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Routine Vaccination Against Pertussis and the Risk of Childhood Asthma: A Population-Based Cohort Study

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What's Known on This Subject

Vaccination coverage in industrialized countries remains suboptimal, partly because parents fear adverse health effects. Epidemiologic studies of the association between childhood vaccinations and asthma have provided conflicting results, probably because of the many potential biases affecting this type of research.

What This Study Adds

This large cohort study, which minimized potential biases, does not provide evidence for an increased risk of childhood asthma because of routine vaccination against pertussis in infancy. These results should help general practitioners and pediatricians provide evidence-based counseling of concerned parents.

ABSTRACT

BACKGROUND. In industrialized countries vaccination coverage remains suboptimal, partly because of perception of an increased risk of asthma. Epidemiologic studies of the association between childhood vaccinations and asthma have provided conflicting results, possibly for methodologic reasons such as unreliable vaccination data, biased reporting, and reverse causation. A recent review stressed the need for additional, adequately controlled large-scale studies.

OBJECTIVE. Our goal was to determine if routine childhood vaccination against pertussis was associated with subsequent development of childhood wheezing disorders and asthma in a large population-based cohort study.

METHODS. In 6811 children from the general population born between 1993 and 1997 in Leicestershire, United Kingdom, respiratory symptom data from repeated questionnaire surveys up to 2003 were linked to independently collected vaccination data from the National Health Service database. We compared incident wheeze and asthma between children of different vaccination status (complete, partial, and no vaccination against pertussis) by computing hazard ratios. Analyses were based on 6048 children, 23 201 person-years of follow-up, and 2426 cases of new-onset wheeze.

RESULTS. There was no evidence for an increased risk of wheeze or asthma in children vaccinated against pertussis compared with nonvaccinated children. Adjusted hazard ratios comparing fully and partially vaccinated with nonvaccinated children were close to one for both incident wheeze and asthma.

CONCLUSION. This study provides no evidence of an association between vaccination against pertussis in infancy and an increased risk of later wheeze or asthma and does not support claims that vaccination against pertussis might significantly increase the risk of childhood asthma. *Pediatrics* 2009;123:944–950

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Key Words

childhood immunizations, asthma, wheezing, cohort studies

Abbreviations

DTP—diphtheria tetanus pertussis
Hib—*Haemophilus influenzae* type b
MMR—measles, mumps, and rubella
HR—hazard ratio
CI—confidence interval
SES—socioeconomic status

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DESPITE THE DOCUMENTED public health benefits of routine vaccination in childhood, insufficient population coverage results episodically in outbreaks of vaccine-preventable disease.^{1–3} Fears about vaccine safety are among the most common reasons cited by parents for refusing vaccination.^{4,5} An important concern relates to a possible association between routine vaccination and the risk of asthma.⁶

Several observational studies reported an increased risk of asthma and atopic disease in vaccinated compared with nonvaccinated children, particularly for vaccination against pertussis.^{7–11} Other studies, including a randomized clinical trial,^{12,13} found no or only inconclusive evidence for an association,^{14–23} and some reported that vaccination against pertussis may protect from atopy.^{24–27} These differences are partly because of the biases affecting this type of research. Reliable vaccination data are often difficult to obtain and many studies have therefore relied on parental or personal recall.^{10,11,18,20–22} Recall may be influenced by whether children have suffered from adverse health outcomes. Other studies have used large computerized databases of general practices or health maintenance organizations.^{9,14,15,23} In these studies, the assessment of outcomes may depend on the frequency of health service use which may not be independent of vaccine uptake. In addition, children with early allergic symptoms or a family

history of atopic disease may be less likely to receive vaccinations, such that an apparent protective effect of vaccination could be because of reverse causation. A recent review noted the many potential biases in previous observational studies and stressed the need for additional, adequately controlled large-scale studies.²⁸

We linked prospectively collected data on the incidence of wheeze and asthma from a large population-based childhood cohort with routine data on childhood vaccination to assess whether vaccination against pertussis was associated with the development of wheezing disorders and asthma. We had information on both the age of onset of wheeze and of vaccination dates, which allowed us to avoid problems of reverse causation. Furthermore, independent data sources for vaccinations and health outcomes allowed the risk of differential misclassification to be minimized. We focused on primary vaccination against pertussis because this vaccine had been most frequently implicated in increasing the risk of asthma.

