The relationship between vaccine refusal and self-report of atopic disease in children

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Background: In the last 3 decades, there has been an unexplained increase in the prevalence of asthma and hay fever.
Objective: We sought to determine whether there is an association between childhood vaccination and atopic diseases, and we assessed the self-reported prevalence of atopic diseases in a population that included a large number of families not vaccinating their children.
Methods: Surveys were mailed to 2964 member households of the National Vaccine Information Center, which represents people concerned about vaccine safety, to ascertain vaccination and atopic disease status.
Results: The data included 515 never vaccinated, 423 partially vaccinated, and 239 completely vaccinated children. In multiple regression analyses there were significant ($P < .0005$) and dose-dependent negative relationships between vaccination refusal and self-reported asthma or hay fever only in children with no family history of the condition and, for asthma, in children with no exposure to antibiotics during infancy. Vaccination refusal was also significantly ($P < .005$) and negatively associated with self-reported eczema and current wheeze. A sensitivity analysis indicated that substantial biases would be required to overturn the observed associations.
Conclusion: Parents who refuse vaccinations reported less asthma and allergies in their unvaccinated children. Although this relationship was independent of measured confounders, it could be due to differences in other unmeasured lifestyle factors or systematic bias. Further research is needed to verify these results and investigate which exposures are driving the associations between vaccination refusal and allergic disease. The known benefits of vaccination currently outweigh the unproved risk of allergic disease. (J Allergy Clin Immunol 2005;115:737-44.)

Key words: *Immunization, asthma, allergic rhinitis, eczema, prevalence, cross-sectional survey*

Abbreviations used
DTP: Diphtheria, tetanus, and pertussis
HiB: *Haemophilus influenzae* B
MMR: Measles, mumps, and rubella
NVIC: National Vaccine Information Center
RR: Rate ratio

Asthma is a chronic disease that causes substantial disability, death, and economic burden.[1] Hay fever, which is more common than asthma, is not life-threatening, but the costs of care and treatment are high.[2] Asthma, hay fever, and eczema are separate but related atopic diseases. Over the last 20 to 30 years, the prevalence of these 3 atopic diseases in westernized countries has increased.[3] Recent surveys of self-reported asthma prevalence in the United States and Canada suggest rates of 11% to 17%.[4,5] In developed societies, between 25% and 32% of children typically report allergic rhinitis.[5,6]

Previous studies examining the relationship between asthma and vaccinations have yielded inconsistent results.[7-15] Presently, nearly all children receive vaccinations, and published studies have included few completely unvaccinated children. This study examines the association between vaccinations and atopic disease in a large number of unvaccinated children.

METHODS

Population

Nonimmunized children include families that intended to use immunizations but have not yet done so and a distinct, smaller population of families that consciously refuse immunizations because of religious, philosophical, or safety concerns.[16] This study sampled the mailing list of the National Vaccine Information Center (NVIC), the members of which choose to refuse vaccination. Families might join the NVIC because they believe vaccinations have caused or contributed to their child's illness, frequently autism. The organization focuses on immunization issues, but its members embrace diverse alternative health care philosophies.

Any selected household in the NVIC with children aged 3 to 18 years was eligible to participate in the study. The NVIC assigned a unique study identification number to each selected household to ensure participant anonymity. Thus the investigators never knew participant identities nor had access to information that could be used to identify households. The Institutional Review Board of the University of Illinois at Chicago reviewed and approved the study protocol.

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Supported by the Sprague Institute of Chicago.
Received for publication October 26, 2004; revised December 23, 2004; accepted for publication December 27, 2004.

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0091-6749/$30.00

doi:10.1016/j.jaci.2004.12.1128

Five hundred households received a pilot survey in October 2002. New households (n = 2464) plus nonresponding households (n = 336) from the pilot mailing were contacted in March 2003 and received a reminder postcard 2 weeks later. Households not responding to this mailing received the survey and reminder postcard again in May 2003. The response rate to the survey was 41%, which was calculated by dividing the total number of eligible responses by the estimated total number of eligible households (American Association for Public Opinion Research formula number 3[17]).

