Neonatal BCG vaccination has no effect on recurrent wheeze in the first year of life: A randomized clinical trial

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Background: Recurrent wheeze (RW) is frequent in childhood. Studies have suggested that BCG vaccination can have nonspecific effects, reducing general nontuberculosis morbidity, including respiratory tract infections and atopic diseases. The mechanisms behind these nonspecific effects of BCG are not fully understood, but a shift from a T_H2 to a T_H1 response has been suggested as a possible explanation.

Objective: We hypothesized that BCG at birth would reduce the cumulative incidence of RW during the first year of life.

Methods: The Danish Calmette Study is a multicenter randomized trial conducted from 2012-2015 at 3 Danish hospitals. The 4262 newborns of 4184 included mothers were randomized 1:1 to BCG (SSI strain 1331) or to a no-intervention control group within 7 days of birth; siblings were randomized together as one randomization unit. Exclusion criteria were gestational age of less than 32 weeks, birth weight of less than 1000 g, known immunodeficiency, or no Danish-speaking parent. Information was collected through telephone interviews and clinical examinations at 3 and 13 months of age; data collectors were blind to randomization group. RW was defined in several ways, with the main definition being physician-diagnosed and medically treated RW up to 13 months of age.

Results: By 13 months, 211 (10.0%) of 2100 children in the BCG group and 195 (9.4%) of 2071 children in the control group had received a diagnosis of RW from a medical doctor and received antiasthma treatment (relative risk, 1.07; 95% CI, 0.89-1.28). Supplementary analyses were made, including an analysis of baseline risk factors for development of RW.

Conclusion: Neonatal BCG had no effect on the development of RW before 13 months of age. (J Allergy Clin Immunol 2017;140:1616-21.)

Key words: *BCG, vaccination, infant, recurrent wheeze, heterologous immunity, nonspecific effects*

Especially during the winter season, recurrent wheeze (RW) is frequent in young children in high-income countries, where every third child less than 6 years of age has been reported to have asthma-like symptoms during the preceding winter.[1] A task force under the European Respiratory Society recommends the division of RW into "episodic viral wheeze," which is exclusively triggered by viral airway infections, and "multiple trigger wheeze," when the wheezing is also present between episodes of airway tract infections.[2] Thus RW is closely linked to airway infections but not necessarily to atopy and allergy[2,3]; in fact, differential effects of risk factors on infant wheeze and atopic dermatitis emphasize a different etiology.[4] However, the treatment used for RW is essentially the same as the symptomatic treatment used for asthmatic children because many of the symptoms are similar.[2]

BCG vaccine is recommended to prevent tuberculosis,[5] but as shown in 2 systematic reviews,[6,7] BCG has also been suggested as a protective measure against atopy. According to the hygiene

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Supported by the Danish National Research Foundation (DNRF 108) and the 3 involved hospitals (Danish National Hospital in Copenhagen, Hvidovre Hospital, and Kolding Hospital). The BCG vaccine was produced by Statens Serum Institute, Copenhagen, Denmark, and bought by the Danish Calmette Study.

Disclosure of potential conflict of interest: L. G. Stensballe and J. Kjærgaard have received a grant from the Danish National Research Foundation (DNRF 108). A. K. G. Jensen and C. S. Benn have received grants from the Danish National Research Foundation. The rest of the authors declare that they have no relevant conflicts of interest.

Trial Registration: ClinicalTrials.gov, trial registration number NCT01694108 at https://clinicaltrials.gov.

Received for publication October 12, 2016; revised November 22, 2016; accepted for publication December 23, 2016.

Available online March 25, 2017.

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0091-6749

http://dx.doi.org/10.1016/j.jaci.2016.12.990

Abbreviations used
MANCAS: Manchester Community Asthma Study
NSE: Nonspecific effect
RCT: Randomized clinical trial
RR: Risk ratio
RW: Recurrent wheeze

hypothesis,[8] skewed immunologic stimulation might explain some of the increase in the incidence of atopic diseases observed in recent decades. BCG has been shown to cause a strong immunologic stimulation, resulting in an IFN-γ response,[9] which could counterbalance the greater T_H2 response found in atopic subjects.[10] However, the picture is much more complicated than just a T_H1 response instead of a T_H2 response, and the exact mechanism of the BCG effect on a cellular level has been the subject of immunologic research in recent years. An English questionnaire–based study published in 2007 found neonatal BCG vaccination associated with a significant reduction in asthma symptoms in children aged 6 to 11 years.[11] However, an updated systematic review from 2014 found any protective effect of BCG against asthma likely to be transient.[7]

Randomized clinical trials (RCTs)[12,13] and observational studies[14-16] have supported that BCG can have beneficial nonspecific effects (NSEs) reducing all-cause morbidity and mortality. In West Africa early BCG vaccination of low-birth-weight infants decreased neonatal mortality, mainly by reducing the incidence of neonatal sepsis, respiratory tract infections, and fever.[12]

Since the beginning of the 1980s, BCG is no longer a part of the Danish Childhood Vaccination Program, and BCG vaccination is now only recommended for specific risk groups.

