potentially reducing the likelihood of allergic diseases, such as atopic asthma. This potential of BCG vaccination to protect against atopy, asthma, or both has been investigated in many studies,[2-19] with conflicting results. Our earlier study (the Manchester Community Asthma Study [MANCAS]) investigating the effect of neonatal BCG vaccine found a clinically important lower risk of wheeze for children age 6 to 11 years.[11] The study came about because of an error in dosage of BCG vaccine administered to 857 neonates in St Mary's Hospital, Manchester, United Kingdom, in 1994. These infants were given approximately 5 times the upper limit of the recommended BCG vaccine dose.[20] Once the error was discovered, the hospital suspended its policy of routine BCG vaccination for infants. This change in policy resulted in the creation of 3 separate groups, which provided a unique opportunity to study the relationship between BCG vaccination and atopic diseases: (1) children born when BCG vaccine was routinely administered, (2) children born when BCG vaccine was not routinely available, and (3) children

From [a]the University of Manchester, Manchester Academic Health Science Centre, University Hospital South Manchester NHS Foundation Trust, NIHR South Manchester Respiratory and Allergy Clinical Research Facility; [b]the Allergy and Respiratory Research Group, Centre for Population Health Sciences, University of Edinburgh; [c]the University of Manchester, Manchester Academic Health Science Centre, Clinical Epidemiology and Public Health Unit, Manchester; and [d]the Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston.

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Corresponding author: Mary F. Linehan, PhD, GP Research Unit, 2nd Floor, Education and Research Centre, Wythenshawe Hospital, Manchester M23 9LT, United Kingdom. E-mail: mary.linehan@manchester.ac.uk.

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Abbreviations used
ISAAC: International Study of Asthma and Allergies in Childhood
MANCAS: Manchester Community Asthma Study
OR: Odds ratio
PCT: Primary Care Trust
RR: Relative risk
SPT: Skin prick test

born after the policy of routine neonatal BCG vaccination was reinstated. Children eligible for vaccination when the higher than recommended dose of BCG vaccine was used were excluded from the original study. The main outcomes investigated were as follows: wheeze in the past 12 months, as determined from questionnaire responses, and atopic status, determined by skin prick test (SPT) responses to common aeroallergens. MANCAS found a reduced risk of wheeze in children given a standard dose of neonatal BCG vaccination (relative risk [RR], 0.73; 95% CI, 0.62-0.88).

We subsequently undertook a systematic review and meta-analysis investigating the relationship between BCG vaccination and atopic allergic disorders.[21] Most of the evidence uncovered was epidemiologic in nature but nonetheless suggested that BCG vaccination was associated with a protective effect against the development of asthma (odds ratio [OR], 0.73; 95% CI, 0.56-0.95). However, there was no associated protection in the risk of sensitization, as judged by specific IgE test results (OR, 1.31; 95% CI, 1.07-1.60) or SPT responses (OR, 0.87; 95% CI, 0.67-1.13), with this indicating that any possible benefits in relation to asthma outcomes were likely to be in relation to nonatopic asthma phenotypes, which have a relatively good prognosis in childhood.[22]

In this final follow-up to the MANCAS cohort, we sought to investigate whether the benefits in relation to wheeze and related outcomes were maintained during adolescence (age 13-17 years), and this time we included the group eligible for vaccination when the higher than recommended dose of BCG vaccine was in use to explore the possibility of a dose-response relationship. To contextualize these data in light of recent international evidence, we also updated our earlier meta-analysis.[21]

METHODS

Overview of methods

The details of MANCAS and our systematic review and meta-analysis have been previously reported in the *Journal of Allergy and Clinical Immunology.*[11,21,23] For the present analysis, we conducted a 2-phase program of work in which we first collected additional follow-up data from MANCAS (hereafter referred to as MANCAS 2) and then reran our earlier searches to identify additional recent studies to synthesize the findings from MANCAS 2 into an updated systematic review.

Ethical approval was obtained from the Manchester Local Research Ethics Committee, Manchester, United Kingdom.

