

ORIGINAL REPORT

Infant vaccinations and childhood asthma among full-term infants

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SUMMARY

Purpose To determine if infant vaccinations are associated with childhood asthma among full-term infants. The secondary objective was to describe relationships between characteristics of infant wheezing and childhood asthma.

Methods We used baseline data from a study of infant wheezing that selected full-term infants born into a health maintenance organization (HMO) during 1991–1994, continuously enrolled for at least 12 months and without perinatal pulmonary or other selected conditions. Information had been abstracted for infancy (0–18 months) regarding wheezing, vaccinations and asthma risk factors. Using automated data, we identified asthma cases in 1998 among those enrolled for at least 6 months during the year.

Results A total of 1778 full-term infants met our study criterion and 9% had asthma in 1998. Childhood asthma was not significantly associated with having received Hepatitis B vaccine or age at first Hepatitis B vaccine; number of whole-cell pertussis, *Haemophilis influenzae* type b or oral polio vaccine doses; having received measles, mumps, rubella vaccine; or total number of vaccine doses combined. Childhood asthma was significantly associated with number of infant wheezing episodes.

Conclusions Our findings do not support concerns that vaccines are associated with increased risk of asthma but confirm that frequency of infant wheezing is associated with childhood asthma. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — asthma; wheezing; vaccination; vaccine safety; child

BACKGROUND

The prevalence of asthma has been increasing in many countries, including the United States,¹ but much remains unknown about asthma's natural history.² Some speculate that vaccines may directly or indirectly shift the immunologic balance towards a more allergic response and may be partly responsible for

the increase in the incidence of atopic diseases.³ Few studies have investigated vaccines as potential risk factors for asthma or wheezing, and the findings from these studies have been inconsistent.^{4–12}

A study at our health maintenance organization (HMO) by Mullooly *et al.*¹¹ investigated the relationship between infant wheezing and recency of vaccination among full-term infants. No evidence was found of an association between infant wheezing and recency of hepatitis B vaccine (HBV), *Haemophilis influenzae* type b vaccine (Hib), measles, mumps, rubella vaccine (MMR), oral polio vaccine (OPV) or whole-cell pertussis vaccine. Although the results of this first study are reassuring, they do not directly address the risk of asthma after infancy. Mullooly *et al.* used infant wheezing as an endpoint because infant wheezing is related to childhood asthma. However, while wheezing

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episodes in some infants are likely associated with an increased future risk of asthma, in other infants wheezing episodes appear to be transient.² Having persistent wheezing in later childhood has been linked to having more frequent infant wheezing episodes and having infant wheezing without upper respiratory disease.² In addition, having bronchiolitis in association with respiratory syncytial virus (RSV) during infancy appears to be associated with an increased risk of developing asthma.¹³

In the current study, we follow up on the infants from the study by Mullooly *et al.* to determine which ones had evidence of asthma in later childhood. Our primary objective was to determine if infant vaccinations are associated with childhood asthma among full-term infants. Our secondary objective was to describe the relationships between characteristics of infant wheezing and childhood asthma.

METHODS

Study population and measures

The Vaccine Safety Datalink (VSD) project is sponsored by the Centers for Disease Control and Prevention and links medical encounters, immunizations and demographic database information on over 1 000 000 children enrolled in four West Coast HMOs.¹⁴ The current study was conducted at Kaiser Permanente Northwest (KPNW) as part of the VSD project. KPNW is a HMO, serving approximately 450 000 members in northwest Oregon and southwest Washington.