Survey instrument

The mailed survey packet included a cover letter that briefly described the study as a survey of allergic disease and invited households to return the survey or an enclosed postcard indicating they were either ineligible to participate (no children aged 3-18 years) or chose not to participate in the survey. The NVIC leadership reviewed the survey before distribution. The survey could not ask, for example, why the family initially joined the organization nor could it collect zip codes. Parents answered questions regarding their eligible children's vaccination history, family medical history, early and current home environment, and their current and cumulative experience of symptoms of hay fever or asthma.

The survey asked ''Has this child ever received an immunization or vaccination?'' and ''Did this child receive all vaccinations as recommended by your health care provider?'' Each child was then classified as refusing all vaccines, refusing some vaccines, or completely vaccinated. From additional questions, children were further classified by exposure to individual vaccines. Parents were instructed to refer to written immunization records, and as vaccine activists, they were likely to know their children's vaccination status.

Primary outcomes were defined by answers to a single question. For example, questions included ''Has a doctor ever said this child has asthma?,'' ''Has this child ever had hay fever (seasonal or environmental allergies)?,'' and ''Has a doctor ever said this child has eczema?'' Additional questions asked about current symptoms of atopic disease.

Parents were asked to identify a single ''primary source of medical care.'' In adjusted models any family that reported using an MD or a DO was classified as exposed to traditional medicine, regardless of their concurrent use of alternative health care providers.

Statistical methods

Subjects were characterized by asthma status and vaccine exposure. The Pearson χ^2 statistic tested the significance of differences between groups for all covariates. Preliminary analyses included calculating rate ratios (RRs) stratified by all available covariates to assess the potential for confounding and effect modification.

Multiple logistic regression models adjusted for confounding variables (age, sex, source of medical care, antibiotic use, and family clustering). Age was entered as a continuous variable, and sex (male/female), source of medical care (see traditional MD/only alternative provider), and exposure to antibiotics in the first year of life (ever/never) were dichotomous variables. Statistically significant ($P < .05$) terms for effect modifiers were included in models and were not the same for all examined outcomes. The model for asthma included interaction terms for family history of asthma and exposure to antibiotics during infancy. Family history of hay fever was the only effect modifier for the association between vaccine refusal and hay fever. There were no effect modifiers for eczema or current wheeze.

Mixed-effects multiple logistic regression models adjusted for familial clustering of observations by estimating both a model intercept and a random intercept for each family cluster to account for covariance. Estimates for random intercepts and predictive variables were calculated through iterative marginal maximum likelihood calculations.[18] When calculating estimated prevalence rates, parameter estimates were transformed to represent the average family cluster by using the method outlined by Neuhaus et al,[19] and calculations used the study average values for age, sex, exposure to antibiotics, source of medical care, and family history of asthma or allergies (eczema and current wheeze only). The prevalence RR is presented with a 95% CI. The *P* value for trend was calculated by entering vaccine refusal as an ordinal variable in the mixed-effects multiple logistic regression models.

We performed a sensitivity analysis to assess the potential effect of nonrandom error caused by response bias and differential misclassification. The prevalence of asthma was 20.3%, 11.8%, and 15% among fully vaccinated, partially vaccinated, and ever-vaccinated children, respectively. Because of the high prevalence of asthma among fully vaccinated children, we hypothesized that NVIC member families with fully vaccinated children might be more likely to respond to the survey if their children had asthma. If true asthma prevalence among fully vaccinated children in the NVIC was 15%, then there could be a response bias as high as 30%. Differential misclassification was also possible because vaccine-refusing families were more likely to use alternative health care and therefore might not receive diagnoses. Similarly, families that vaccinate despite concerns might be less tolerant of symptoms and more likely to seek diagnosis. For example, the children of vaccine refusers who reported current wheezing were 2.6 times less likely than wheezing vaccinated children to report an asthma diagnosis.

