

ORIGINAL REPORT

Wheezing lower respiratory disease and vaccination of full-term infants[†]

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SUMMARY

Purpose There have been speculations that increases in vaccinations have caused recent increases in wheezing lower respiratory disease during infancy. We assess possible associations between vaccines and incidence of wheezing in full-term infants.

Methods We conducted a matched case–control study of full-term infants born into the Kaiser Permanente Northwest health plan during 1991–1994 and continuously enrolled for at least 12 months ($n = 1366$ case–control pairs). Potential cases of wheeze were ascertained from medical care databases and verified by chart review. Vaccinations, demographic factors, and wheeze risk factors were abstracted from charts. Adjusted relative risks of first onset of wheeze during post-vaccination exposure windows were estimated by conditional logistic regression. We also conducted case-series analyses of wheeze onsets.

Results We found no evidence that risk of wheeze during infancy is associated with recency of vaccination with whole-cell pertussis (DTP), hepatitis b (HBV), *Haemophilus influenzae* type b (HIB), oral polio (OPV), or measles, mumps and rubella (MMR) vaccines. We also found no evidence that risk of first wheeze is associated with exposure to HBV or MMR.

Conclusions Recent increases in wheezing during infancy do not appear to be related to increases in vaccinations of full-term infants. Published in 2002 by John Wiley & Sons, Ltd.

KEY WORDS — wheezing lower respiratory disease; wheeze; vaccinations; full-term infants; vaccine safety; population-based case–control study; case-series analysis

INTRODUCTION

The simultaneous increase in childhood vaccination coverage and asthma prevalence in developed countries has led to speculations of possible indirect and direct effects of vaccines on asthma risk in children.¹ Studying possible associations between asthma prevalence and ever/never exposure to vaccines in populations with high vaccine coverage rates requires

very large study populations and is threatened by confounding factors in the small select population of unvaccinated children. In addition to the increase in asthma prevalence, there has been an increase in wheezing during infancy, which increases the risk of childhood asthma.² There has been a dramatic increase since 1985 in bronchiolitis hospitalizations during the first year of life in the US.³ Consequently, we assess possible associations between recency of vaccination and onset of wheeze during infancy.

Wheezing in early life is prominently associated with lower respiratory tract viral infections, especially for respiratory syncytial virus (RSV) infection. It is known that RSV infection is associated with IgE production, airway inflammation, and increased

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airway responsiveness in susceptible children.⁴ Infants who respond to RSV infection with wheezing lower respiratory tract illness are more likely to have an atopic response and to have asthma by age 6 years.⁵ Conversely, infants who have non-wheezing lower respiratory tract illnesses do not have IgE elevations and are less likely to have asthma or persistent wheezing at age 6 years. An association between recency of vaccination and wheeze during RSV seasons would suggest vaccine-related immunologic suppression effects that increase the risk of RSV infection and/or bronchopulmonary effects that increases the risk of RSV infection leading to wheezing. No such associations or effects have been reported.

It has been suggested that vaccines have indirectly increased the prevalences of asthma and allergic diseases by nearly eliminating early childhood infections that prevent allergic sensitization by boosting the immune system.¹ Recent epidemiological studies support negative associations between infections in early childhood and allergic sensitization.^{6–9} T-helper lymphocytes that secrete cytokines of the Th2 class are thought to play an etiologic role in allergic asthma.¹⁰ According to this hypothesis, factors that increase Th2 responses and decrease Th1 responses may lead to the development of asthma. Some studies suggest that intracellular bacteria and viruses, including measles and mycobacteria, induce specific immune responses of the Th1 type.^{11,12} Such responses may provide immunological protection from development of the Th2 phenotype associated with childhood asthma.

It has been speculated that vaccines such as diphtheria, tetanus, pertussis (DTP) may have a direct effect on asthma risk by shifting the immunologic balance toward a more allergenic Th2 response.¹ Current laboratory evidence on the effect of vaccines in general, and pertussis-containing vaccines in particular, on Th1/Th2 balance is inconclusive.¹³ Hepatitis B vaccine (HBV) is the one vaccine that was until recently usually administered at birth. Th2 cells predominate at birth in children who develop atopy.^{14,15} An alternative mechanism for associations of wheezing and vaccines is direct IgE-potentiating effects of vaccines or their adjuvants.^{16–19} Pertussis antigens (natural infection and vaccination) are known to stimulate IgE antibody responses, but clinical implications are unknown.

