

*Original article***Is the prevalence of wheeze in children altered by neonatal BCG vaccination?**

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Background: The prevalence of asthma and atopic disease has increased in recent decades, but precise reasons for this increase are unknown. BCG vaccination is thought to be among a group of vaccines capable of manipulating the immune system toward T_H1 dominance and therefore reducing the likelihood of atopic disease.

Objective: The aim of this study was to determine the influence of neonatal BCG vaccination on the prevalence of wheeze in a large community population of children.

Method: In a historical cohort study, a parent-completed questionnaire was used to identify the prevalence of wheeze in BCG-vaccinated and nonvaccinated children in Manchester, England.

Results: There were 2414 participants aged between 6 and 11 years. In a univariate analysis neonatal BCG vaccination was associated with a significantly lower prevalence of wheeze (odds ratio, 0.69; 95% CI, 0.55-0.86), and statistical significance was retained when the analysis was adjusted for potential confounders (odds ratio, 0.68; 95% CI, 0.53-0.87).

Conclusion: These results demonstrate an association between asthma symptom prevalence and neonatal BCG vaccination, relating to a possible 27% reduction in prevalence, and are therefore of considerable public health importance.

Clinical implications: The capacity of neonatal BCG vaccination to reduce the prevalence of respiratory symptoms in children warrants further investigation. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Wheeze, children, BCG, questionnaire, prevalence

Abbreviations used

OR: Odds ratio

PCT: Primary Care Trust

The prevalence of asthma and atopic disease has increased in recent decades, particularly in industrialized countries.¹ The precise reasons for this increase are unknown, but the hygiene hypothesis has been suggested as a possible explanation.² According to this theory, reduced early-life exposure to microorganisms might predispose to an increased risk of atopic diseases. The hygiene hypothesis gained support from immunologic studies demonstrating distinct antagonistic T_H1 and T_H2 immune pathways. Viruses and intracellular bacteria were shown to induce a T_H1-mediated immune response, whereas allergens were associated with T_H2 immune responses, and early childhood was identified as the period when the dominant pathway is established.^{3,4} Although more recent studies suggest that the process is more complex than that explained purely by a straightforward shift from a T_H1 to a T_H2 immune pathway,^{5,6} studies that investigated cytokine responses in relation to atopic disease prompted investigation of the role that vaccinations can play in influencing the development of the dominant T-cell immune environment.^{7,8} BCG vaccine is thought to be among a group of vaccines capable of manipulating the immune system toward T_H1 dominance and therefore reducing the likelihood of atopic disease.⁹

Previous studies have investigated the relationship between BCG vaccination and atopy, with conflicting results. In a Japanese study the prevalence of atopy was lower in children who had a positive response to a tuberculin test, although a genetic relationship between tuberculin test response and atopic status could not be excluded.¹⁰ A study in Sweden, with 48% power to detect a 50% reduction in atopy, reported no difference in prevalence between 216 children who had been vaccinated with BCG before the age of 6 months and 358 children who had not, all of whom had a genetic predisposition to atopy.¹¹

The purpose of this article is to report on the results of an epidemiologic study investigating an association between neonatal BCG vaccination and wheeze in children.

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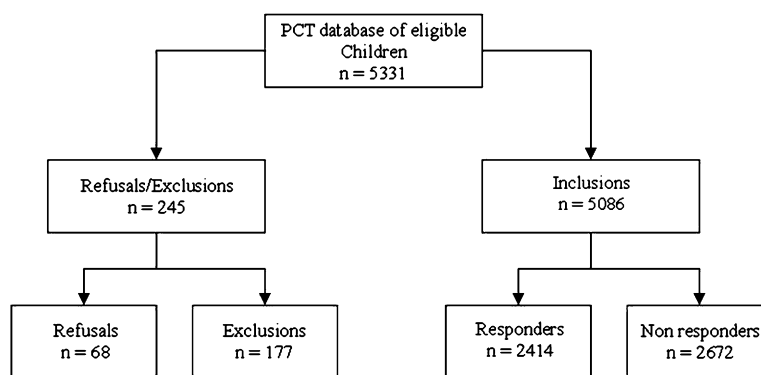


FIG 1. Study cohort.