For the current study, we used baseline data on infancy from our previous investigation of infant wheezing among full-term infants. That investigation, which is described in detail elsewhere,¹¹ was a matched-pair case-control study and matched infants who wheezed (cases) to infants who did not wheeze (controls). To select cases and controls, that study used all full-term infants born during 1991 and 1994 and randomly selected half of full-term infants born during 1992 and 1993. To be eligible for that study, infants had to be born into the HMO during 1991 to 1994 and had to be continuously enrolled for at least 12 of the first 18 months of their life. Infants were excluded if they had perinatal pulmonary conditions or other selected conditions (i.e. cancer with chemotherapy or radiation therapy, congenital HIV infection, major congenital malformations, cystic fibrosis, immune deficiency syndrome, digitalis drug treatment, 'cardiac asthma') during the first 18 months of life or were premature. To exclude premature infants, we used birth discharge

diagnoses with International Classification of Diseases, ninth revision (ICD9) codes 765.xx. These codes indicate a gestation of less than 38 weeks and/or a birth weight of less than 2500 grams. Cases and controls were matched on date of birth, gender and Medicaid status at birth. Information was abstracted from medical records for the first 18 months of life regarding wheezing onset dates, vaccination dates and asthma risk factors. In the current article, we refer to the first 18 months of life as 'infancy'.

If the wheezing onset date was not specified in the medical record, it was imputed to be the date of the medical care encounter during which the diagnosis was made. In the baseline case-control study, 41% (1819) of 4459 wheezing onset dates were imputed.¹¹ If the medical care provider stated that the wheeze was related to an underlying non-lower respiratory disease, it was excluded. Separate wheezing episodes were defined by wheezing onset dates at least 14 days apart. Information on concurrent upper respiratory diagnoses at the time of wheezing was also abstracted. We did not abstract information on RSV infection. However, we classified wheezing episodes by RSV season. We defined RSV season as January through April based on surveillance data for Seattle.¹⁵ The seasonal distribution of wheezing episodes in the baseline study was consistent with this RSV season.¹¹ That study had found that the peak in wheezing onset dates was in February/March and the trough was in July/August.

We focused our investigation on five vaccines: HBV, whole-cell pertussis vaccine, Hib, OPV and MMR. We calculated the number of doses of each of these vaccines and the sum of all of these vaccine doses (total number of vaccine doses combined). We used the number of vaccine doses to investigate a possible dose-response effect.

We considered the following asthma risk factors from the medical records: race, birth weight, not breastfeeding at 2 months of age, family history of asthma, maternal age, maternal marital status and maternal smoking. Birth weight was categorized based on the 25th percentile of birth weight for all subjects at baseline (3205 gm). Family history of asthma included history of asthma among parents or siblings. Maternal age was categorized as less than or equal to 22 years old versus 23 or older. Maternal smoking was defined as a mother's smoking during pregnancy or during the infant's first 18 months of life.

Information on maternal age was available for all subjects. Information was not available on race, breast feeding at 2 months and maternal marital status for 2%, 3% and 2% of all subjects at baseline;¹¹ their values were imputed to be white, not breast feeding and

Table 1. Descriptive statistics for infant characteristics among the infants in the follow-up study and among the infants lost to follow-up

Factor	In follow-up study	Lost to follow-up	<i>p</i> -value*
	No. (% of 1778)	No. (% of 954)	
Male	1043 (59)	549 (58)	0.573
Non-white	247 (14)	113 (12)	0.132
Birth weight < 3205 gm	441 (25)	244 (26)	0.657
Breastfed at 2 months old	1008 (57)	487 (51)	0.005
Mean age in years on 1 January 1998 $\pm$ SD	4.8 $\pm$ 1.3	5.0 $\pm$ 1.3	< 0.001
Eligible for 12 months in 1998	1589 (89)	—	—
Family history of asthma	355 (20)	198 (21)	0.625
Maternal age $\leq$ 22 years	315 (18)	259 (27)	< 0.001
Maternal marital status: married	1412 (79)	671 (70)	< 0.001
Maternal smoking	263 (15)	191 (20)	0.001
Medicaid recipient	228 (13)	214 (22)	< 0.001
Hives, atopy, eczema, drug, other allergy	441 (25)	198 (21)	0.017

SD, standard deviation.