Increased risks of asthma and wheeze in children who received pertussis vaccine have been reported from an uncontrolled retrospective cohort study²⁰ and from an uncontrolled prospective cohort study.²¹ A recent controlled study using data from the Third National Health and Nutrition Examination Survey

(NHANES) found that DTP or tetanus vaccination appeared to increase the risk of allergies and related respiratory symptoms in children and adolescents.²² No increased risk of wheezing illnesses in young children who received pertussis vaccine was found in a controlled prospective cohort study.²³

Increased risk of atopic disorders (eczema, hay fever, asthma) in children who received whole cell pertussis vaccine was reported by a retrospective cohort study.²⁴ A randomized trial found that children vaccinated with whole cell or acellular pertussis vaccines by age 2.5 years had similar cumulative incidence rates of symptoms (wheezing, itching, sneezing) consistent with later development of allergic diseases.²⁵ A parental interview study of a British national birth cohort found that both measles infection and measles vaccination in childhood reduced the risk of hay fever in children with multiple older sibling contacts.²⁶ A cross-sectional study of anthroposophic (Steiner) schools and neighboring control schools in Stockholm, Sweden found that MMR vaccination increased the risk of atopy, however lifestyle factors associated with anthroposophy were not controlled.²⁷

We assessed possible associations between exposure to childhood vaccines and incidence of wheeze during the first 18 months of life in full-term infants overall and during respiratory syncytial virus (RSV) seasons. A separate study of premature infants is planned.

METHODS

We used a case-control design to assess possible associations between recency of vaccinations and the risk of first wheeze incidence. Cases and controls were pair-matched on birth date, gender, Medicaid status, and duration of health plan eligibility during the first 18 months of life.

We also investigated possible associations between exposure to HBV and MMR and the risk of first wheeze incidence. Whole-cell pertussis (DTP), oral polio (OPV), and *Haemophilus influenzae* type b (HIB) vaccination coverage in this HMO population was too high for ever/never-vaccinated comparisons of wheeze risk.

The following wheeze risk factors were statistically controlled by conditional logistic regression: family history of asthma, race (white/non-white), maternal smoking, low maternal age (<23 years), bottle-feeding at 2 months, and day-care attendance. We also controlled for proxies for health care-seeking behavior (number of illness and well-baby visits prior to the reference date).

In addition to case-control analyses, we also conducted case-series analyses of wheeze incidence rates to completely eliminate confounding by between-infant differences.^{28,29} The counts of events in exposure windows are assumed to be independent Poisson variates. Relative incidence is estimated using multinomial regression, conditional on the observed number of events and the vaccination history for each case.

We used a broad definition of wheezing lower respiratory diseases and attempted to distinguish RSV infections from other causes of wheezing by estimating relative risks during months of peak RSV circulation (January–April) and during non-peak months.

Study population

The study setting is the Kaiser Permanente Northwest (KPNW) health plan, a large, group practice HMO serving 450 000 residents of northwest Oregon and southwest Washington. KPNW is participating in the CDC-sponsored Vaccine Safety Datalink (VSD) project, which links immunizations, medical encounters, and demographic database information on more than 1 million children enrolled in four West Coast HMOs.³⁰

The study population was defined as KPNW members born into the HMO at full-term during 1991–1994 and continuously eligible for at least 12 months of their first 18 months of life. We included all full-term infants who were born during 1991 and 1994 and randomly selected half of full-term infants born during 1992 and 1993. It was not feasible to abstract the medical records of all potential cases and their matched controls in the entire 1991–1994 birth cohorts. The recommendation for universal hepatitis B vaccine (HBV) within 12 h of birth became effective in KPNW in April of 1994.