METHODS

The study population consisted of children born in a single maternity hospital in the northwest of England between July 1, 1993, and December 31, 1993, and between November 18, 1994, and March 31, 1997. This hospital offered BCG vaccination for all children born there until November 1994 and then changed to a policy of not offering routine BCG vaccination. In October 1996, routine BCG vaccination was reintroduced for children born at this hospital. Thus inclusion of children born within the dates outlined above gave the study a cohort of children born during a 6-month period when routine neonatal BCG vaccination was offered, a 22½-month period during which it was not offered, and a further 6-month period when routine BCG vaccination was offered.

Eligible children were identified from a Primary Care Trust (PCT) database of all children in its area. Parental agreement to disclose contact details and medical information held by the PCT was sought before release of the data to the study team. Children who were considered to be vulnerable (on an at-risk register) and children not living with a long-term caregiver were excluded from the study by the PCT. Ethical approval was obtained from the Manchester Local Research Ethics Committees.

A parent-completed questionnaire, based on the International Study of Asthma and Allergies in Childhood asthma questionnaire¹² with some additional questions (Appendix A), was used. Wheeze was determined by response to a question asking whether the child had wheezing or whistling in the chest in the previous 12 months. Neonatal BCG was defined as BCG vaccination given within the first 12 weeks of life. Children given BCG vaccination after the age of 12 weeks (late BCG) were considered to be a separate group.

Questionnaires were posted to parents-guardians, and approximately 100 were sent out on a weekly basis in chronologic order, with the oldest children in the study being selected first. Reminders were sent to nonresponders after 4 and 8 weeks, and a final reminder was sent to all nonresponders once questionnaire distribution had been completed.

BCG vaccination status was determined from immunization records held by the PCT. Vaccination status for other recommended vaccinations was also determined from available immunization records. At the time that these children would have been considered for childhood vaccinations, the schedule consisted of a primary vaccination of diphtheria, tetanus, whole cell pertussis, oral polio, and *Haemophilus influenzae* type B vaccine at 8, 12, and 16 weeks of age and a measles, mumps, and rubella vaccine at 13 months of age. Meningitis C vaccination was introduced into the vaccination schedule in 2000 with the recommendation that children over the age of 12 months be given 1 dose. A preschool booster of diphtheria, tetanus, and polio was also recommended, and in 2002, acellular pertussis was added to the preschool booster. In 1997, a second dose of

measles, mumps, and rubella vaccination, administered at the same time as the preschool booster, was introduced.

The date a questionnaire was sent and the date a response was received were logged on a database by the principal researcher. Questionnaire responses were entered onto a separate database by another member of the study team. The principal researcher did not have access to the questionnaire responses or the immunization records during the data collection phase of the study. At the end of the data collection period, questionnaire responses were linked to immunization records, with data identified only by a study number.

Analyses were performed with SPSS for Windows software.¹³ Univariate analyses (χ^2 and Fisher exact tests, as appropriate) were carried out to examine relationships between neonatal BCG vaccination and wheeze and to identify potential confounding factors. Logistic regression analyses were then carried out to examine the effect of neonatal BCG vaccination after adjustment for potential confounding factors.

RESULTS

After allowing for refusals and exclusions, 5086 children were included in the study (Fig 1). The response rate was 47.5%, resulting in a study population of 2414 children aged between 6 and 11 years at the time of questionnaire response.