METHODS

Participants

Details of the second Leicester respiratory cohort study are described elsewhere.^{29–32} Briefly, this cohort is based on a random sample of 8700 children aged 1 to 4 years in 1998 (5400 aged 1, and 1100 aged 2, 3, and 4 years, respectively) drawn from the Health Authority Child Health Database of records for all children born and living in Leicestershire, a county in the English Midlands. Parents were sent respiratory questionnaires in 1998, 1999 (4300 children from the youngest age group only), 2001, and 2003. Response rates, after discounting known invalid addresses, were 80% (6811 of 8500) in 1998 and 51% (4234 of 8276) in 2003.

Vaccination Data

Vaccination data including type, date, and dose were obtained from Specialist Community Child Health Services, Leicester City Primary Care Trust which coordinates routine vaccination for children residing in Leicestershire. Vaccinations are provided by primary care services and reported back to Specialist Community Child Health Services where they are centrally documented. Records were extracted in May 2005, when the youngest children were 8 years old. Whole-cell *Bordetella pertussis* vaccine was usually administered as part of a diphtheria tetanus pertussis (DTP) triple vaccine (brands: Wellcome [London, United Kingdom] before September 1995 and Evans Medical [Leatherhead, United Kingdom] after September 1995) before October 1996 and as part of a 4-component vaccine including *Haemophilus influenzae* type b (Hib) (Pasteur Mérieux, [Lyon, France]) from then on. In accordance with recommendations³³ children were scheduled to receive 3 doses of DTP, polio, and Hib at 2, 3, and 4 months, measles, mumps, and rubella (MMR) at 13 months, and DTP and MMR boosters at 48 months after birth. We focused on primary vaccination against pertussis and defined vaccination status as fully vaccinated (all 3 doses of pertussis re-

ceived), partially vaccinated (1–2 doses of pertussis received) and nonvaccinated (no dose of pertussis received). Vaccinations against hepatitis B, pneumococcal and meningococcal diseases and varicella had not been introduced for infants in the United Kingdom at this time.

Wheeze and Asthma Outcomes

Information on incidence of wheeze and asthma was obtained from repeated parental questionnaires (1998, 1999, 2001, and 2003) which each included a question on the age at first episode of wheeze (in years and months). Based on data from all 4 surveys we defined a date of onset of wheeze as the midmonth date corresponding to the age of onset mentioned in the first questionnaire reporting wheeze. The primary outcome for our analysis was onset of wheeze of any severity and phenotype, including wheeze occurring only during viral infection.^{34,35} We also defined a secondary outcome: onset of wheeze if, in any survey, parents reported that their child had been diagnosed with asthma. This represents a group of children with clinically more relevant disease. We refer to this outcome as “diagnosed asthma.”

Potential Confounders

We considered potential confounding of the relationship between exposure and outcome by gender, birth year, mother's age at delivery, ethnicity (white or south Asian, the predominant local ethnic minority group), number of older siblings, gestational age and birth weight (data obtained from the Health Authority Database), duration of breastfeeding, single parenthood, duration of full-time education of father or mother (with priority to father if both available), crowding, parental history of asthma and hay fever, maternal smoking during pregnancy, exposure to environmental tobacco smoke, nursery school or day care attendance, central heating, gas cooking, pets at home (data from parental questionnaires in 1998) and the Townsend score, a locality-based deprivation score based on 1991 census data.³⁶

