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Effects of Diphtheria-Tetanus-Pertussis or Tetanus Vaccination on Allergies and Allergy-Related Respiratory Symptoms Among Children and Adolescents in the United States

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ABSTRACT

Background: Findings from animal and human studies confirm that diphtheria and tetanus toxoids and pertussis (DTP) and tetanus vaccinations induce allergic responses; associations between childhood vaccinations and subsequent allergies have been reported recently.

Objective: The association of DTP or tetanus vaccination with allergies and allergy-related respiratory symptoms among children and adolescents in the United States was assessed.

Methods: Data were used from the Third National Health and Nutrition Examination Survey on infants aged 2 months through adolescents aged 16 years. DTP or tetanus vaccination, lifetime allergy history, and allergy symptoms in the past 12 months were based on parental or guardian recall. Logistic regression modeling was performed to estimate the effects of DTP or tetanus vaccination on each allergy.

Results: The odds of having a history of asthma was twice as great among vaccinated subjects than among unvaccinated subjects (adjusted odds ratio, 2.00; 95% confidence interval, 0.59 to 6.74). The odds of having had any allergy-related respiratory symptom in the past 12 months was 63% greater among vaccinated subjects than unvaccinated subjects (adjusted odds ratio, 1.63; 95% confidence interval, 1.05 to 2.54). The associations between vaccination and subsequent allergies and symptoms were greatest among children aged 5 through 10 years.

Conclusions: DTP or tetanus vaccination appears to increase the risk of allergies and related respiratory symptoms in children and adolescents. Although it is unlikely that these results are entirely because of any sources of bias, the small number of unvaccinated subjects and the study design limit our ability to make firm causal inferences about the true magnitude of effect. (J Manipulative Physiol Ther 2000; 23:81-90)

Key Words: Vaccination; Iimmunization; Asthma; Allergic Rhinitis; Sinusitis; Allergic Hypersensitivity

INTRODUCTION

The prevalence of allergic disorders has increased 50% to 100% among adults and more than doubled among children during the past 20 years.[1-4] Asthma and other allergies currently affect 30 to 50 million persons in the United States.[5,6] An estimated 17.3 million persons had symptomatic physician-diagnosed asthma in 1998.[7] Asthma and allergic rhinitis, accounting for 9.1 and 8.4 million office visits, respectively, in 1996, are 2 of the 20 most common principal diagnoses given to patients of office-based physicians.[8] Asthma is also one of the primary reasons for visiting a hospital outpatient department,[9] with 900,000 visits. Chronic sinusitis, which is often associated with asthma and allergic rhinitis, is the most common chronic condition in the United States,[10] resulting in 14.3 million office visits per year.[8] Allergic rhinitis, sinusitis, and asthma are 3 of the 5 most common principal diagnoses given to children and adolescents (aged 15 years and younger) in ambulatory care, accounting for 9.4 million visits annually and 5.8% of all visits.[11] The total cost of asthma care alone was estimated as $6.21 billion in 1990.[12] Although there is speculation about the causes of the increased prevalence of asthma and other allergic conditions,[1-4] no agent or set of agents has been shown to be responsible for the increase. In addition, the upward trend is probably not entirely a result of the increased public recognition of allergies, diagnostic coding, measurement error, or other nonclinical factors.[1,3,4]

Studies in animals and human beings have demonstrated that components of diphtheria and tetanus toxoids and pertussis (DTP) and tetanus vaccines have adjuvant effects[13-15] and are associated with elevated levels of total and specific immunoglobulin E antibodies.[16-18] There is evidence that these components cause a Th1 to Th2 shift in CD4 cells,[19,20] resulting in interleukin-4 (IL-4) production and greater stimulation of mast cells, subsequent release of histamine and other inflammatory mediators, and allergic symptomatology.[21] Pertussis and DTP vaccines have also been shown to enhance rodents' and human beings' sensitivity to histamine.[22,23]

The biologic plausibility of a causal vaccination-allergy association is bolstered by cases of anaphylaxis immediately after immunization with the DTP and tetanus vaccines (2 cases per 100,000 injections or 6 per 100,000 children given 3 doses of DTP)[24] and the high incidence of local immediate hypersensitivity reactions to tetanus toxoids,[25-28] diphtheria,[29] and the development of IgE antibodies after tetanus and diphtheria toxoids vaccinations.[30,31] Two committees convened by the Institute of Medicine (the Committee to Review the Ad-