The majority of the children were born during the period when BCG vaccine was not offered, but BCG vaccination status did not always reflect BCG vaccination policy at the time of birth (Table I). Of the 5086 children, 1900 (37.4%) had been given BCG vaccination before the age of 12 weeks, which was defined as the neonatal period, and 2535 (49.8%) children had never received BCG vaccination. BCG vaccination had been given to 651 (12.8%) children after the age of 12 weeks (late BCG). BCG vaccination status stratified by response status is shown in Table II.

Univariate analysis

The overall prevalence of wheeze was 20.3%. When stratified by BCG vaccination status, the prevalence was 23.2% for children who never had BCG vaccination, 20.3% for children given late BCG vaccination, and 17.2% for children given neonatal BCG vaccination. The differences in proportions were statistically significant (χ^2 for trend = 11.36, $P < .01$).

TABLE I. Percentage of children by BCG status and BCG policy at birth

	BCG offered, DoB 7/1/1993-12/31/1993 (n = 792)	BCG not offered, DoB 11/18/1994-9/30/1996 (n = 3324)	BCG resumed, DoB 10/1/1996-3/31/1997 (n = 970)
Neonatal BCG (n = 1900)	26.5 (n = 210)	29.4 (n = 977)	73.5 (n = 713)
Late BCG (n = 651)	0.9 (n = 7)	18.4 (n = 610)	3.5 (n = 34)
No BCG (n = 2535)	72.6 (n = 575)	52.3 (n = 1737)	23.0 (n = 223)

χ^2 for difference in proportions = 880.53, $P < .01$.
DoB, Date of birth.

TABLE II. Percentage of children by BCG vaccination status and response status

	Responders (n = 2414)	Nonresponders (n = 2672)
Neonatal BCG (n = 1900)	40.6 (n = 979)	34.5 (n = 921)
No BCG (n = 2535)	44.7 (n = 1079)	54.5 (n = 1456)
Late BCG (n = 651)	14.7 (n = 356)	11.0 (n = 295)

χ^2 for difference in proportions = 50.60, $P < .01$.

When children given late BCG vaccination were excluded from the univariate analysis, the odds ratio (OR) for wheeze was 0.69 (95% CI, 0.55-0.86) for children who had received neonatal BCG vaccination compared with children who had never been given any BCG vaccination (Table III).

Table III also shows all other factors that were examined in univariate analyses. Male sex, history of hay fever or eczema, family history of asthma, single adult households, and adult smokers in the home were all factors significantly associated with an increased prevalence of wheeze in children. Although there was no statistically significant association with any of the other childhood vaccinations, they followed the same trend as that noted for BCG vaccination, with a lower prevalence of wheeze for vaccinated children, and therefore they were included in the regression analysis.

The prevalence of wheeze in relation to BCG policy at birth was also examined in a univariate analysis. Prevalence was 18.8% for children born during the first period when BCG vaccination was offered, 21.1% for those born when BCG vaccination was not offered, and 19.1% for children born during the second period when BCG vaccination was offered. The difference in proportions was not statistically significant (χ^2 for trend = 1.57, $P = 0.46$). However, there was a significant difference in uptake of neonatal BCG vaccination across the 3 birth periods in the study (Table I), and therefore birth period was included in the regression analysis.

Children who were given late BCG vaccination (n = 356) were excluded from the regression analysis because the study aim was to investigate the influence of neonatal BCG vaccination on the prevalence of wheeze and these children were given BCG vaccination after the neonatal period. Children given an incomplete course of primary vaccinations (n = 113) and children given pertussis as part of their preschool booster (n = 26) were also excluded

because their vaccinations differed from those given to the majority of children in the study.

Regression analysis

Table IV shows the results of a stepwise logistic regression analysis performed with wheeze as the dependent variable. Neonatal BCG vaccination was significantly associated with a lower prevalence of wheeze (OR, 0.68; 95% CI, 0.53-0.87). The relative risk of wheeze for children given neonatal BCG vaccination was derived from the OR by using a conventional formula (ie, relative risk = $OR \times [1 - p_2]/[1 - p_1]$) and estimated to be 0.73, suggesting a 27% reduction in risk of wheeze for vaccinated children. Sex, history of hay fever or eczema, and family history of asthma all retained statistical significance.