**p*-value for comparison of those with and without follow-up; based on chi-square or *t*-test.Table 2. Associations between infant characteristics and childhood asthma (*n* = 1778)

Factor	Proportion with childhood asthma (%)	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
Sex			
Female	66/735 (9)	Referent	Referent
Male	91/1043 (9)	0.97 (0.70–1.35)	1.06 (0.75–1.49)
Race			
White	126/1531 (8)	Referent	Referent
Other	31/247 (13)	1.60 (1.05–2.43)	1.63 (1.04–2.57)
Birth weight			
$\geq$ 3205 gm	117/1337 (9)	Referent	Referent
< 3205 gm	40/441 (9)	1.04 (0.71–1.52)	0.91 (0.61–1.35)
Breastfed at 2 months old			
No	79/770 (10)	Referent	Referent
Yes	78/1008 (8)	0.73 (0.53–1.02)	0.90 (0.63–1.30)
Age on 1 January 1998 [†]	—	1.01 (0.99–1.02)	1.00 (0.99–1.02)
Eligible for 12 months in 1998			
No	21/189 (11)	Referent	Referent
Yes	136/1589 (9)	0.75 (0.46–1.22)	0.84 (0.50–1.40)
Family history of asthma			
No	93/1423 (7)	Referent	Referent
Yes	64/355 (18)	3.15 (2.23–4.43)	3.16 (2.23–4.48)
Maternal age			
>22 years	122/1463 (8)	Referent	Referent
$\leq$ 22 years	35/315 (11)	1.37 (0.92–2.04)	1.15 (0.72–1.84)
Maternal marital status			
Married	116/1412 (8)	Referent	Referent
Not married	41/366 (11)	1.41 (0.97–2.05)	1.08 (0.67–1.73)
Maternal smoking			
No	131/1515 (9)	Referent	Referent
Yes	26/263 (10)	1.16 (0.74–1.80)	1.01 (0.63–1.62)

*Adjusted for the factors listed in the table.

[†]OR is for a 1-month increase.

OR, odds ratio; CI, confidence interval.

married, respectively. Birth weight was not indicated for one subject at baseline; it was assumed to be at least 3205 gm. Information for family history of asthma and maternal smoking was obtained from items marked on forms in the medical records. Items not recorded in the records were interpreted as absence of the factor.

The present study was limited to those subjects who were enrolled in our HMO for at least 6 months during 1998. We identified asthma cases during the entire calendar year of 1998 using automated medical data. An asthma case was defined as: at least one diagnosis of asthma (ICD9 codes 493.x) and at least one dispensing of asthma medication, or at least one dispensing of inhaled beta agonist and at least one dispensing of cromolyn/nedocromil sodium or inhaled corticosteroids, or at least five dispensings of asthma medications.

Asthma medications included beta agonists, theophylline, corticosteroids, cromolyn/nedocromil sodium, adrenergic drugs not elsewhere specified and unclassified asthma medications. This asthma definition was adapted from a previous study conducted at our HMO¹⁶ and is similar to those used in other VSD studies.^{12,17} The onset of childhood asthma occurs by 3 years of age in 80% of childhood asthma¹⁸ and children in this study were at least 3 years old in 1998.

Analyses

We compared characteristics of those in the current study with those lost to follow-up (i.e. those who were in the baseline study but were not eligible for the current study), using the Pearson chi-square test, Mantel-Haenszel chi-square test for trend or t-tests.

We calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to assess associations between childhood asthma and infant vaccination and infant wheezing. We used logistic regression to calculate adjusted ORs and corresponding 95% CIs. We adjusted for sex, race, birth weight, breast feeding at 2 months of age, age in 1998 and duration of eligibility in 1998, family history of asthma, maternal age, maternal marital status and maternal smoking.

Because the subjects in this study were from a case-control study of infant wheezing, we had over sampled infants who wheezed. To assess the impact of this sampling scheme on our findings, we investigated interactions between infant wheezing and vaccination and between infant wheezing and other risk factors.