Exclusions

Birth hospital discharge diagnoses of ICD9 = 765.xx were used to exclude premature infants. These codes imply a birth weight less than 2500 g and/or a gestation less than 38 weeks. Infants with perinatal pulmonary conditions were also excluded from the study. Exclusionary ICD9 diagnosis and procedure codes were bronchopulmonary dysplasia (diagnoses 770.7, 770.1, 770.3, 770.0) and ventilation support in nursery (procedures 96.9, 96.7, 96.70, 96.71, 96.72, 93.90, 93.91). We also excluded infants with cancer chemotherapy or radiation therapy, congenital HIV infection, major congenital malformations, cystic

fibrosis, immune deficiency syndrome, digitalis drug treatment, and 'cardiac asthma' during the first 18 months of life. Exclusions were based on automated inpatient diagnoses, outpatient pharmacy records, and KPNW's tumor registry.

WLRD case ascertainment

To identify potential cases of wheezing lower respiratory disease (wheeze), we used automated ICD9-coded hospital discharge diagnoses, urgent care and emergency room diagnostic text strings, and outpatient drug dispensings. Diagnoses made at non-urgent outpatient encounters were not automated during the study period. Hospital discharge diagnoses included bronchiolitis (466.1), bronchitis NOS (490), and asthma (493.x). Urgent care and ER diagnostic text strings included asthma, wheeze, bronchospasms, and reactive airway disease (RAD). Anti-asthma medications included beta agonists, theophylline, cromolyn, and prednisone. Medical records of potential cases were reviewed to verify diagnoses and to ascertain onset dates and concurrent upper respiratory diseases. When an onset date was not recorded in the medical record, it was imputed to be the date on which the diagnosis was made at a medical care encounter. Wheeze was defined as lower respiratory disease unless the provider stated that it was related to an underlying non-LRD cause.

Control selection

Controls were matched to cases on birth date, gender, and Medicaid status at birth (a proxy for socioeconomic status (SES)). Potential controls were selected after cases were verified and wheeze onset dates were determined. All medical care encounters, including office visits and phone calls, by potential controls were abstracted to verify the absence of wheeze during the first 18 months of life. The control reference date was defined as the first wheeze onset date of the matched case.

Data abstraction

Vaccinations during the first 18 months of life, including those given in the nursery (HBV), were abstracted from inpatient and outpatient medical records. Abstractors were blinded to the case status of the subject. Once a potential wheeze case was verified, onset dates, lower respiratory disease diagnoses and concurrent upper respiratory diagnoses, symptoms and signs, allergies, and anti-asthma medications were

abstracted for all medical care encounters for wheeze during the first 18 months of life. Wheeze case information was abstracted independently of vaccination data. The prenatal medical history and well-baby visit forms were the primary sources of risk factor information. The numbers of illness and well-baby visits prior to the reference date were determined from KPNW's automated medical office appointment and registration system.

Analysis

The associations between recency of vaccination and risk of first WLRD incidence were assessed by comparing times since most recent vaccination in case-control pairs prior to the case's first wheeze onset date. We analyzed all first wheeze onset dates, whether imputed or not, and also analyzed non-imputed first onset dates only. Vaccine exposures in cases and controls were compared in exposure windows of 1–7, 8–14, 15–30, 31–44 days and 45+ days prior to the reference date. Never-vaccinated infants were included in a 'No exposure' category.

We included a same-day exposure category in initial analyses and found large elevations in wheeze risk on day 0. All of these apparent same-day associations were found to be spurious upon chart review. Chart documentation indicated either clinician observation of wheezing prior to vaccination or parental reports of prior wheezing without documentation of onset dates. There were no documented cases of wheeze onset after vaccination. Subsequent analyses reclassified the exposure status of the first wheeze onset relative to the most recent vaccination prior to the onset date.

Case-control differences in risk factors and medical-care-seeking behavior were controlled using conditional logistic regression. A single model was used for simultaneous estimation of the effects of the several exposure windows. Adjusted odds ratios and likelihood profile 95% confidence intervals were estimated. The SAS Logistic procedure was used for conditional logistic regression analyses.