Statistical Analysis

We considered a subject to be at risk from 4 months of age (scheduled time for third dose) until onset of wheeze (event) or until the date on which the last questionnaire was completed (right censoring). We defined a time-dependent exposure variable reflecting current vaccination status. Thus a child who had not received any vaccination by the age of 4 months was initially considered nonvaccinated and was reclassified as partially vaccinated from the time of the first dose until completion of primary vaccination (3 doses), at which point the child was considered fully vaccinated. Cox-proportional hazards models were fitted to estimate relative hazard rates comparing fully and partially vaccinated to nonvaccinated children. We adjusted for gender, age, ethnicity, and for any confounders listed, which altered the exposure log hazard ratio (HR) by >2%.

An essential part of our analysis strategy was to rule out reverse causation. First, onset of wheeze in early

childhood may prompt parents and doctors to delay vaccinations. This form of reverse causation was dealt with by excluding from the analysis those children with onset of wheeze in the first 4 months of life, (ie, before scheduled completion of primary vaccination). Second, children with respiratory symptoms other than wheeze, for instance cough associated with viral infections, might also have their vaccinations postponed, contrary to recommendations.³³ Although it is possible that vaccinations may be delayed for several months because of recurrent colds it is implausible that such delays extend for several years. We therefore performed a secondary analysis using only the time window after the age of 36 months. The cutoff at 36 months was chosen a priori and represents a widely accepted cutoff to define “late-onset wheeze,” an asthma phenotype associated with atopy and relatively poor long-term prognosis.³⁴

To examine the robustness of our findings, we performed the following sensitivity analyses: (1) including only the birth cohort of children who were aged 1 year in 1998 and thus provided the most detailed information on the first year of life; (2) including only data from children whose parents, in a nested study,³² had a documented correct understanding of the term “wheeze”; (3) including only data from children who participated beyond the initial survey; and (4) using diphtheria, tetanus, and MMR vaccines as exposures instead of pertussis. We avoided including exposure to different concurrently administered vaccines simultaneously because of problems of collinearity. All analyses were conducted using Stata 8.2 statistical software (Stata Corp, College Station, TX).

This study was approved by the Leicestershire Research Ethics Committee.

RESULTS

Study Subjects and Vaccination Coverage

Of the 8700 randomly selected children, 6811 participated in the initial survey in 1998. Vaccination records were available for all except 18 of these children. An additional 156 children were excluded because of inconsistent records for primary pertussis vaccination (Fig 1). Of the remaining 6637 children, 6428 (96.9%) were fully vaccinated, 117 (1.8%) were partially vaccinated, and 92 (1.4%) were nonvaccinated against pertussis at the time when vaccination records were extracted. Coverage was lower in the older children within the cohort, and those with more than 2 older siblings (Table 1). Among the children fully vaccinated against pertussis (6428), 69.5% received the third vaccine dose at 4 months as scheduled, 26.6% received it with up to 3 months delay, and only 3.9% received it with >3 months' delay.

The 6637 children with consistent pertussis vaccination records were followed up to a mean age of 70 months (median: 76 months [range: 12–122 months]) and 3015 (45.4%) of them reported ever having an attack of wheeze. Of those with reported wheeze ever, 248 did not mention an age of onset, whereas the others reported onset of wheeze at a mean age of 17 months