Detailed methods for sensitivity analysis have been published by Greenland.[20] Briefly, the analysis dichotomized vaccine exposure (ever/never) and assumed up to 50% differential misclassification bias by multiplying (dividing) observed prevalence rates by a combined total of up to 0.5 and reapplying the adjusted prevalence rate to vaccinated (unvaccinated) marginal totals. The RR was multiplied by 0.7 to assess the potential effect of response bias. Because modifications were made to summary counts, there is no adjustment for confounding in the sensitivity analysis.

Analyses were performed with SAS version 8.0 (Cary, NC), Mixor version 2.0 (Chicago, Ill), and EpiInfo version 3 (Atlanta, Ga).

RESULTS

Table I characterizes respondents demographically by self-reported asthma status. Children with asthma were older, more frequently male, and more likely to report a family history of asthma. Children with asthma were also less likely to see chiropractors, had less educated mothers, and were more likely to be exposed to cigarette smoke, formula feedings, and vaccines. Table II provides data by vaccination refusal: 515 children received no vaccines, 423 received some vaccines, and 239 were fully vaccinated. Among the partially vaccinated children, 92 (20%) had received no vaccines in the first year of life, and overall, 69% were exposed to diphtheria, tetanus, and pertussis (DTP) vaccine; 56% were exposed to measles, mumps, and rubella (MMR) vaccine; and 77% received polio vaccine (not shown). Parents who refused vaccines had younger children, higher maternal education, less exposure to cigarettes, were more likely breast-fed, and had a lower prevalence of a family history of asthma, had less exposure to antibiotics, had more contact with alternative health

TABLE I. Demographic and disease characteristics by parent-reported asthma status in a set of 1177 children enrolled in a study of allergic disease and vaccine refusal

		Asthma = yes, n = 120, n (%)	Asthma = no, n = 1057, n (%)	Total	*P* value
Age (y)	3-5	20 (16.7)	315 (29.8)	335	
	6-10	43 (35.8)	407 (38.5)	450	
	11-14	29 (24.2)	215 (20.3)	244	
	15-18	28 (23.3)	120 (11.3)	148	.0002
Sex	Male	86 (71.7)	536 (50.7)	622	
	Female	34 (28.3)	521 (49.3)	555	<.0001
Race	White	105 (87.5)	938 (88.7)	1043	
	Other	15 (12.5)	119 (11.3)	134	.7
Source of medical care	MD only	51 (42.9)	394 (37.5)	445	
	Integrative care	40 (33.6)	241 (22.9)	281	
	Chiropractor	14 (11.8)	297 (28.3)	311	
	Other	14 (11.8)	119 (11.3)	133	.0009
	Missing	7			
Mother's education	≤High school	28 (23.3)	86 (8.2)	114	
	Some college	33 (27.5)	197 (18.7)	230	
	College	37 (30.8)	364 (34.5)	401	
	Postgraduate degree	22 (18.3)	407 (38.6)	429	<.0001
	Missing	3			
Smoking during pregnancy	Yes	15 (12.7)	61 (5.8)		
	No	103 (87.3)	989 (94.2)	1,092	0.004
	Missing	9			
Duration of Breast-feeding	Never	35 (29.4)	75 (7.2)	110	
	<6 mo	20 (16.8)	148 (14.2)	168	
	6-<12 mo	23 (19.3)	225 (21.5)	248	
	12-<24 mo	24 (20.2)	328 (31.4)	352	
	>24 mo	17 (14.3)	270 (25.8)	287	<.0001
	Missing	12			
Family history of allergies	Yes	77 (68.7)	609 (61.6)	686	
	No	35 (31.2)	379 (38.4)	414	.1
	Missing	77			
Family history of asthma	Yes	51 (46.4)	168 (16.4)	219	
	No	59 (53.6)	858 (83.6)	917	<.0001
	Missing	41			
Courses of antibiotics in year 1	Never	34 (28.8)	626 (59.6)	660	
	Ever	84 (71.2)	424 (40.4)	508	<.0001
	Missing	9			
Vaccination exposure	Refused all vaccines	19 (15.8)	496 (46.9)	515	
	Refused some vaccines	50 (41.7)	373 (35.3)	423	
	Fully vaccinated	51 (42.5)	188 (17.8)	239	<.0001
Current wheeze	Yes	73 (61.3)	83 (7.9)	156	
	No	46 (38.7)	968 (92.1)	1014	<.0001
	Missing	7			
Ever had hay fever	Yes	78 (67.2)	275 (26.7)	353	
	No	38 (32.7)	753 (73.3)	791	<.0001
	Missing	33			
Ever had eczema	Yes	34 (29.1)	153 (14.6)	187	
	No	83 (70.9)	896 (85.4)	979	<.0001
	Missing	11			