Case-series (self-control) analyses of wheeze onsets were also conducted. Case-series analyses used conditional Poisson models to test associations between recency of vaccination and rate of wheeze onsets. Conditional on the total number of events, the numbers of events in exposure windows are multinomially distributed. Relative incidence is estimated using multinomial regression, conditional on the observed number of events and the vaccination history for each case. Wheeze episodes were defined as

sequences of wheeze onset dates separated by less than 14 days. Case-series analysis avoids potential confounding by uncontrolled among-subject factors (i.e. residual confounding). Each case serves as its own control for the comparison of within-subject rates of wheeze onsets during time periods recently exposed and not recently exposed to vaccines. Only cases with at least one vaccination are included in case-series analyses. A single model was used for simultaneous estimation of the effects of the several exposure windows. Age intervals (0–1, 2–3, 4–5, 6–7, 8–11, 12–18 months) were controlled in the model. Separate analyses were conducted for onsets during and outside the RSV season. We adapted a special-purpose conditional Poisson analysis program (Paul G) using SAS Interactive Matrix Language (IML) (SAS Institute, Cary, NC).

RESULTS

Incidence of wheeze onsets

Wheezing occurred in 22% (1366/6291) of full-term infants (see Table 1). The wheeze incidence rate is an underestimate, because non-ER outpatient cases not treated with asthma medications were not included. KPNW's outpatient database did not become available until 1996.

Wheeze risk during infancy varied considerably with age. The inter-quartile range of *first* onset was 4–10 months. The inter-quartile range of *all* onsets was 5–13 months. Imputation of onset dates did not change the age distribution.

Asthma/RAD were the most frequent diagnoses of first wheeze (45%), followed by bronchiolitis (27%), wheeze/bronchospasm (14%), bronchitis (2%), and pneumonia (2%). Of the cases 11% had multiple diagnoses.

Table 1. Study population size and frequency of WLRD onset dates, KPNW full-term birth cohorts: 1991–1994

Base population	6291
Sample size	2732*
No. infants with at least one WLRD onset	1366
No. infants with at least one non-imputed WLRD onset date	894
No. of controls (infants without WLRD)	1366
No. WLRD onset dates	4459 (1819 [†])
No. onsets with upper respiratory disease	2618 (1057 [†])
No. onsets without upper respiratory disease	1728 (674 [†])
No. unclassified WLRD onsets	113 (88 [†])
No. onset dates per infant with WLRD	3.3

*Individually matched cases and controls.

[†]Non-imputed dates.