Phase 1: MANCAS 2

MANCAS 2 was a retrospective cohort study carried out in 2009-2010 in which vaccination status was determined from health authority records and follow-up data on respiratory/allergy symptoms were collected by using a postal questionnaire (incorporating questions from the International Study of Asthma and Allergies in Childhood [ISAAC] instrument).[24]

The MANCAS 2 cohort included the children eligible for inclusion in the first phase of MANCAS and also the children eligible for vaccination when the higher than recommended dose of BCG vaccine was in use, regardless of whether they had actually received the vaccine. In essence, all children born in St Mary's Hospital between July 1, 1993, and March 31, 1997, and still residing or attending schools in Manchester were eligible for inclusion unless they were considered "vulnerable" (ie, on an at-risk register) or were living with a short-term caregiver. Eligible children were identified from the Primary Care Trust (PCT) database, and the PCT then sent a letter of invitation to the child's parent or parents/caregiver or caregivers. The invitation letter advised that return of the questionnaire in the prepaid envelope to the study team would constitute consent to participate in the study and thereby allow the study team to access medical data held by the PCT. Reminders were sent to nonresponders after 4 and 8 weeks. The addresses of nonresponders were checked, and a further letter/questionnaire was sent to nonresponders for whom an alternative address was identified.

Vaccination status for BCG and all other immunizations was determined for responders from the PCT immunization records database.[11] The PCT database documented BCG vaccination before 12 weeks of age as neonatal BCG and after 12 weeks of age as simply BCG vaccination but did not document the dose or strain of BCG. However, the Evans BCG vaccine was the official BCG vaccine in use in the United Kingdom at the time, and the recommended dose was 0.05 mL for infants less than 3 months old and 0.1 mL for those older than 3 months.[25]

Questionnaire responses were entered onto a database by the principal researcher (M.F.L.), who did not have access to immunization records during the data collection phase. At the end of the data collection period, questionnaire responses were linked to immunization records, with data identified only by a study number. The main outcomes of interest were wheeze in the past 12 months and hay fever/eczema status.

Statistical methods for MANCAS 2

Analyses were performed with SPSS for Windows software (version 16; SPSS, Chicago, Ill). Univariate analyses (χ^2 tests, as appropriate) were carried out to examine relationships between BCG vaccination and wheeze and hay fever/eczema. RRs were calculated to estimate the effect of BCG vaccination, with values of less than 1 indicating a protective effect of BCG vaccination, whereas a value of greater than 1 was considered to suggest an increased risk. ORs were calculated to compare the difference in risk between those who were not given any BCG vaccination and those given a recommended dose of BCG during the neonatal period, a recommended dose of BCG after the neonatal period, and a higher than recommended dose of BCG. The 95% CI around each of these RRs and ORs was also calculated, and the summary measures of risk were only considered significant if the 95% CI did not include the value of 1.00. The effect of age on the protective ability of BCG vaccination was examined by applying the McNemar test to a 2×2 contingency table of the subgroup of responders to both phases of MANCAS, who had all received neonatal BCG vaccination.

Phase 2: Updated systematic review and meta-analysis

We updated our systematic review by using the same search strategy (see the Methods section in this article's Online Repository at www.jacionline.org) and critical appraisal technique used in our earlier systematic review.[21] We report here only on those outcomes for which additional data were available: (1) asthma, (2) sensitization, (3) eczema/atopic dermatitis, (4) rhinoconjunctivitis, and (5) allergy in general.

Because the main cohort remained essentially the same for both phases of MANCAS, it was necessary to ensure that data were not included twice for the same respondent. The databases were cross-checked and those who responded to both phases were identified to prevent double entry for individual respondents. Responders were then stratified into 3 separate groups: (1) those who responded only to the first phase of MANCAS, (2) those who responded to both phases, and (3) those who responded only to MANCAS 2. Because the most recent information provided by each responder was considered the most appropriate data to use, responders were then recategorized into 2 groups: those who responded only to the first phase of MANCAS and those who responded to both phases and to MANCAS 2 (Table I). This allowed data from

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