P values are calculated from the Pearson χ^2 test statistic.

care providers, and reported less wheezing, asthma, hay fever, and eczema. Overall, 10.2% of subjects reported asthma, with 21.3%, 12%, and 3.7% of fully, partially, and never vaccinated children reporting asthma, respectively (Table II). Vaccine refusal was even more strongly associated with current asthma, defined as self-reported asthma plus current wheeze (Table II).

Before and after adjusting for age, sex, exposure to traditional health care, family history of asthma or allergies, exposure to antibiotics, and family clustering, parents who refused vaccines were 11 times less likely to report asthma only for children with no family history of the disease and no exposure to antibiotics during infancy (Table III). There were nonsignificant

TABLE II. Demographic and self-reported atopic disease characteristics by vaccine exposure in a set of 1177 children enrolled in a study of allergic disease and vaccine refusal

		Fully vaccinated, n = 239, n (%)	Refused some vaccines, n = 423, n (%)	Refused all vaccines, n = 515, n (%)	*P* value
Age	3-5	33 (13.8)	124 (29.3)	178 (34.6)	
	6-10	90 (37.7)	161 (38.1)	199 (38.6)	
	11-14	69 (28.9)	80 (18.9)	95 (18.4)	
	15-17	47 (19.7)	58 (13.7)	43 (8.3)	<.0001
Sex	Male	141 (59.0)	222 (52.5)	259 (50.3)	
	Female	98 (41.0)	201 (47.5)	256 (49.7)	.08
Race	White	211 (88.3)	384 (90.8)	448 (87.0)	
	Other	28 (11.7)	39 (9.2)	67 (13.0)	.2
Source of medical care	MD only	149 (62.9)	190 (45.0)	106 (20.7)	
	Integrative care	55 (23.2)	124 (29.4)	102 (20.0)	
	Chiropractor	16 (6.7)	56 (13.3)	239 (46.8)	
	Other	17 (7.2)	52 (12.3)	64 (12.5)	<.0001
	Missing	7			
Maternal education	≤High school	37 (15.5)	42 (9.9)	35 (6.8)	
	Some college	60 (25.2)	87 (20.6)	83 (16.2)	
	College	92 (38.7)	178 (42.1)	131 (25.5)	
	Postgraduate degree	49 (20.6)	116 (27.4)	264 (51.5)	<.0001
	Missing	3			
Smoking during pregnancy	Yes	26 (11.0)	26 (6.2)	24 (4.7)	
	No	210 (89.0)	394 (93.8)	488 (95.3)	.005
	Missing	9			
Duration of Breast-feeding	Never	51 (21.6)	34 (8.1)	25 (4.9)	
	<6 mo	51 (21.6)	73 (17.3)	44 (8.7)	
	6-<12 mo	59 (25.0)	86 (20.4)	103 (20.3)	
	12-<24 mo	56 (23.7)	130 (30.8)	166 (32.7)	
	≥24 mo	19 (8.0)	99 (23.5)	169 (33.3)	<.0001
	Missing	12			
Family history of allergies	Yes	166 (73.8)	253 (64.4)	267 (55.4)	
	No	59 (26.2)	140 (35.6)	215 (44.6)	<.0001
	Missing	77			
Family history of asthma	Yes	69 (30.0)	85 (21.4)	65 (12.8)	
	No	161 (70.0)	313 (78.6)	443 (87.2)	<.0001
	Missing	41			
Courses of antibiotics in year 1	Never	49 (20.8)	195 (46.3)	416 (81.4)	
	Ever	187 (79.2)	226 (53.7)	95 (18.6)	<.0001
	Missing	9			
Current wheeze	Yes	52 (21.9)	66 (15.7)	38 (7.4)	
	No	185 (78.1)	355 (84.3)	474 (92.6)	<.0001
	Missing	7			
Asthma diagnosis	Yes	51 (21.3)	50 (11.8)	19 (3.7)	
	No	188 (78.7)	373 (88.2)	496 (96.3)	<.0001
Asthma plus current wheeze	Yes	30 (12.5)	35 (8.3)	8 (1.5)	
	No	209 (87.5)	388 (91.7)	507 (98.4)	<.0001
Ever hay fever	Yes	115 (49.6)	148 (36.5)	90 (17.7)	
	No	117 (50.4)	257 (63.5)	417 (82.2)	<.0001
	Missing	33			
Ever eczema	Yes	55 (23.2)	86 (20.6)	46 (9.0)	
	No	182 (76.8)	331 (79.4)	466 (81.0)	<.0001
	Missing	11			