RESULTS

Of 2732 full-term infants with baseline data, 1778 (65%) met our 1998 enrollment criterion. Of these

1778 infants, over half were male and most were White (Table 1). One quarter of them had hives, atopy, eczema, drug allergy or other allergy indicated in their medical chart during the first 18 months of life. In 1998, all infants were enrolled for at least 6 months and 1589 (89%) were enrolled in KPNW for all 12 months. Their mean age was 4.8 years in January 1998 (range: 3–7 years). Overall, 157 (9%) met our definition for asthma in 1998.

Those lost to follow-up (i.e. were not enrolled in our HMO for at least 6 months during 1998) were significantly more likely to have fewer doses of HBV, pertussis, Hib, OPV and MMR. They were also significantly more likely to have certain asthma risk factors (i.e. less likely to have been breastfed at 2 months of age, more likely to have a young mother, more likely to have an unmarried mother, more likely to have a mother who smoked and more likely to be on Medicaid) and to be older in January 1998, but less likely to have hives, atopy, eczema, drug allergy or

Table 3. Descriptive statistics for infant vaccination in first 18 months of life

Infant vaccination measure	No. (% of 1778)
HBV	
0 doses	574 (32)
1 or more doses	1204 (68)
Age at first HBV	
0 doses of HBV	574 (32)
<1-week-old at first HBV	1079 (61)
≥ 1-week-old at first HBV	125 (7)
Pertussis	
0 doses	16 (1)
1–2 doses	107 (6)
3 doses	383 (22)
4 or more doses	1272 (72)
Hib	
0 doses	13 (1)
1–2 doses	107 (6)
3 doses	397 (22)
4 or more doses	1261 (71)
OPV	
0 doses	11 (1)
1–2 doses	298 (17)
3 doses	1270 (71)
4 or more doses	199 (11)
MMR	
0 doses	383 (22)
1 or more doses	1395 (78)
Mean total no. of vaccine doses combined ± SD (range)	12.9 ± 2.8 (0–17)
Total no. of vaccine doses combined (categorical)	
0–11 doses	338 (19)
12 doses	494 (28)
13–17 doses	946 (53)

other allergy (Table 1). Those lost to follow-up were not significantly different from those not lost to follow-up with respect to family history of asthma, sex, race, birth weight or infant wheezing.

In unadjusted analyses, sex, birth weight, being breastfed at 2 months of age, age in 1998, duration of eligibility in 1998, maternal age, maternal marital status and maternal smoking were not significantly associated with childhood asthma (Table 2). Non-White race and a family history of asthma were significantly associated with childhood asthma. Adjusting for each of the other risk factors, non-White race and family history of asthma remained significantly associated with childhood asthma.

Within the first 18 months of life, about two-thirds of infants had at least one dose of HBV, with most having the first dose within the first week of life (Table 3). Most infants had at least three doses of pertussis, Hib and

OPV. Because only 1% of infants had zero doses of each of these vaccinations, we grouped zero doses together with one and two doses for subsequent analyses. More than three quarters of the infants had received at least one dose of MMR. The mean number of total infant vaccine doses combined was approximately 13. In unadjusted analyses, childhood asthma was not significantly associated with having received HBV; age at first HBV; number of pertussis, Hib or OPV doses; having received MMR; or total number of vaccine doses combined (Table 4). The inferences were consistent in adjusted analyses. We also conducted unadjusted analyses to investigate the impact of our grouping zero, one and two doses of pertussis, Hib and OPV. When we did not group these doses, number of doses of each of these vaccines was still not significantly associated with asthma. In addition, the percentage with childhood asthma was 13% among

Table 4. Associations between infant vaccination and childhood asthma ($n = 1778$)