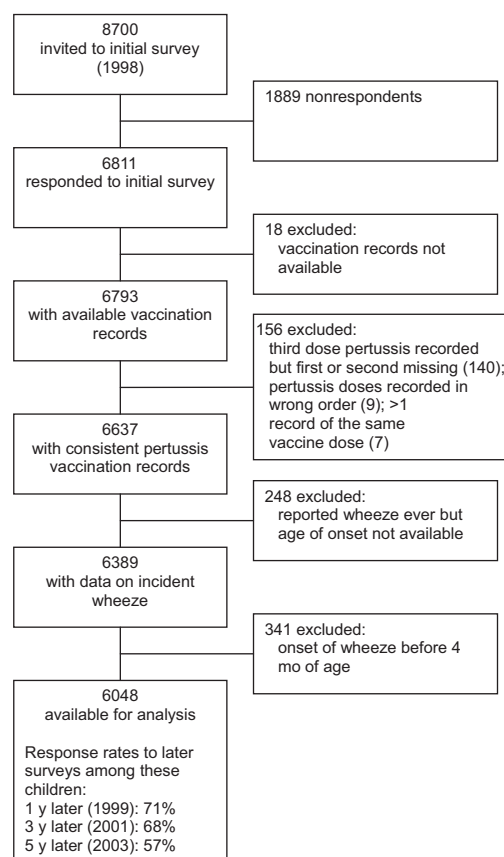


FIGURE 1
Flow diagram of children available for analysis.

(median: 11 months [range: 0–114 months]). Children with onset of wheeze before the age of 4 months, when primary pertussis vaccination should normally be complete, were also excluded ($n = 341$). This left 6048 children for analysis (Fig 1).

Association Between Vaccination Status and Incidence of Wheeze

For the whole follow-up period beginning at the age of 4 months Kaplan-Meier curves indicated a decreased incidence of any wheeze in children fully vaccinated against pertussis compared with partially and nonvaccinated children (Fig 2A). In the restricted time period beginning at 36 months there was a similar tendency for a decreased risk of new-onset wheeze in fully vaccinated children compared with partially and nonvaccinated children (Fig 2B).

The crude HR comparing fully vaccinated with nonvaccinated children was 0.84 (95% confidence interval [CI]: 0.62–1.15; $P = .28$) for the whole observation period (beginning at 4 months old) and 0.50 (95% CI: 0.25–1.02; $P = .06$) for late-onset wheeze (incidence at ≥ 36 months). HRs adjusted for 10 confounders comparing fully with nonvaccinated children were 0.84 (95% CI: 0.62–1.15; $P = .29$) and 0.54 (95% CI: 0.26–1.10; $P = .09$) for the whole and the late period, respectively. The values were similar for diagnosed asthma although

TABLE 1 Selected Characteristics of Children in the Sample (*N* = 6048) According to Status of Vaccination Against Pertussis

Characteristic	Vaccination Status, <i>n</i> (%)			<i>P</i> ^a
	Fully Vaccinated (<i>N</i> = 5863)	Partially Vaccinated (<i>N</i> = 106)	Nonvaccinated (<i>N</i> = 79)	
Gender				
Female	2842 (48.5)	43 (40.6)	43 (54.4)	.150
Male	3021 (51.5)	63 (59.4)	36 (45.6)	—
Ethnicity				
White	4247 (72.4)	77 (72.6)	64 (81.0)	.240
South Asian	1616 (27.6)	29 (27.4)	15 (19.0)	—
Birth cohort				
May 1996–April 1997	3596 (61.3)	67 (63.2)	33 (41.8)	.005
May 1995–April 1996	708 (12.1)	9 (8.5)	16 (20.3)	—
May 1994–April 1995	786 (13.4)	10 (9.4)	13 (16.5)	—
May 1993–April 1994	773 (13.2)	20 (18.9)	17 (21.5)	—
Townsend score ^b				
1st–3rd quintile	3766 (64.2)	62 (58.5)	44 (55.7)	.173
4th quintile	1084 (18.5)	18 (17.0)	17 (21.5)	—
5th quintile	913 (15.6)	24 (22.6)	16 (20.3)	—
Data missing	100 (1.7)	2 (1.9)	2 (2.5)	—
Gestational age, weeks				
<37	343 (5.9)	9 (8.5)	5 (6.3)	.266
37–41	5225 (89.1)	87 (82.1)	69 (87.3)	—
>41	285 (4.9)	9 (8.5)	4 (5.1)	—
Data missing	10 (0.2)	1 (0.9)	1 (1.3)	—
Sibling structure				
0–2 older siblings	5409 (92.3)	92 (86.8)	60 (76.0)	<.001
>2 older siblings	444 (7.6)	14 (13.2)	19 (24.1)	—
Data missing	10 (0.2)	0 (0.0)	0 (0.0)	—
Any parental asthma ever				
No	5220 (89.0)	96 (90.6)	66 (83.5)	.280
Yes	643 (11.0)	10 (9.4)	13 (16.5)	—