P values calculated from the Pearson χ^2 test statistic.

($P > .05$) negative trends between vaccine refusal and asthma among children with either a positive family history of asthma or exposure to antibiotics during infancy. There was also a nonsignificant ($P > .05$) positive association between vaccine refusal and asthma among children with a positive family history of asthma and early exposure to antibiotics. The negative association between vaccine refusal and self-reported asthma was also stronger among children whose mothers had post–high school education (not shown). Parents of unvaccinated children were 10 times less likely to report hay fever among children with no family history of hay fever. Nonvaccinating parents were also 2.5 times less likely to report eczema and current wheeze.

TABLE III. Estimated prevalence rates and RRs of parent-reported atopic disease from multiple logistic regression models in a sample (n = 1177) of children from the member households of the NVIC (2003)*

	Fully vaccinated	Refused some vaccines	Refused all vaccines	
a. Asthma model includes interaction terms for family history of asthma and antibiotic exposure.				
Results for children who have:	Prevalence rate (RR)	Prevalence rate (RR [95% CI])	Prevalence rate (RR [95% CI])	*P* trend†
No family history of asthma and unexposed to antibiotics during infancy	11.4 (1 [referent])	5.1 (0.2 [0.07-0.5])	1.0 (0.09 [0.03-0.3])	.0001
No family history of asthma and exposed to antibiotics during infancy	11.8 (1 [referent])	8.8 (0.7 [0.2-2.0])	5.9 (0.3 [0.2-1.7])	.1
Positive family history of asthma and no exposure to antibiotics during infancy	23.5 (1 [referent])	12.2 (0.7 [0.3-2.5])	9.4 (0.4 [0.2-1.2])	.1
Positive family history of asthma and exposed to antibiotics during infancy	23.2 (1 [referent])	19.3 (2.0 [0.9-5.0])	38.6 (1.7 [0.7-5.0])	.4
b. Hay fever model includes an interaction term for family history of hay fever–eczema.				
RRs for children who have:	Prevalence rate (RR)	Prevalence rate (RR [95% CI])	Prevalence rate (RR [95% CI])	*P* trend†
No family history of hay fever–eczema	23.3 (1 [referent])	15.2 (0.2 [0.07-0.4])	2.5 (0.1 [0.05-0.3])	.0002
Positive family history of hay fever–eczema	41.4 (1 [referent])	37.6 (1.0 [0.4-1.8])	37.6 (0.9 [0.5-2.5])	.5
c. Models with no interaction terms				
RRs refer to all children.	Prevalence rate (RR)	Prevalence rate (RR [95% CI])	Prevalence rate (RR [95% CI])	*P* trend†
Outcome = eczema	18.7 (1 [referent])	17.0 (0.5 [0.3-0.7])	8.5 (0.4 [0.3-0.7])	.003
Outcome = current wheeze	16.1 (1 [referent])	11.7 (0.6 [0.4-1.0])	7.3 (0.4 [0.3-0.7])	.003