Infant vaccination measure	Proportion with childhood asthma (%)	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
HBV			
0 doses	54/574 (9)	Referent	Referent
1 or more doses	103/1204 (9)	0.90 (0.64–1.27)	1.06 (0.57–1.96)
Age at first HBV			
0 doses of HBV	54/574 (9)	Referent	Referent
< 1-week-old at first HBV	96/1079 (9)	0.94 (0.66–1.33)	1.15 (0.61–2.17) [†]
≥ 1-week-old at first HBV	7/125 (6)	0.57 (0.25–1.29)	0.72 (0.29–1.82) [†]
Pertussis			
0–2 doses	12/123 (10)	Referent	Referent
3 doses	31/383 (8)	0.82 (0.41–1.64)	0.88 (0.43–1.81)
4 or more doses	114/1272 (9)	0.91 (0.49–1.70)	1.01 (0.52–1.95)
Hib			
0–2 doses	11/120 (9)	Referent	Referent
3 doses	35/397 (9)	0.96 (0.47–1.95)	1.01 (0.49–2.11)
4 or more doses	111/1261 (9)	0.96 (0.50–1.83)	1.06 (0.53–2.11)
OPV			
0–2 doses	25/309 (8)	Referent	Referent
3 doses	111/1270 (9)	1.09 (0.69–1.71)	1.15 (0.71–1.85)
4 or more doses	21/199 (11)	1.34 (0.73–2.47)	1.39 (0.74–2.63)
MMR			
0 doses	32/383 (8)	Referent	Referent
1 or more doses	125/1395 (9)	1.08 (0.72–1.62)	1.19 (0.78–1.82)
Total no. of vaccine doses combined [‡]	—	1.00 (0.94–1.06)	1.02 (0.95–1.09)
Total no. of vaccine doses combined (categorical)			
0–11 doses	31/338 (9)	Referent	Referent
12 doses	46/494 (9)	1.02 (0.63–1.64)	1.02 (0.62–1.68)
13–17 doses	80/946 (8)	0.92 (0.59–1.41)	1.04 (0.63–1.71)

*Adjusted for sex, race, birth weight, breastfeeding at 2 months, age and duration of eligibility in 1998, family history of asthma, maternal age, maternal marital status and maternal smoking.

[†] $p = 0.26$ for comparison of effects of <1-week-old at first HBV and ≥1-week-old at first HBV.

[‡]OR is for a 1-dose increase.

OR, odds ratio; CI, confidence interval; HBV, hepatitis B vaccine; Hib, *Haemophilis influenzae* type b vaccine; OPV, oral polio vaccine; MMR, measles, mumps, rubella vaccine.

Table 5. Descriptive statistics for infant wheezing

Infant wheezing measure	No. (% of 1778)
Number of wheezing episodes	
0	881 (50)
1	369 (21)
2–3	348 (20)
4 or more	180 (10)
Number of wheezing episodes without concurrent upper respiratory disease	
0	1274 (72)
1	281 (16)
2 or more	223 (13)
Number of wheezing episodes during RSV season	
0	1121 (63)
1	415 (23)
2 or more	242 (14)
Number of wheezing episodes outside RSV season	
0	1174 (66)
1	326 (18)
2 or more	278 (16)
Mean age in months at first wheezing onset $\pm$ SD (range)*	6.7 $\pm$ 4.1 (0–17)
Mean age in months at last wheezing onset $\pm$ SD (range)*	10.9 $\pm$ 4.5 (0–17)

*Only includes infants who had at least 1 wheezing episode ($n = 897$).

RSV, respiratory syncytial virus; SD, standard deviation.

those with 0 doses of pertussis, 15% among those with 0 doses of Hib and 18% among those with 0 doses of OPV. These percentages are all higher than the percentage with childhood asthma among the entire study sample (9%).

Because these full-term infants were from a baseline matched-pair case-control study of infant wheezing, half of them had a wheezing episode within the first 18 months of life (Table 5). Ten percent had four or more wheezing episodes. Approximately one-quarter of the infants had a wheezing episode without concurrent upper respiratory disease and 13% had two or more such episodes. Approximately one-third of infants had a wheezing episode during RSV season and 14% had two or more such episodes. The mean age at first wheezing onset was approximately 7 months and the mean age at last wheezing onset was 11 months. In unadjusted analyses, experiencing more infant wheezing episodes and age at last wheezing onset were significantly associated with childhood asthma, but age at first wheezing onset was not (Table 6). In the adjusted analyses, the inferences were consistent although many of the ORs were closer to 1. Even after number of wheezing episodes was in the model, family history of asthma remained significantly associated

with childhood asthma (OR = 2.27; 95%CI: 1.57–3.28).