The Danish Calmette Study aimed to study NSEs of neonatal BCG vaccination in a high-income country. The RCT was powered to study hospital admissions as the primary outcome and atopic dermatitis as a secondary outcome.[17]

Based on the observed effect of BCG on respiratory tract infections and the link between respiratory tract infections and RW, we hypothesized that neonatal BCG would reduce the cumulative incidence of RW in the first year of life. The aim of the present study was to determine the effect of neonatal BCG on the secondary outcome of cumulative incidence of physician-diagnosed and medically treated RW up to 13 months of age.

METHODS

The Danish Calmette Study was an RCT conducted at 3 Danish hospitals. Newborns were enrolled from October 2012 to November 2013. Exclusion criteria were gestational age of less than 32 weeks, birth weight of less than 1000 g, known immunodeficiency, or no Danish-speaking parent. Within 7 days of birth, the newborns were allocated 1:1 to BCG vaccination (SSI strain 1331) or no intervention; in case of multiple births, siblings were randomized together as one randomization unit. The randomization was stratified by maturity. Before randomization, informed consent was obtained, and a structured telephone interview was conducted to collect data on demographics and atopic predisposition. Follow-up consisted of telephone interviews and clinical examinations at 3 and 13 months of age. The methods have been described in detail elsewhere.[17]

Outcome assessment

The main outcome of the present study was the cumulative incidence of physician-diagnosed and medically treated RW until 13 months of age, according to telephone interviews at 3 and 13 months of age. In telephone interviews parents were asked whether their child had ever had RW since birth (3-month interview) or since the last interview (13-month interview). If that was the case, they were asked about use of antiasthma treatment, duration of the treatment, and whether the diagnosis had been confirmed by a medical doctor. At both 3 and 13 months of age, the parents were asked whether their child also had wheezing in periods without respiratory tract infections. At 13 months of age, they were asked whether their child had been coughing at night in periods without respiratory tract infections and whether the child had exercise-induced dyspnea.

RW is defined by recurrent episodes of wheeze, and thus at least 2 episodes of wheeze must have been observed to use the diagnosis of RW. Generally, in Denmark the clinical diagnosis of RW is used for children with 3 or more episodes of wheezing. The Danish term for RW is "asthmatic bronchitis," a term primarily used by persons who have been in contact with the health care system.

At 3 and 13 months, the children were invited for a clinical examination at the study site, where study staff evaluated the child's breathing and made an auscultation. Telephone interviews were conducted by medical doctors, nurses, midwives, and medical students. Clinical examinations were conducted by medical doctors, specially trained nurses, and medical students.

Blinding

During telephone interviews and at clinical examinations, parents were instructed not to reveal the BCG vaccination status of the child to the study staff and to cover the vaccination site on the left shoulder with a plaster before the clinical examinations, irrespective of the child's randomization group.

Definition of atopic predisposition

A child was considered to have atopic predisposition if at least 1 first-degree relative (biological parent or full sibling) currently had or previously had 1 or more of the following atopic diseases with a diagnosis from a medical doctor: food allergy, atopic dermatitis, hay fever, or asthma. RW exclusively triggered by viral airway infections was not considered an atopic disease.

Definition of RW outcome

We defined RW as physician-diagnosed and medically treated RW based on confirmative answers given by the parents to both of the following 2 questions in the telephone interview at 13 months of age: "Has a doctor said that your child has (had) RW?" and "Has the RW been treated with anti-asthmatic treatment?" All types of antiasthma treatment were included: β_2-agonists, long-acting β-agonists, inhaled glucocorticoids, systemic glucocorticoids, and leukotriene receptor antagonists.

Objective signs of RW from the clinical examination were used as a secondary outcome.

The main definition of RW proposed in the analysis plan included all cases of parent-suspected RW, all RW diagnoses given by a medical doctor, and all signs of RW found at the clinical examinations of the Danish Calmette Study, including any rhonchus or prolonged expiration heard at auscultation.

The more specific definition of RW mentioned in the analysis plan was "clinically diagnosed RW," which was RW diagnosed by a medical doctor or by the Danish Calmette Study staff. A prior publication has documented a higher specificity of diagnosis-based than symptoms-based questions regarding asthma, allergic rhinitis, and conjunctivitis.[18] Although the present study looked for RW (and not asthma), the same might apply for RW. *Post hoc*, we decided to emphasize this more specific definition and further enhanced the specificity of the diagnosis by requiring both an RW diagnosis given by a medical doctor and treatment with antiasthma medication.

For comparison, results with respect to the broadly predefined diagnosis from the analysis plan are shown in Table E1 in this article's Online Repository at www.jacionline.org.