*All models adjust for age, sex, exposure to traditional medicine, family history of asthma or allergies, exposure to antibiotics, and familial clustering. The estimated prevalence rates and RRs apply to the average child in the average family.
†The *P* value for trend was calculated by inclusion of an ordinal term for vaccine refusal.

The results of strata-specific analyses for all measured covariates were similar to the results of the multiple regression models (not shown). Other potential confounding variables that were evaluated include duration of breast-feeding, neighborhood (city, suburb, or rural), race, birth order, family size, daycare attendance, prematurity, history of measles, history of chickenpox, history of ear infections, autism spectrum disorder, and current or historical exposures to cigarette smoking, pets, and mold or dampness in the home. None of these potential confounders altered the relationship between vaccine refusal and atopic disease (not shown).

Refusal of any single vaccine (DTP, MMR, *Haemophilus influenzae* B [HiB], hepatitis B, or polio) was associated with decreased rates of self-reported asthma and hay fever (not shown). Few children reported exposure to a single vaccine, although many parents refused either DTP or MMR.

Fig 1 shows the proportion of wheezing subjects that report asthma by vaccination status. Parents of unvaccinated children were significantly less likely to report that their wheezing children had asthma ($P = .002$). Children with current symptoms of hay fever reported the condition at roughly equal rates, regardless of their vaccination exposure.

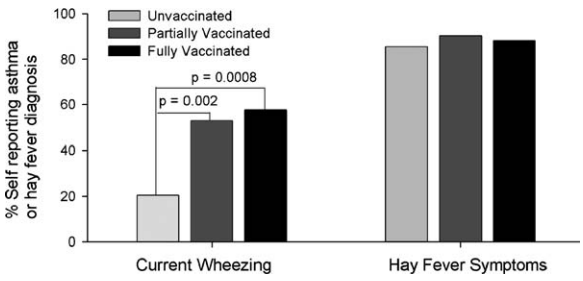

FIG 1. Proportion of subjects reporting current symptoms of allergic disease who also report the presence of allergic disease stratified by vaccination status. Parents of study subjects who wheeze were more likely to report a diagnosis of asthma if their child was vaccinated.

Fig 2 shows crude RRs, adjusted RRs, and the results of the sensitivity analysis. The estimates of bias used in the sensitivity analysis were based on asthma data and are less applicable for the outcomes of hay fever, wheeze, or eczema. In Fig 2 vaccine refusal is dichotomous (accept any/refuse all) to accommodate the sensitivity analysis, and the adjusted models for asthma estimate the independent effect of vaccination refusal in a population of average children with average exposure to antibiotics.