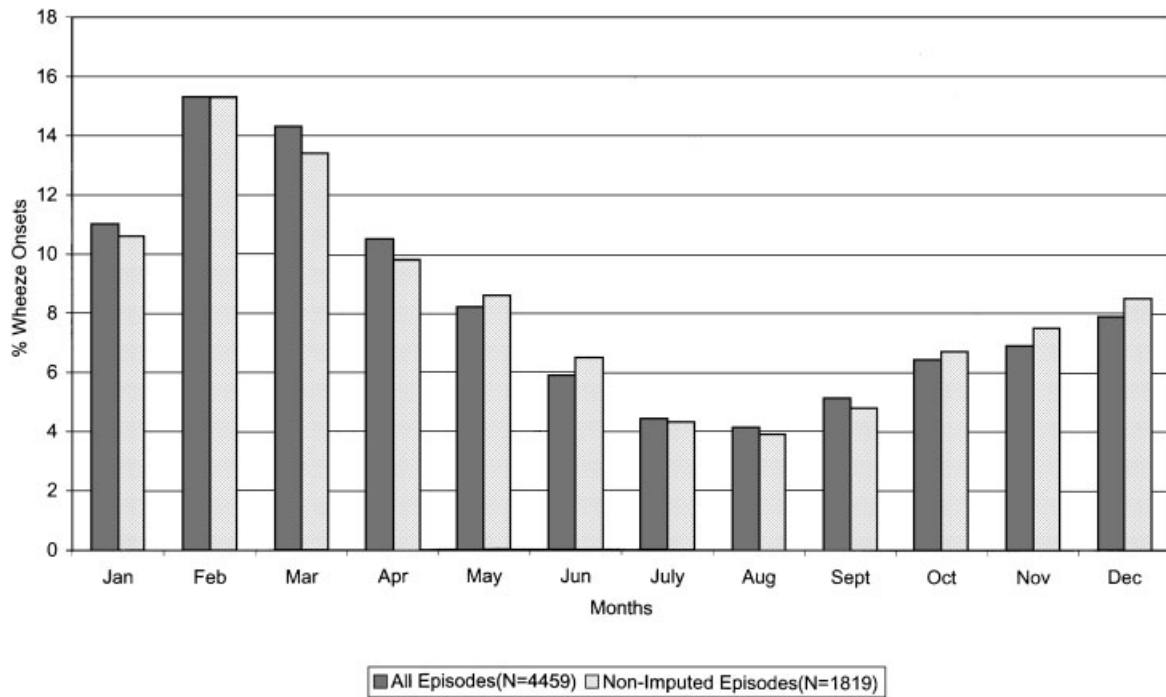


Figure 1. Monthly distribution of wheeze onsets, full-term infants, 1991–1996, ages 0–18 months

The distribution of wheeze onset dates was highly seasonal, with the peak in February/March and the trough in July/August (Figure 1). Virologic surveillance data were not available for the Portland, Oregon area, but the monthly distributions of wheeze onset dates were consistent with the seasonal circulation of RSV in neighboring Seattle during October through May of 1993–1994 and 1996–1997.³¹ Half of the wheeze onsets occurred during the 4-month RSV season (January–April). Bronchiolitis diagnoses were relatively more frequent (36%) during RSV seasons than during other months.

The relative frequencies of wheeze diagnoses at first onset varied by age. At age 0–1 month, bronchiolitis accounted for 58% of diagnoses. By age 12–17 months, the relative frequency of bronchiolitis diagnoses decreased to 13%. There were corresponding age-related increases in the relative frequency of asthma/RAD diagnoses from 12 to 58%.

Exposure to vaccines

Most study infants had multiple exposures to the common infant vaccines, except for HBV and MMR, during their first 18 months of life (Table 2). A fourth

OPV at 18 months was included in an obsolete vaccination schedule. The percentages of infants who received at least one HBV were 2.6, 74.2, 97.8 and 97.5, respectively, for the 1991–1994 birth cohorts.

Wheeze risk factors

Maternal age was available for all subjects. No information was available on race and bottle-feeding at 2 months for 2 and 3% of subjects, respectively. We used probabilistic individual imputation to assign values according to their distributions in the complete

Table 2. Frequency distribution of number of vaccinations by type, $n = 2732$

	Number of vaccinations					
	0	1	2	3	4	5
HBV	35.1%	1.6	7.5	54.3	1.5	0
Pertussis	1.1%	1.9	5.3	24.0	66.9	0.8
OPV	0.8%	2.5	16.5	70.0	10.2	0.04
HIB	0.9%	2.0	5.1	24.7	66.5	0.8
MMR	25.3%	74.3	0.4	0	0	0

Table 3. Comparison of risk factors among matched cases and controls

Risk factor	Cases (<i>N</i> = 894)* (%)	Controls (<i>N</i> = 894) (%)	<i>p</i> -Value [†]
Race, white	88.7	84.9	0.015
Low maternal age, (less than 23 years)	23.0	19.6	0.049
Maternal smoking	20.1	13.6	0.001
Bottle feeding at 2 months	48.0	40.7	0.002
Day-care attendance	33.6	18.9	0.001
Family history of asthma	32.3	8.6	0.001

	Mean $\pm$ SD (Range)	Mean $\pm$ SD (Range)	<i>p</i> -Value [‡]
Number of infant ill visits	4.60 $\pm$ 4.86 (0–43)	3.3 $\pm$ 3.6 (0–31)	0.001
Number of well-baby visits	2.38 $\pm$ 1.41 (0–7)	2.5 $\pm$ 1.41 (0–6)	0.016

*Includes only those cases with non-imputed onsets and their matched controls.

[†]*p*-Value based on McNemar's test statistic.

[‡]*p*-Value based on *t*-test for matched pairs.

data samples. The other risk factors were obtained from items circled or checked on medical history forms. Unchecked items were interpreted as absence of risk factors.

Wheeze risk factors were more prevalent in cases than controls (Table 3). Cases had more medical care visits for illnesses prior to the wheeze reference date and slightly fewer well-baby visits than controls.