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verse Consequences of Pertussis and Rubella Vaccines and the Vaccine Safety Committee) concluded that there is a causal relation between the DTP vaccine and anaphylaxis[24] and tetanus toxoid and anaphylaxis.[32] More recently, pertussis has been shown to increase the risk of asthma in children aged less than 2½ years.[33] The authors of 3 retrospective cohort studies found strong associations between pertussis or DTP immunization and the diagnosis of asthma and other atopic disorders in children aged more than 4 years.[34,35,36]

We hypothesize that the DTP or tetanus vaccination is associated with subsequent risk of asthma and other allergies and episodes of sinusitis or sinus problems and other allergy-related respiratory symptoms among infants, children, and adolescents between the ages of 2 months and 16 years in the United States.

METHODS

Data Source and Subject Selection

We used data from the Third National Health and Nutrition Examination Survey (NHANES III), conducted by the National Center for Health Statistics from 1988 to 1994.[37,38] NHANES III is based on a complex sample design with oversampling of certain groups.[39] Sample weights are used to adjust for differential selection probabilities, noncoverage, and nonresponse; the weighted sample is designed to represent the civilian noninstitutionalized population of the United States.[39]

This analysis uses data from the 13,944 infants, children, and adolescents aged 2 months through 16 years who were interviewed (by proxy, usually a parent or guardian) during the 6 years of NHANES III. Interviews were conducted in English and Spanish by trained field staff.[40] The interview included the question: "Has [subject] ever received a DPT or tetanus shot? A DPT shot is to prevent diphtheria, tetanus, and pertussis or whooping cough." Respondents for 5930 subjects referred to immunization records during the interview. There were 332 (2.4%) missing or "don't know" responses to the DTP item in the total sample and 65 missing or "don't know" responses among subjects with available shot records.

Outcome Variables

The interview included questions about history of physician-diagnosed asthma and hay fever, history of severe reactions from allergy shots or tests, and having to give up or avoid a pet because of allergies. Respondents from phase 1 (1988-1991) were asked about severe allergic reactions occurring within an hour after an insect sting, whereas respondents from phase 2 (1991-1994) were asked about severe allergic reactions occurring within an hour after eating something. Severe allergic reactions were defined as reactions that involved itching all over, trouble breathing, flushing, hives, or swelling of the face, hands, or feet.[37] The interview also asked about allergy-related respiratory symptoms during the past 12 months, including sinusitis or sinus problems, wheezing or whistling in chest, and episodes of stuffy, itchy, or runny nose and watery, itchy eyes.

To estimate the associations between vaccination and history of allergic reaction, allergy-related respiratory symptoms in the past 12 months, and allergy history or related symptoms in the past 12 months, 3 composite variables were created by combining the specific allergy variables.

Other Variables

Potential confounders included age, race, sex, household income, poverty status (poverty income ratio ≤1.0), education level of family reference person (referred to in earlier NHANES as "head of the household"), parents' birthplaces (inside or outside the United States), area of residence (metropolitan/suburban or rural), geographic region (northeast, midwest, south, or west), the presence of a smoker in the home, household size, pets in the home, and physician-diagnosed asthma or hay fever in the child's parent's lifetime. Children and adolescents aged 6 through 16 years were eligible to receive allergy skin tests administered by a trained health technician in the mobile examination center.[38] Immediate hypersensitivity reactions to 10 Food and Drug Administration-approved standardized allergens (house mite, cat, German cockroach, short ragweed, perennial rye, *Alternaria alternata*, Bermuda grass, Russian thistle, white oak, and peanut) were assessed in 84.4% of the 5683 subjects aged 6 through 16 years. Wheals with a mean diameter greater than 3 mm with associated flare and no reaction to the negative control were considered positive reactions.[41] Subjects with at least 1 positive reaction were considered atopic. Data on smoking status during pregnancy was obtained for subjects aged 11 years or younger, and breastfeeding status were obtained for subjects aged 5 years or younger.