Number of infant wheezing episodes without upper respiratory disease had a similar relationship with childhood asthma as the total number of infant wheezing episodes (Table 6). The associations between number of infant wheezing episodes within RSV season and asthma were not significantly different from the associations between number of infant wheezing episodes outside RSV season and asthma.

To assess the impact of the sampling scheme on our findings, we investigated interactions between infant wheezing and vaccination as well as between infant wheezing and other risk factors. We did not find statistical evidence of significant interactions between infant wheezing and vaccination or risk factors. We were unable to directly test for the interactions for Hib and pertussis vaccination because there were no childhood asthma cases among subjects with 0–2 Hib doses or with 0–2 pertussis doses; however, neither Hib nor pertussis vaccination doses were significantly associated with childhood asthma when we stratified by infant wheezing. In Table 7, we present the unadjusted associations between infant vaccination and childhood asthma stratified by infant wheezing.

DISCUSSION

This study builds on a previous case-control study of infant wheezing and recency of vaccination at KPNW.¹¹ In the current study, we did not find evidence that infant vaccination was associated with an increased risk of childhood asthma.

The current study also supplements findings from another retrospective cohort study from the VSD project that involved four HMOs.¹² That study did not find significant associations between OPV, diphtheria/tetanus/whole-cell pertussis vaccination (DTP) or MMR and development of asthma (median follow up was 28 months). It found both Hib and HBV were possibly associated with developing asthma but attributed these associations to medical care utilization bias. That study had the advantage of having a very large sample size ($n > 160\,000$) which provided much more power than the current study and enabled them to investigate not ever being vaccinated for particular vaccines. However, it lacked the current study's abstracted data on infant wheezing, race, birthweight, breastfeeding at 2 months of age, family history of asthma, maternal age, maternal marital status and maternal smoking.

Other studies of a relationship between vaccination and asthma or wheezing have had inconsistent

Table 6. Associations between infant wheezing and childhood asthma ($n = 1778$)

Infant wheezing measure	Proportion with childhood asthma (%)	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
Number of wheezing episodes			
0	43/881 (5)	Referent	Referent
1	29/369 (8)	1.66 (1.02–2.71)	1.47 (0.89–2.42)
2 or more	85/528 (16)	3.74 (2.55–5.49)	2.99 (1.98–4.52)
Number of wheezing episodes without concurrent upper respiratory disease			
0	78/1274 (6)	Referent	Referent
1	28/281 (10)	1.70 (1.08–2.67)	1.48 (0.93–2.37)
2 or more	51/223 (23)	4.55 (3.09–6.70)	3.61 (2.39–5.46)
Number of wheezing episodes during RSV season			
0	65/1121 (6)	Referent	Referent
1	49/415 (12)	1.85 [†] (1.23–2.77)	1.79 [‡] (1.19–2.70)
2 or more	43/242 (18)	2.33 [†] (1.47–3.69)	2.22 [‡] (1.39–3.55)
Number of wheezing episodes outside RSV season			
0	71/1174 (6)	Referent	Referent
1	34/326 (10)	1.46 [†] (0.94–2.28)	1.27 [‡] (0.81–2.00)
2 or more	52/278 (19)	2.55 [†] (1.66–3.91)	2.09 [‡] (1.34–3.27)
Age at first wheezing onset [§]	—	1.01 (0.96–1.06)	1.02 (0.97–1.07)
Age at last wheezing onset [§]	—	1.17 (1.11–1.24)	1.17 (1.11–1.23)

*Adjusted for sex, race, birth weight, breastfeeding at 2 months, age and duration of eligibility in 1998, family history of asthma, maternal age, maternal marital status and maternal smoking.