The number of adults in the household and living in a household with 1 or more smokers lost statistical significance; other vaccinations and BCG policy at time of birth were not significantly associated with wheeze prevalence. BCG policy at the time of birth was not found to influence the relationship between wheeze and neonatal BCG vaccination (where influence was assessed by including period of birth as both a main factor and an interaction factor in the regression analysis).

DISCUSSION

This study investigated the prevalence of wheeze in children with and without neonatal BCG vaccination. It used questionnaire data to identify the prevalence of wheeze and PCT immunization records to establish BCG vaccination status. There was a statistically significant association between neonatal BCG vaccination and a lower prevalence of wheeze in children aged 6 to 11 years after correction for confounding factors and with no influence of other vaccinations.

Overall, there were 2414 responders, and the study had 80% power to detect a difference in prevalence of wheeze of 5% or more (eg, between 15% and 20%) when comparing children who had neonatal BCG vaccination and children who were never given a BCG vaccination.

This study had a low response rate (47.5%). Although the initial correspondence regarding the study was sent from the PCT, all subsequent communication to study participants came directly from the study team, an entity largely unknown to the study population, and this might have influenced willingness to participate. However, the

TABLE III. Univariate analyses for wheeze

Variable	Percentage (n)	OR	95% CI
Neonatal BCG	47.5 (975)	0.69	0.55-0.86
Male sex	53.7 (1292)	1.33	1.08-1.62
History of hay fever/eczema	38.8 (918)	3.44	2.79-4.24
Family history of asthma	59.7 (1414)	2.85	2.26-3.61
One adult household	27.6 (656)	1.42	1.14-1.75
Adult smokers in household	46.3 (1050)	1.31	1.07-1.61
Only child in household	15.9 (370)	1.20	0.92-1.57
Older children in household	59.5 (1342)	1.11	0.90-1.37
White ethnic origin	57.7 (1365)	0.92	0.75-1.12
Primary vaccinations	93.9 (2261)	0.84	0.57-1.25
MMR vaccination	96.6 (2327)	0.83	0.49-1.40
Men C vaccination	77.6 (1869)	0.97	0.76-1.23
Preschool vaccination (diphtheria, tetanus, polio)	88.4 (2129)	0.95	0.70-1.29
Preschool MMR vaccination	82.0 (1975)	0.99	0.76-1.27

MMR, Measles, mumps, and rubella; Men C, meningitis C.

TABLE IV. Stepwise regression analysis for wheeze

	OR	95% CI
Neonatal BCG	0.68	0.53-0.87
Male sex	1.36	1.06-1.74
History of hay fever or eczema	3.20	2.49-4.12
Family history of asthma	2.04	1.55-2.70

Wythenshawe Community Asthma Project, a prospective study of respiratory symptoms in a similar geographic area in the northwest of England, where questionnaires were accompanied by a letter from the recipient's general practitioner's practice, reported a progressive decrease in response rates over an 8-year period,^{14,15} and low response rates have also been noted in other community studies in the United Kingdom.¹⁶ The low response rate in this study is likely to reflect current attitudes and willingness to participate in questionnaire surveys.

Some significant differences between responders and nonresponders were noted. Responders were more likely to be male than nonresponders, but this might reflect the higher prevalence of respiratory symptoms in boys.¹⁷ Responders were likely to be older than nonresponders, but the questionnaires were sent out over a 2-year period, with the oldest children receiving their questionnaires first. Thus less time had elapsed between the period when the PCT informed parents about the study and receipt of questionnaires for the older children. A higher proportion of responders than nonresponders had been vaccinated in each vaccination category. This might reflect parental attitude to medical services and consequently willingness to respond to a medical questionnaire.