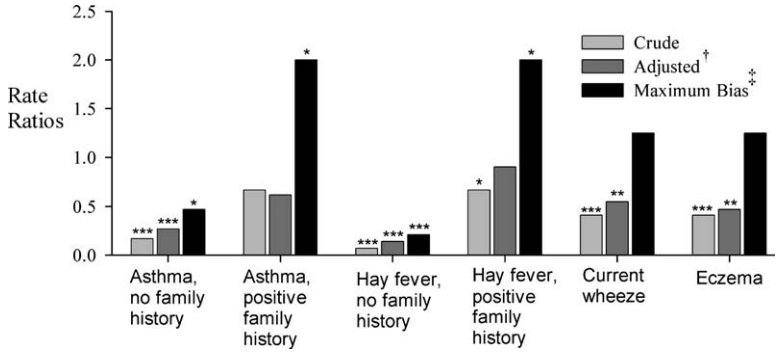

FIG 2. The prevalence of RRs for the relationship between vaccination refusal and parent-reported atopic disease in crude analysis, multivariate adjusted models, and sensitivity analysis. Results for asthma and hay fever are stratified by family history of asthma or allergies. *$P < .05$; **$P < .005$; ***$P < .0005$. †Adjusted for familial clustering, age, sex, exposure to traditional medicine, antibiotic use in the first year of life, family history of asthma (wheeze only), family history of allergies (eczema only), and an interaction between vaccine exposure and antibiotic use (asthma only). The asthma adjusted rate ratios refer to children with average antibiotic exposure. ‡The hypothetical crude rate ratio assuming response bias of 30% and misclassification bias of 50%.

This changed the relative strength of relationships: vaccine refusal is most strongly associated with hay fever (RR, 0.1) and less strongly associated with asthma (RR, 0.3). Under the maximum bias assumptions of the sensitivity analysis, the significant negative association between vaccine refusal and self-reported asthma among children with no family history of asthma persisted (RR, 0.5; 95% CI, 0.3-0.8).

DISCUSSION

Parents who chose not to vaccinate their children were significantly less likely to report asthma only when they also reported no family history of asthma or exposure to antibiotics during infancy. Likewise, children of parents who refused vaccines were less likely to report hay fever only when there was no family history of allergies. All children of vaccine abstainers were less likely to have eczema or current wheeze. These associations persisted after controlling for measured confounders (age, sex, source of medical care, antibiotic exposure, and familial clustering). There were dose-response relationships; asthma, hay fever, eczema and wheeze were reported most frequently among completely vaccinated children and somewhat less frequently among partially vaccinated children.

A recent analysis of a British birth cohort found that children unexposed to DPT, polio, and MMR vaccines were less likely to have asthma and eczema.[15] Cohort studies from New Zealand and England that enrolled infants in the late 1970s also found significant positive associations between vaccination and atopic disease.[8,21] Likewise, an analysis of cross-sectional data from the National Health and Nutrition Examination Survey III showed that DTP vaccine was significantly associated with allergies.[11] Finally, A cross-sectional survey of HiB vaccination and allergic disease in Germany showed that HiB vaccine was significantly and positively associated with asthma.[12]

Conversely, a longitudinal German study of asthma etiology, with prospective ascertainment of exposures and standard definitions of allergic disease, found that vaccine exposure was negatively associated with asthma. In the German study half of the study population was at high risk of allergies (increased cord blood IgE levels, a positive family history of allergic disease, or both), and only 6% of the children were classified as having received 0 to 11 vaccines. This German study also identified an interaction: there was no association between vaccines and markers of allergy among children not at high risk for allergies.[9]

Two analyses of health maintenance organization records from the Vaccine Safety Datalink project found no persistent significant associations between vaccines and asthma but were potentially limited by incomplete or inaccurate medical information.[7,13]

A British cohort examined the relationship between pertussis vaccine alone and asthma or wheeze and found no significant associations after adjusting for confounders and following children to 7 years of age.[10,14] A randomized trial of pertussis vaccination also found no association between pertussis and asthma, although children received all other vaccines and were only followed to 2½ years of age.[22]

Most of these previous studies of the relationship between vaccine use and asthma focused on a single vaccine,[8,10-12,14,22] in part because sufficient numbers of children unexposed to a single vaccine were available for study. Two studies looked at cumulative vaccine doses but combined data from all children who had received 0 to 11 doses of childhood vaccines.[7,9]

We collaborated with the NVIC, which has many members allied with the antivaccine movement. In this population complete and partial vaccine refusal is conscious and deliberate. Many member families of the NVIC, both vaccinating and nonvaccinating, use alternative health care practices. For example, some families are

vegetarians, whereas others follow diets that encourage the consumption of carefully farmed meat and dairy products. Most families breast-feed extensively, avoid medications, and carefully select health care providers. Member families have varied lifestyles, and although the observed relationships between vaccine exposure and atopic disease were independent of measured confounders, there could be other significant lifestyle differences.