[†]Model contained terms for both the number of wheezing episodes during RSV season and the number of wheezing episodes outside RSV season.

[‡]Model contained terms for both the number of wheezing episodes during RSV season and the number of wheezing episodes outside RSV season; $p = 0.32$ for comparison of effects of 1 wheezing episode during RSV season and 1 wheezing episode outside RSV season, and $p = 0.88$ for comparison of effects of 2 or more wheezing episodes during RSV season and 2 or more wheezing episodes outside RSV season.

[§]OR is for a 1-month increase. Model only includes infants who had at least 1 wheezing episode ($n = 897$).

OR, odds ratio; CI, confidence interval; RSV, respiratory syncytial virus.

findings.^{4–10} The evidence of a relationship is primarily for whole-cell pertussis vaccination and comes from observational studies.^{4–6,9} Unlike the present study, these studies were limited by their cross-sectional design and use of self-reported data,^{4,9} inability to control for potential confounding factors^{4,5} or reliance on medical record data from a single physician's practice.⁶ In contrast, a prospective cohort study which relied on self-reported measures did not find evidence of an association between whole-cell pertussis vaccination and wheezing.⁸ And, a randomized controlled trial of pertussis vaccination did not find evidence of associations between whole cell or acellular pertussis vaccination and asthma.⁷ Of all the studies, this one had the best design but it had a relatively small sample size ($n = 669$) and focused only on pertussis vaccination. In addition to these studies, a recent ecologic study found that higher tuberculosis, measles and DTP vaccination rates were not significantly associated with an increased prevalence of wheezing.¹⁰

The present study also offers some additional information about the relationship between infant wheezing and childhood asthma. We found that the number of infant wheezing episodes was significantly associated with childhood asthma. This finding is consistent with those of Martinez *et al.*² who found that children who had persistent wheezing in later childhood were more likely to have had more frequent infant wheezing episodes. They also found that children who had persistent wheezing were more likely to have had infant wheezing without upper respiratory disease. However in our study, the number of infant wheezing episodes without upper respiratory disease did not have a substantially stronger relationship with childhood asthma than did the total number of infant wheezing episodes. Although RSV bronchiolitis has been linked with development of asthma,¹³ we did not find evidence that infant wheezing during RSV season is more strongly associated with childhood asthma than infant wheezing outside of RSV season. We may not have been able to detect such differences by wheezing

Table 7. Associations between infant vaccination and childhood asthma by infant wheezing

Infant vaccination measure	Unadjusted OR (95%CI)	
	Had infant wheezing (<i>n</i> = 897)	Did not have infant wheezing (<i>n</i> = 881)
HBV		
0 doses	Referent	Referent
1 or more doses	0.90 (0.60–1.37)	0.89 (0.47–1.69)
Age at first HBV		
0 doses of HBV	Referent	Referent
< 1-week-old at first HBV	0.93 (0.61–1.42)	0.91 (0.47–1.76)
≥ 1-week-old at first HBV	0.58 (0.20–1.71)	0.73 (0.21–2.59)
Pertussis		
0–2 doses	Referent	*
3 doses	0.55 (0.25–1.18)	—
4 or more doses	0.62 (0.32–1.22)	—
Hib		
0–2 doses	Referent	†
3 doses	0.50 (0.27–1.30)	—
4 or more doses	0.67 (0.34–1.35)	—
OPV		
0–2 doses	Referent	Referent
3 doses	1.06 (0.62–1.80)	1.21 (0.50–2.97)
4 or more doses	1.23 (0.59–2.59)	1.78 (0.58–5.46)
MMR		
0 doses	Referent	Referent
1 or more doses	1.05 (0.65–1.70)	1.20 (0.55–2.63)
Total no. of vaccine doses combined [‡]	0.97 (0.91–1.04)	1.08 (0.95–1.22)

*Model could not be fit because there were no childhood asthma cases among the 59 subjects with 0–2 pertussis vaccine doses (5% of those with 3 doses and 5% of those with 4 or more doses had childhood asthma). Based on Fisher's exact test, $p = 0.19$ for association between pertussis vaccine doses and childhood asthma.