Family history of asthma/wheeze was the strongest independent risk factor for infant wheeze. The adjusted odds ratio was 4.5 (CI: 3.3–6.1). White infants were at higher risk of wheezing than non-white infants, 1.4 (CI: 1.0–2.0). Maternal smoking, bottle-feeding at 2 months of age, and day care attendance also independently increased the risk of infant wheeze. The adjusted odds ratios were 1.5 (1.1–2.0), 1.2 (1.0–1.6), and 2.0 (1.6–2.6). Low maternal age (OR = 1.2, CI: 0.9–1.6) was not associated with wheeze. Frequency of illness visit prior to the reference date increased the risk of wheeze (OR = 1.09; 1.05–1.13) but the number of well-baby visits was unrelated to wheeze risk (OR = 0.90, CI: 0.80–1.02).

Vaccinations and WLRD

Conditional logistic regression analyses of first wheeze incidences with documented (non-imputed) onset dates found no increased risks for any of the

common childhood vaccines in any of the vaccination windows, relative to 45+ days post-vaccination (see Table 4). The significant reductions in wheeze risk 1–7 days after pertussis and Hib vaccinations suggest that some parents avoid bringing their infants in for vaccinations when they have respiratory illnesses (a 'healthy-vaccinee' effect). Alternatively, some parents may be less likely to seek care for wheeze if their infants were recently seen at a vaccination visit (negative ascertainment bias). Restricting the analyses to wheeze cases with no concurrent upper respiratory diseases and to cases that had their first onset during the RSV season gave similar results. Results of the analyses of all first onset dates (including imputed dates) were also similar to Table 4.

It is seen from the differences between the unadjusted and adjusted odds ratios that the adjustments had their greatest effects on the no-exposure (No Exp) category (Table 4). This is consistent with these factors being associated with both ever/never exposure and wheezing and not with the relative timing of vaccination and wheeze onset. Except for HVB, the adjustments lowered the odds ratio for the No Exp category. The odds ratios for the 1–7 days and 8–14 days post-HBV also increased, but they were based on few onsets.

Conditional logistic regression analyses of first wheeze incidences with documented (non-imputed) onset dates found no increased risks for exposure to HBV (OR: 1.28, CI: 0.68–2.43) or MMR (OR: 0.90, CI: 0.39–2.04).

The results of the case-series analyses of documented (non-imputed) onset dates are shown in Table 5. The number of included cases varies by vaccine type, because only cases vaccinated at least once during their first 18 months of life contribute to these analyses. Age was controlled in the conditional Poisson models. A 14-day blackout interval was used to distinguish separate episodes of wheezing.

The results of the case-series analyses of wheeze onsets were similar to the results of the case-control analyses of first wheeze onset. Case-series analyses found no increased risk of wheeze for any of the common childhood vaccines in any of the vaccination exposure windows. More of the risk reductions 1–7 days after vaccinations were statistically significant because of the greater precision of case-series estimates. Restricting case-series analyses to wheeze onsets that occurred during RSV seasons gave similar results. The results of case-series analyses for all onset dates (including imputed onset dates) and for onsets that did not have concurrent URD were also similar to Table 5.

Table 4. Relative risk of first onset of wheeze by recency of vaccination, non-imputed onset dates

	Recency of vaccination					
	No exp	1–7 days	8–14 days	15–30 days	31–44 days	45+ days
HBV						
Adj OR*	0.73	0.59	1.46	0.60	0.85	1
CI	0.38–1.39	0.22–1.59	0.63–3.41	0.32–1.12	0.45–1.62	
Unadj OR	0.53	0.38	1.19	0.68	0.80	1
CI	0.30–0.94	0.15–0.96	0.55–2.55	0.39–1.18	0.46–1.39	
Cases/Controls	320/334	8/17	21/15	39/47	49/51	457/430
Pertussis						
Adj OR	1.11	0.49	1.07	0.79	0.66	1
CI	0.61–2.00	0.27–0.91	0.64–1.80	0.52–1.19	0.43–1.02	
Unadj OR	1.18	0.47	1.01	0.87	0.69	1
CI	0.71–1.96	0.27–0.81	0.64–1.59	0.61–1.26	0.47–1.01	
Cases/Controls	92/80	24/47	52/45	117/116	91/111	518/495
HIB						
Adj OR	1.18	0.50	1.09	0.85	0.71	1
CI	0.65–2.14	0.27–0.92	0.65–1.83	0.56–1.29	0.46–1.09	
Unadj OR	1.43	0.51	1.05	0.96	0.77	1
CI	0.86–2.37	0.30–0.87	0.67–1.67	0.67–1.38	0.53–1.12	
Cases/Controls	94/77	25/48	51/45	118/115	92/109	514/500
OPV						
Adj OR	1.25	0.56	1.08	0.86	0.77	1
CI	0.67–2.33	0.29–1.10	0.61–1.91	0.55–1.35	0.48–1.26	
Unadj OR	1.34	0.55	1.03	0.91	0.79	1
CI	0.80–2.26	0.31–1.00	0.62–1.69	0.61–1.34	0.52–1.20	
Cases/Controls	91/77	21/37	42/38	99/101	77/88	564/553
MMR						
Adj OR	0.89	2.00	0.85	0.27	1.81	1
CI	0.30–2.62	0.30–13.45	0.12–6.09	0.05–1.50	0.23–14.15	
Unadj OR	1.02	1.29	1.12	0.32	2.29	1
CI	0.44–2.35	0.29–5.79	0.22–5.66	0.08–1.35	0.39–13.42	
Cases/Controls	854/851	5/4	4/4	5/12	6/3	20/20