Ethnic origin and socioeconomic status might have confounded the relationship between wheeze and neonatal BCG vaccination. A separate question about socioeconomic status was not included in the questionnaire because it would have added to questionnaire length and might have adversely affected the response rate, and therefore family size and single-parent status were used as

markers. No statistically significant effect was found for ethnic group or family size in the univariate analyses, and the effect of single-parent status was not seen in the subsequent regression analysis.

The study population was informed that the study was investigating the relationships between vaccinations and asthma-atopy without specific reference to BCG to avoid a systematic bias between BCG and asthma-atopy. Nonetheless, more responders than nonresponders had been given neonatal BCG vaccination. Although the prevalence of wheeze among the nonresponders is unknown, it is likely that parents of children with wheeze were more likely to participate than the parents of children who did not wheeze. Thus it is possible that there were more children with wheeze, as well as more children who had been given neonatal BCG vaccination, among responders. If such a bias exists, then this study would have underestimated the statistical significance of the association identified between neonatal BCG vaccination and the prevalence of wheeze in the past 12 months.

The changes in policy with regard to neonatal BCG vaccination for children born at this particular hospital during the 1990s provided an ideal and unique opportunity to examine the association between neonatal BCG vaccination and the prevalence of atopic disease in children. The children were aged between 6 and 11 years when the study was carried out, increasing the likelihood that wheeze in these children was a symptom of asthma or atopic disease.¹⁸ All of the children were born in the same hospital and, at the time of participation in the study, still lived, went to school, or both in the area. BCG vaccination policy at the time of birth determined whether neonatal BCG vaccination was offered, although parental choice will have influenced whether BCG vaccination was actually given. Parents might have declined it or might have opted to have their child vaccinated at another venue. This means that there was some cross-over in BCG vaccination status between the study cohorts, but the finding that BCG vaccination policy at birth was not significantly associated with the prevalence of wheeze in either the

univariate or the logistic regression analyses suggests that there were no important cohort effects during the study period.

A fundamental problem in attempts to investigate the prevalence and cause of asthma is the lack of a standardized, universally accepted definition of asthma. Wheeze has been identified as the most important symptom for identifying persons with asthma,¹ and because it can be measured relatively easily, without invasive or expensive tests, it is frequently used as an outcome measure in questionnaire-based epidemiologic studies. The self-reported 12-month prevalence of wheeze shows a strong correlation with bronchial hyperresponsiveness and with physician-diagnosed asthma,^{1,19} and parental report of wheezing was found to be consistent with subsequent child-recorded diary reports of wheeze in an Australian study of 8-to-11-year-olds.²⁰ Although subjective interpretation of the term "wheeze" might affect the reported prevalence of wheeze,^{21,22} this study was concentrated in one geographic area, somewhat limiting the potential for a wide disparity in the perception of the meaning of the term wheeze.

Previous research investigating a role between BCG vaccination and asthma-atopy has produced conflicting results. One of the problems in attempting to interpret the results is that the studies have not all tested the relationship in the same way. Some studies examined tuberculin response,^{10,23,24} others investigated BCG vaccination,^{11,25,26} some investigated both,^{27,28} and tuberculosis infection has also been investigated.²⁹ Outcomes measured also differed and included asthma, defined in a number of different ways; atopy; and manifestations of atopic disease, as well as respiratory symptoms, such as wheeze.

When a review of the literature is restricted to BCG vaccination and wheeze, conflicting results are still seen. In a United Kingdom study no statistically significant difference was noted in the prevalence of exercise-induced wheeze or wheeze with a cold between BCG-vaccinated and nonvaccinated 11-to-18-year-olds.²⁷ Mommers et al³⁰ found that there was a similar number of children with and without respiratory symptoms among a cohort of BCG-vaccinated 7-to-8-year-olds.