†Model could not be fit because there were no childhood asthma cases among the 58 subjects with 0–2 Hib doses (6% of those with 3 doses and 5% of those with 4 or more doses had childhood asthma). Based on Fisher's exact test, $p = 0.14$ for association between Hib doses and childhood asthma.

‡OR is for a 1-dose increase.

OR, odds ratio; CI, confidence interval; HBV, hepatitis B vaccine; Hib, *Haemophilis influenzae* type b vaccine; OPV, oral polio vaccine; MMR, measles, mumps, rubella vaccine.

type, in part because of misclassification of the wheezing episodes. For example, physicians may not have always documented upper respiratory disease in the medical charts reviewed for our study. In addition, some of the infant wheezing episodes during our defined RSV season were undoubtedly not due to RSV.

When we simultaneously considered number of infant wheezing episodes and many asthma risk factors as potential predictors of childhood asthma, only number of infant wheezing episodes and family history of asthma were significant predictors. Number of infant wheezing episodes can be viewed as being in the causal pathway between asthma risk factors and childhood asthma. After adjusting for number of infant wheezing episodes, the OR for family history of asthma decreased from 3.2 to 2.3, but it remained an important predictor. Indeed, family history is the best recognized risk factor for asthma.¹ In addition, others have found maternal asthma to be significantly associated with

persistent wheezing and late-onset wheezing, but not transient early wheezing.²

One limitation of this study is its relatively small sample size and high vaccination coverage rates. Therefore, we did not assess associations between childhood asthma and having ever received Hib, having ever received OPV or having ever received pertussis vaccine, but we were able to look at the number of doses of these vaccines to assess whether there was a dose-response effect. In addition, our CIs for the associations between childhood asthma and having ever received HBV or with having ever received MMR were fairly wide. For example, the adjusted OR for the association between having received HBV and childhood asthma was 1.06 with a 95%CI of 0.57–1.96. Based on these results, we calculated sample size requirements for future studies to detect these levels of association. We assumed a significance level of 0.05. If 70% of the infants received HBV and 9% of those not

KEY POINTS

- We did not find evidence that infant vaccination was associated with childhood asthma among full-term infants.
- Our findings do not support concerns that infant vaccination is associated with increased risk of asthma.
- We found that the number of infant wheezing episodes was significantly associated with childhood asthma.

vaccinated had childhood asthma, we would need a sample size of over 39 000 for 80% power to detect a significant OR of 1.1 between having received HBV and asthma, if it truly existed.

This study has some other limitations. First, we abstracted vaccination data only for the first 18 months of life. Second, by using the baseline data from the case-control study of full-term infants, we sampled by infant wheezing. However, we did not find statistical evidence of interactions between wheezing and the vaccination or risk factor measures. Third, those subjects lost to follow-up appeared to be less likely to have been vaccinated and to differ with respect to some of the risk factors. Therefore, the results are not generalizable to those lost to follow-up. Fourth, we cannot generalize these results to premature infants but we are planning a larger cohort study of wheezing and vaccination among premature infants. Last, although our follow-up data were restricted to those who had at least 6 months of eligibility in our HMO in 1998, we had less than 12 months of eligibility for 11% of the subjects and may have misclassified them with respect to asthma diagnosis. In addition, our reliance on the automated databases to determine asthma diagnoses may have also led to misclassification. We would expect such misclassification to bias our OR estimates towards one.

In conclusion, our findings among full-term infants add to the evidence from other studies that vaccines are not associated with increased risk of asthma. Our findings did confirm that frequency of infant wheezing is associated with childhood asthma. This study did not investigate associations between infant vaccinations and atopy, but that is an area for further study.

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