Statistical Methods

Weighted and unweighted binary logistic regression modeling was used to estimate the effects of DTP or tetanus vaccination on each type of allergy and allergic reaction. Because the effect estimates derived from the weighted and unweighted analyses were similar, only the weighted results are presented. The final weights, which were scaled down so that the sum of the weights was equal to the unweighted sample size (N = 13,944), were used for these analyses. Because NHANES III uses a complex sample design involving both clustering and stratification, estimated crude odds ratios (ORs) and ORs adjusted for the effects of confounders and 95% confidence intervals (CIs) were obtained with SUDAAN (Research Triangle Institute, Research Triangle Park, NC), which has the capability of estimating complex sample variances.[42] SAS (SAS Institute, Cary NC) was used for preliminary statistical analysis.[43]

Logistic models with the vaccination variable as the only predictor were fit to estimate crude effects of vaccination on allergies. Additional models were chosen to estimate the effects of vaccination on each allergy outcome, controlling for potential confounders one at a time and simultaneously. Potential confounders were identified a priori as those variables thought to be risk factors for allergies and associated with vaccination. Smoking status during pregnancy and

Table 1. *Number and weighted percent of subjects aged 2 months to 16 years from NHANES III, 1988-1994, by category of selected sociodemographic and other variables (N = 13,944)*

Variable	Number*	Weighted%†
Age (y)		
<5	7151	30.0
5-10	3980	35.7
11-16	2813	34.3
Race		
White	9048	77.9
Black	4328	16.5
Other	568	5.6
Sex		
Male	6894	51.2
Female	7050	48.8
Household income		
<$10,000	2786	12.9
$10,000-29,999	5626	37.4
$30,000-49,999	2582	26.9
$50,000 and above	1689	22.8
Poverty status		
At or below poverty level	4887	24.9
Above poverty level	7797	75.1
Area of residence		
Metropolitan/suburban area	7204	49.1
Nonmetro/rural area	6740	50.9
Geographic region		
Northeast	1707	18.7
Midwest	2576	23.0
South	5826	34.7
West	3835	23.7
Smoking in home		
At least 1 smoker in home	5376	39.0
No smokers in home	8526	61.0
Pets in home		
At least 1 pet in home	4565	47.6
No pets in home	9345	52.4
Parental asthma or hay fever‡		
Both parents	261	2.5
Father only	1028	10.1
Mother only	1310	12.7
Neither parent	11086	74.7

*Unweighted number. Total for each variable may not add to N because of missing data.

†Weighted to account for probability of selection, nonresponse, and age, sex, and race composition of the United States.

‡Physician-diagnosed asthma or hay fever in subject's parent's lifetime.

Table 2. *Number and weighted percent of subjects aged 2 months to 16 years from NHANES III, 1988-1994, by category of DTP or tetanus vaccination and allergy variables (N = 13,944)*

Variable	Number*	Weighted %†
DTP or tetanus vaccination		
Yes	13328	99.0
No	284	1.0
Asthma history‡		
Yes	1025	9.4
No	12915	90.6
Hay fever history§		
Yes	482	6.2
No	13461	93.8
Insect reaction‖		
History of insect reaction	355	6.5
No insect reaction history	6976	93.5
Food reaction¶		
History of food reaction	313	6.7
No food reaction history	6281	93.3
Allergy shot/test reaction#		
History of shot/test reaction	108	3.3
No shot/test reaction history	5650	96.7
Pet allergy		
History of pet allergy	353	4.2
No pet allergy history	13550	95.8
Any reaction (other than asthma or hay fever)		
History of allergic reaction	1030	11.0
No allergic reaction history	12865	89.0
Asthma, hay fever, or allergic reaction		
History of any allergy/reaction	2059	20.4
No allergy/reaction history	11838	79.6
Sinusitis or sinus problems (past 12 months)		
Yes	1670	17.8
No	12244	82.2
Wheezing or whistling (past 12 months)		
Yes	2920	19.3
No	11022	80.7
Nose and eye symptoms**(past 12 months)		
Yes	3902	31.1
No	10022	68.9
Any allergy-related respiratory symptom (past 12 months)††		
Yes	6045	46.7
No	7879	53.3
Any lifetime allergy history or 12-month symptoms‡‡		
Yes	6618	51.7
No	7286	48.3

*Unweighted number. Total for each variable may not add to N because of missing data.

†Weighted to account for probability of selection, nonresponse, and age, sex, and race composition of the United States.

‡Physician-diagnosed asthma in subject's lifetime.

§Physician-diagnosed hay fever in subject's lifetime.

‖Item included in only phase 1 of NHANES III (1988-1991) (N = 7344).

¶Item included in only phase 2 of NHANES III (1991-1994) (N = 6600).