A study in Brazil used BCG vaccination scar as evidence of neonatal BCG vaccination and reported a significant reduction in the prevalence of wheezing after exercise in 12-to-16-year-olds.³¹ In an Australian study children with a family history of hay fever or eczema who had been given neonatal BCG vaccination had a lower prevalence of wheeze than those who had not, but the reduction was significant only for children who had 4 or more episodes of wheezing in the previous 12 months.³²

Asthma was defined as wheeze in the past 12 months in a Spanish study that used the International Study of Asthma and Allergies in Childhood questionnaire to identify prevalence and local BCG vaccination policy to determine vaccination status among 6-to-7-year-olds in 4 different areas in Northern Spain. This study reported a statistically significant lower prevalence of asthma

(12-month prevalence of wheeze) for BCG-vaccinated children.³³

The Spanish study is similar to the present study in that both used a large sample to investigate parental reports of wheeze in the past 12 months in children with and without neonatal BCG vaccination, and both reported an inverse relationship between neonatal BCG vaccination and wheeze in the previous 12 months.

By examining the prevalence of parent-reported wheeze, this study found a statistically significant association between neonatal BCG vaccination and a reduced prevalence of wheeze and lends further support to the possibility of an inverse association between neonatal BCG vaccination and subsequent childhood wheeze. A large randomized prospective vaccine study would appear to be the next logical step in investigating an association between neonatal BCG vaccination and asthma and atopic disease.

These results demonstrate an association between asthma symptom prevalence and neonatal BCG vaccination, relating to a possible 27% reduction in prevalence, and are therefore of considerable public health importance.

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APPENDIX A.

To be completed by the Parent or Guardian - Please tick the appropriate box

What is your child's date of birth?

Is your child

FEMALE ☐ MALE ☐

1. Has your child had wheezing or whistling in the chest **in the last 12 months?**

NO ☐ YES ☐

IF 'NO' PLEASE GO TO QUESTION 7

2. How many attacks of wheezing has your child had **in the last 12 months?**

None ☐ 1 to 3 ☐ 4 to 12 ☐ More than 12 ☐

3. **In the last 12 months**, how often, on average, has your child's sleep been disturbed due to wheezing?

Never woken with wheezing
Less than one night per week
One or two nights per week
More than 2 nights per week

☐
☐
☐
☐

4. **In the last 12 months**, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

NO ☐ YES ☐

5. Has your child been woken by an attack of wheezing **in the last 12 months?**

NO ☐ YES ☐

6. **In the last 12 months**, has your child's chest sounded wheezy during or after exercise?

NO ☐ YES ☐

7. **In the last 12 months**, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection

NO ☐ YES ☐

8. Has your child had more than 3 courses of antibiotics
for respiratory infections (chest, ears or throat)
in the last 12 months?

NO ☐ YES ☐

9. Is your child currently taking any medicine for asthma?
(including inhalers, aerosols or tablets)

NO ☐ YES ☐

10. Has your child had an attack of asthma
in the last 12 months?

NO ☐ YES ☐

11. Has your child had hay fever or eczema

NO ☐ YES ☐

12. Has anyone in your child's family (parents, grandparents,
sisters or brothers had asthma?

NO ☐ YES ☐

13. How many adults live in your house?
How many of these adults smoke?

14. How many children live in your house?
How many of these children are older than the
child for whom you have answered this questionnaire?

15. What is **your child's** ethnic group?

Please tick as appropriate (listed in alphabetical order)

Bangladeshi	☐
Black-African	☐
Black-Caribbean	☐
Black-other	☐
Please describe	
Chinese	☐
Indian	☐
Pakistani	☐
White	☐
Any other ethnic group	☐
Please describe	

In line with other Health Authorities in the UK, we are required to collect information on the ethnic origin of the children and families for whom we provide services. We collect this information to ensure that we are providing services fairly and equitably to all those who need them.

THANK YOU FOR YOUR HELP.

PLEASE RETURN THIS FORM TO US IN THE REPLY-PAID ENVELOPE.