Vaccination is defined as the final vaccination status at the time when vaccination records were extracted (age 8–12 years). Children were considered fully vaccinated if they received all 3 scheduled doses of pertussis vaccine, partially vaccinated if they received 1 to 2 doses, and nonvaccinated if they received no doses of pertussis vaccine. For analysis vaccination status was treated as a time-varying exposure variable. Thus, many of the children counted here as fully vaccinated contributed to time at risk in the other categories while they were still nonvaccinated or only partially vaccinated.

^a For Fisher's exact test.

^b A locality-based deprivation score with high values (fourth and fifth quintiles) indicating greater deprivation. Due to negligible differences in vaccination coverage, the first three quintiles were subsumed to 1 category.

CIs were generally wider reflecting the smaller number of cases. HRs comparing partially with nonvaccinated were generally close to 1 with wide 95% CIs (Table 2).

Sensitivity Analyses

The sensitivity analyses yielded similar results. Comparing children fully vaccinated against pertussis with children not vaccinated against pertussis over the whole observation period, adjusted HRs for incident wheeze and asthma were (1) 1.03 (95% CI: 0.66–1.63) and 1.07 (95% CI: 0.51–2.28), respectively, when we included only the subjects aged 1 year at initial survey, (2) 0.86 (95% CI: 0.52–1.44) and 0.68 (95% CI: 0.37–1.23), respectively, when we included only children whose parents correctly defined wheeze, and (3) 0.91 (95% CI: 0.63–1.31) and 0.92 (95% CI: 0.55–1.55) for those who participated in follow-up studies (4906 [81%]). When replacing pertussis vaccination with exposure to other vaccines, corresponding HR estimates were (4) 0.89 (95% CI: 0.57–1.40) and 1.03 (95% CI: 0.51–2.07),

respectively, for diphtheria vaccination (results for tetanus were almost identical to those for diphtheria) and 0.83 (95% CI: 0.67–1.03) and 0.87 (95% CI: 0.63–1.20), respectively, for MMR vaccination.

DISCUSSION

This large population-based cohort study found no evidence of an association between pertussis vaccination and subsequent wheeze or asthma.

Comparison With Other Studies

Our findings contradict several earlier studies reporting a significantly increased risk of asthma or atopic disorders in children vaccinated against pertussis.^{7–11,23} Of these, 1 was based on a small nonvaccinated control group making it susceptible to misclassification of outcomes,⁸ and 2 relied on parental recall of both exposures and outcomes conferring a high risk of recall bias.^{10,11} A large study using data from a general practice research database in