*Adjusted for family history of asthma/wheeze, race, low maternal age, maternal smoking, bottle feeding at 2 months, day care, number of illness visits, number of well-baby visits.

DISCUSSION

We found no evidence that risk of wheezing lower respiratory disease (wheeze) during the first 18 months of life was associated with recency of pertussis, HBV, HIB, OPV, or MMR or with ever/never exposure to HBV and MMR vaccination in full-term infants. We had inadequate power to detect MMR-associated risk because few first wheeze onsets occurred after 15 months of age. The HMO's high vaccination coverage rates for pertussis, HIB and OPV precluded precise estimation of relative risks of wheeze among exposed infants compared with unexposed infants. The point estimates of relative risk of wheeze are greater than 1.0 for infants unexposed to pertussis, HIB and OPV, compared to infants exposed 45 or more days ago, but the confidence intervals include 1.0.

We studied possible associations between vaccinations and wheezing lower respiratory disease inci-

dence during infancy because of their recent increases. WLRD is the primary outcome in this study. It is a risk factor for the development of childhood asthma, not a surrogate outcome for asthma. A follow-up study of these study infants through 1998 is investigating possible associations between infant vaccination and childhood asthma.

This is the first study of possible associations between recency of vaccination and risk of wheezing lower respiratory disease in infants. Previous studies have reported mixed results on possible associations between ever/never exposure to vaccines and risk of asthma and wheeze in children and adolescents. Small numbers of unvaccinated subjects and incomplete control for risk factors likely account for the mixed results.

We confirmed that family history of asthma, maternal smoking, bottle-feeding and daycare attendance are risk factors for wheezing during infancy. The

Table 5. Incidence rate ratio of WLRD by recency of vaccination, 14-day blackout, case-series analysis, non-imputed onset dates

	Recency of vaccination				
	1–7 days	8–14 days	15–30 days	31–44 days	45+ days
HBV					
Adj IDR*	0.41	0.82	0.86	0.95	1
CI	0.24–0.70	0.56–1.22	0.65–1.13	0.72–1.25	
Onsets	14	29	69	66	837
RSV seasons					
Adj IDR	0.44	0.87	1.01	0.82	1
CI	0.21–0.91	0.51–1.48	0.71–1.46	0.55–1.22	
Onsets	8	16	43	31	394
Pertussis					
Adj IDR	0.62	0.86	0.96	0.84	1
CI	0.46–0.82	0.67–1.10	0.81–1.14	0.70–1.01	
Onsets	53	75	191	144	1117
RSV seasons					
Adj IDR	0.74	0.94	1.06	0.71	1
CI	0.51–1.07	0.67–1.32	0.84–1.35	0.53–0.94	
Onsets	33	41	105	61	526
HIB					
Adj IDR	0.62	0.86	0.97	0.86	1
CI	0.47–0.82	0.68–1.10	0.82–1.15	0.72–1.03	
Onsets	53	75	192	146	1112
RSV seasons					
Adj IDR	0.74	0.94	1.06	0.73	1
CI	0.51–1.06	0.67–1.31	0.83–1.34	0.55–0.96	
Onsets	33	41	105	63	523
OPV					
Adj IDR	0.67	0.90	1.00	0.87	1
CI	0.49–0.91	0.69–1.18	0.84–1.21	0.71–1.07	
Onsets	44	61	155	116	1207
RSV seasons					
Adj IDR	0.75	0.98	1.05	0.70	1
CI	0.50–1.12	0.68–1.41	0.81–1.37	0.51–0.97	
Onsets	27	35	85	50	569
MMR					
Adj IDR	0.84	0.50	0.62	1.02	1
CI	0.47–1.49	0.24–1.06	0.39–0.98	0.68–1.53	
Onsets	12	7	19	26	1120
RSV seasons					
Adj IDR	0.65	0.88	0.42	0.94	1
CI	0.24–1.77	0.36–2.16	0.17–1.03	0.49–1.81	
Onsets	4	5	5	10	544