The sensitivity analysis estimated the potential effect of bias, and after assuming very high levels of response bias (up to 30%) and differential misclassification (up to 50%), vaccine refusal remained negatively and significantly associated with self-reported asthma among children with no family history of asthma. Unvaccinated children with no family history of asthma were 5.9, 3.4, and 2.1 times less likely to report asthma in the crude, adjusted, and sensitivity analysis, respectively. The analyses adjusted for measured confounders or estimates of bias but not both. Complete adjustment for unmeasured confounders could, potentially, eliminate the observed associations between vaccines and self-reported allergic disease.

Despite these concerns, there are several reasons not to dismiss completely all study findings. Like many other studies of allergy,[9,11,12,23,24] this study finds that after control for confounders, the exposure of interest was most strongly associated with hay fever, less strongly associated with asthma, and weakly associated with eczema. In all strata, vaccine refusers were half as likely to report eczema and wheeze; additional adjustment for confounders did not change this relationship. Response bias for hay fever was less likely than for asthma. Similarly, misclassification bias was less likely because children with nasal symptoms reported hay fever at roughly equal rates, regardless of their vaccine-exposure status (Fig 1).

In the current study family history of asthma and family history of hay fever were separate questions. Family history of asthma interacted with asthma, and family history of hay fever or eczema interacted with hay fever; the specificity suggests real biologic processes. In these data, vaccine refusal was negatively associated with self-reported asthma only among children with no family history of asthma, whereas the NVIC leadership expected vaccination to adversely affect children with a positive family history of allergic or autoimmune disease. Therefore the findings do not confirm the preconceived beliefs of antivaccinationists.

How vaccine refusal could diminish a child's risk of asthma and allergies among children with no family history of asthma or allergies is not known. Vaccine refusal might be strongly associated with other protective behaviors, such as diet, exercise, or environmental exposures. Alternatively, vaccine components might influence immune system development, especially in the absence of a genetic predisposition to the atopic phenotype. Previously, research has shown that the aluminum adjuvants used in vaccines cause production of IgE antibodies in mice.[25]

This study has many limitations and does not prove that vaccinations cause asthma. The analysis is based on self-reported allergic disease in an atypical population, and interpretation is therefore complicated by concerns regarding generalizability, misclassification bias, and unmeasured confounding. The NVIC membership is not representative of the general population. They have an atypical approach to health care, are predominantly white, and are highly educated.

Although 280 children and youths died from asthma in 2001,[26] before vaccination, 11,000 children died and 50,000 children were seriously affected by diseases like measles, whooping cough, diphtheria, and polio every year in the United States.[27] If vaccination rates decrease, these diseases will return; none of the vaccine-preventable diseases are eradicated. For parents of children at high risk for asthma, these data do not indicate that refusing vaccines will decrease their child's risk of disease. Other parents should remember that vaccines prevent serious and deadly diseases, and the known benefits of vaccination clearly outweigh this hypothetical risk.

These data are limited by potential biases inherent in the population studied, and findings need to be replicated in a more representative group before inferences can be drawn. Further studies should include investigating the variety of alternative health behaviors in this population and examine the safety of current vaccine schedules and adjuvants. Basic laboratory research into the effect of vaccination on the developing immune system could improve our understanding of both vaccine immunology and asthma cause.

In summary, this study suggests that low-risk children in families that refuse vaccination are less likely to report asthma and other allergic symptoms. Universal vaccination remains fundamental to the protection of individual and public health. Policy implications must await additional studies that more clearly define the relevant health behaviors and identify the biologic mechanisms by which these behaviors affect the development of allergic diseases.

We thank the leadership and members of the NVIC because without their help, this study would not have been possible. Helpful comments were graciously offered by Dr Fernando Martinez, Dr Tina Hartert, Dr Pat Doyle, and Dr Robert Wolfe among others.

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