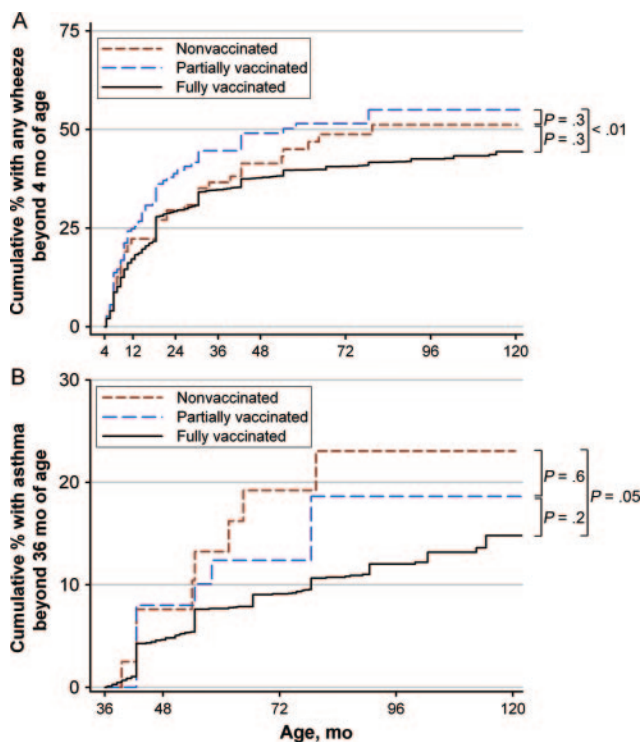


FIGURE 2
Kaplan-Meier estimates of cumulative percentage of children with any wheeze for time periods beginning at 4 months (A) and at 36 months (B) according to completion of primary pertussis vaccination. *P* values are from log-rank tests for equality of survivor functions.

England found a greatly increased risk of asthma in children who received diphtheria, polio, pertussis, and tetanus vaccination compared with those who did not.²³ Stratification by consulting frequency however indicated that the observed association may have been spurious: children with infrequent visits were less likely to have diagnoses recorded and probably less likely to have been vaccinated. Other studies may also have been affected by this form of bias.^{9,14,15}

Four previous studies have found evidence suggesting that vaccination may protect against atopic disorders. Three of these were cross-sectional and thus could not account for temporal relationships between exposures and outcome.^{25–27} Similarly to ours, 1 study was based on data from a population-based cohort with well separated assessment of vaccinations and health outcomes.²⁴ In this study pertussis vaccination was associated with lower prevalence of early atopic dermatitis and allergic sensitization. One previous study used longitudinal analysis with a time-dependent exposure to account for the temporal relationship between vaccination and measured outcomes.¹⁴ This study, which was based on a large data set from 4 health maintenance organizations, found a similar incidence of diagnosed asthma in children vaccinated compared with those not vaccinated against DTP. No significant associations were found between vaccination against pertussis and wheezing or asthma up to the age of 7 years in the only randomized, controlled trial.^{12,13,37}

Strengths and Limitations

The present study has been able to overcome several important methodologic problems. First, it was based on a large representative population sample. This avoided medical care use bias which is common to studies relying on data from health service providers. Second, exposures and outcomes were collected prospectively and independently. Vaccination data were recorded before any symptoms were assessed and neither the vaccine database managers nor the children's parents were aware that the data might later be linked. There was thus no recall bias³⁸ and any misclassification in the outcome was most likely nondifferential. Third, a unique feature of our study is the effort to rule out reverse causation. Knowledge of precise dates of vaccine uptake allowed us to model vaccination status as a time dependent variable and thus to ensure that vaccinations administered after the onset of wheeze did not contribute to the analysis. We also investigated the association between exposure and outcome in a restricted time period (late-onset asthma, with a first episode at the age of >3 years) which was unlikely to have been affected by vaccination delays because of potential precursor symptoms of asthma such as cough during infancy. Lastly, we were able to adjust for a broad range of confounders including several indicators of socioeconomic status (SES).

Limitations of our study include the fact that outcomes were parent-reported and are therefore subject to misclassification. However, asthma diagnosis both in epidemiologic and routine clinical settings is primarily based on reported symptoms,³⁹ with no objective measurement to serve as the gold standard. Results remained unchanged in sensitivity analyses including only children whose parents used the term "wheeze" correctly.³² Age of onset was reported in years and months and if we allow for recall errors the precision of this measure may have been modest. Vaccination status at the time of wheeze onset may therefore have been misclassified in some subjects, but it is unlikely that such misclassification was differential. Although our cohort was large, numbers of nonvaccinated or partially vaccinated children were relatively small, reducing the precision of effect estimates. Finally, because we did not have a direct measure of household SES we used the Townsend score, a locality-based deprivation index which is a commonly used proxy. However, we also included a number of family based measures of SES, including paternal and maternal education, single parenthood, central heating, and cooking with gas.