*Adjusted for age (0–1, 2–3, 4–5, 6–7, 8–11, 12–18 months).

higher risk of wheeze among white infants may be due to health care-seeking differences between races. We did not assess SES as a risk factor since case-control pairs were matched on Medicaid status (a proxy for SES).

The case-series methodology is attractive since it eliminates confounding by between-subject differences in risk factors and estimates vaccination effects from within-subject differences between wheeze onset rates in vaccine exposure windows. Although case-series analysis eliminates potential confounding by inter-infant differences in health care-seeking

behavior, it does not protect against differential wheeze ascertainment bias.

Differential ascertainment of wheezing illnesses is a potential threat to the validity of case-control and case-series analyses. Case ascertainment is differential when the likelihood of wheezing illness coming to medical attention depends on vaccine exposure status. Some parents may be more likely to seek medical attention for recently vaccinated infants because of worries about possible adverse vaccinations events. It is also possible that some parents may be less likely to seek medical attention for recently vaccinated

wheezing infants since they had just seen the doctor/nurse. The plausibility of negative ascertainment bias appears greater for recurrent wheeze episodes than for first onsets of wheeze. Negative case ascertainment bias could account for the significant reductions in wheeze risk 1–7 days after pertussis and HIB vaccinations. The apparent short-term protective effects of pertussis and HIB vaccinations could alternatively be attributable to ‘healthy-vaccinee’ effects that result from some parents being less likely to bring their infants in for vaccinations when they have respiratory illnesses.

Because of incomplete coverage at the time of the study, our medical care databases captured patients with more severe wheezing illnesses. We estimated the degree of completeness of the case ascertainment method used in this study by determining the fraction of infants with WLRD diagnoses in our current comprehensive computerized medical record that would have been identified by the study protocol (i.e. inpatients, ER, and UC diagnoses or anti-asthma medications). We found that approximately 80% of WLRD cases would have been identified by our protocol. The eligibility and age criteria were used for this approximation but exclusionary diagnoses and procedures were not applied.

Our study was limited to full-term infants who were free of perinatal pulmonary conditions and other serious illnesses. The results should not be generalized to all infants. It is possible that the etiology of wheeze is different in premature and other high-risk infants. We are planning a multi-site study of the risk of wheeze after vaccination of premature infants.

Summary

We conclude that recency of vaccination with pertussis, HBV, HIB, and OPV and exposure to HBV and MMR are not associated with risk of wheezing lower respiratory disease among full-term infants. It appears that increases in vaccinations during infancy are not associated with recent increases in wheezing lower respiratory disease incidence during infancy, but studies of premature and other high-risk infants are needed.

The primary outcome in this study, infant wheezing, is a risk factor for the development of childhood asthma, not a surrogate outcome for childhood asthma. Our results appear to exclude associations between infant vaccination and childhood asthma that are mediated by wheezing during infancy. A follow-up study is investigating possible associations between infant vaccination and childhood asthma.

KEY POINTS

- Recency of common childhood vaccinations does not appear to be associated with the risk of wheezing in full-term infants
- Exposure to HBV or MMR does not appear to be associated with risk of first wheeze in full-term infants
- Recent increases in wheezing during infancy do not appear to be related to increases in vaccinations of full-term infants

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