Although overall the participation rate in our cohort study was good, it is possible that attrition affected our results. To examine this, we performed a separate analysis for children who participated in follow-up surveys and found that HRs were larger and closer to unity than in an analysis including children who only participated in the initial survey. This suggests that HRs in our main analysis would have been even lower if the latter group had been followed up and had contributed more person-years at risk. Bias because of attrition, therefore, is likely to have led to an underestimation of a potential protective effect and not to an underestimation of a potential harmful effect.

TABLE 2 Incidence of Any Wheeze or Asthma and HRs Comparing Children Partially and Fully Vaccinated Against Pertussis With Children Nonvaccinated for the Whole Time Period and a Restricted Time Period (Late-Onset Wheeze Beginning After 36 Months of Age)

Age Window	Person-Years	No. of Cases	Crude HR (95% CI)	Adjusted HR (95% CI) ^a
Onset of wheeze				
Month 4 to last follow-up				
Nonvaccinated	320	42	1	1
Fully vaccinated	22061	2165	0.84 (0.62–1.15)	0.84 (0.62–1.15)
Partially vaccinated	820	219	1.22 (0.87–1.70)	1.11 (0.79–1.56)
Month 36 to last follow-up				
Nonvaccinated	147	8	1	1
Fully vaccinated	11238	324	0.50 (0.25–1.02)	0.54 (0.26–1.10)
Partially vaccinated	182	8	0.77 (0.29–2.06)	0.83 (0.31–2.24)
Onset of diagnosed asthma ^b				
Month 4 to last follow-up				
Nonvaccinated	320	21	1	1
Fully vaccinated	22061	986	0.76 (0.49–1.17)	0.80 (0.51–1.23)
Partially vaccinated	820	101	1.16 (0.71–1.87)	1.09 (0.67–1.77)
Month 36 to last follow-up				
Nonvaccinated	147	4	1	1
Fully vaccinated	11238	184	0.57 (0.21–1.55)	0.63 (0.23–1.72)
Partially vaccinated	182	5	0.96 (0.26–3.59)	1.08 (0.29–4.09)

Children were considered fully vaccinated if they received all 3 scheduled doses of pertussis vaccine, partially vaccinated if they received 1 to 2 doses, and nonvaccinated if they received no doses of pertussis vaccine. HRs were estimated by using Cox proportional hazards models.

^a HRs were adjusted for gender, age, ethnicity, Townsend score, overcrowding, single parenthood, duration of breastfeeding, birth weight, maternal smoking during pregnancy and number of smokers at home. For adjusted models the number of person years at risk and the number cases were moderately lower than reported because of missing values in confounders.

^b Onset of wheeze if the child was reported to have been diagnosed with asthma.

Interpretation of Findings and Future Research

The biological mechanisms through which vaccinations early in life might affect the natural history of asthma and allergy need to be clarified. Both harmful and protective mechanisms have been hypothesized.^{40,41}

Our data do not support a clinically significant increase in risk of asthma because of vaccination against pertussis, with upper confidence limits close to unity. Estimated HRs comparing fully vaccinated children with those not vaccinated against pertussis were consistently below 1 (Table 2). Our findings therefore suggest that, if vaccination against pertussis has any effect on the subsequent development of asthma, it is likely to be a protective one.

Because of the concurrent administration of several vaccines, these results also suggest that none of the other vaccines administered together with pertussis (in the United Kingdom at the time, these included diphtheria, tetanus, polio, and Hib) lead to a significant rise in asthma incidence. In fact, effect estimates for exposure to diphtheria, tetanus, and also MMR (which is not administered concurrently) were similar to those for pertussis.

CONCLUSIONS

Our study provides no evidence of an association between vaccination against pertussis in infancy and an increased risk of later wheeze or asthma and does not support claims that vaccination against pertussis might significantly increase the risk of childhood asthma.

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