#Among subjects who received allergy tests or shots (N = 5817).

**Any episodes of stuffy, itchy, or runny nose and watery, itchy eyes during the past 12 months.

††Sinusitis or sinus problems, wheezing or whistling in the chest, or nose and eye symptoms during the past 12 months.

‡‡Any lifetime history of physician-diagnosed asthma or hay fever, or allergic reaction, or sinusitis or sinus problems, wheezing or whistling in the chest, or nose and eye symptoms during the past 12 months.

breastfeeding status were included as covariates in models with populations restricted to subjects aged 11 years or younger and aged 5 years or younger, respectively. Potential confounders were included in the models as sets of 1 or more binary variables. The sample was stratified by age (<12 months, 12 to 23 months, 2 to 4 years, 5 to 10 years, and 11 to 16 years) to assess potential effect modification by age. Although the small number of cases of allergic disease among unvaccinated subjects in many strata precluded the fitting of multivariable logistic models, age-specific vaccination effects were estimated, controlling for each potential confounder one at a time. Subjects aged 6 through 16 years were included in additional analyses to assess the association between vaccination and atopy. Analyses restricted to subjects with shot records were conducted to assess potential bias as a result of inaccurate recall. When available, shot records were used instead of parental or guardian recall to measure DTP or tetanus vaccination status.

Multivariable logistic models initially included the vaccination variable plus age, race, sex, poverty status, education level of family reference person, parents' birthplace, area of residence, geographic region, the presence of a smoker in the home, household size, pets in the home, and physician-

Table 3. *Number and weighted percent of subjects aged 2 months to 16 years from NHANES III, 1988-1994, by category of selected variables and DTP or tetanus vaccination status (N = 13,612)*

	Vaccinated (N = 13,328)		Unvaccinated (N = 284)		Total (N = 13,612)	
Variable	Number*	%†	Number*	%†	Number*	%†
Age (y)						
<5	6706	29.5	236	63.7	6942	29.9
5-10	3892	36.1	24	13.8	3916	35.8
11-16	2730	34.4	24	22.4	2754	34.3
Race						
White	8637	78.1	188	62.2	8825	78.0
Black	4151	16.4	87	26.4	4238	16.5
Other	540	5.5	9	11.4	549	5.5
Sex						
Male	6596	51.1	130	51.2	6726	51.1
Female	6732	48.9	154	48.8	6886	48.9
Household income						
<$10,000	2622	12.6	83	24.6	2705	12.7
$10,000-29,999	5382	37.4	122	42.7	5504	37.5
$30,000-49,999	2485	27.0	46	25.2	2531	26.9
$50,000 and above	1641	23.1	10	7.5	1651	22.9
Poverty status						
At or below poverty level	4621	24.5	140	46.1	4761	24.7
Above poverty level	7510	75.5	121	53.9	7631	75.3
Area of residence						
Metro/suburban area	6882	49.0	151	56.5	7033	49.1
Nonmetro/rural area	6446	51.0	133	43.6	6579	50.9
Geographic region						
Northeast	1628	18.7	25	9.1	1653	18.6
Midwest	2439	22.9	67	28.7	2506	23.0
South	5589	34.7	124	46.1	5713	34.8
West	3672	23.8	68	16.1	3740	23.7
Smoking in home						
Yes	5115	39.0	128	45.0	5243	39.0
No	8174	61.0	155	55.0	8329	61.0
Pets in home						
Yes	4390	47.8	75	34.8	4465	47.7
No	8906	52.2	208	65.2	9114	52.3
Household size (No. of persons)						
1-3	3036	22.1	62	17.6	3098	22.1
4	3869	34.2	61	20.2	3930	34.1
5	2773	23.1	57	20.8	2830	23.1
6+	3650	20.6	104	41.4	3754	20.8
Education level of family reference person (y)						
0-12	9184	58.1	226	76.6	9410	58.3
13-15	2171	19.8	34	9.5	2205	19.7
16+	1736	22.1	19	13.9	1755	22.0
Mother's birthplace						
United States	10,060	83.8	221	77.7	10,281	83.7
Mexico	2167	4.9	41	6.4	2208	4.9
Other	1025	11.3	21	16.0	1046	11.3
Father's birthplace						
United States	9823	83.6	218	77.0	10,041	83.6
Mexico	2325	5.4	42	6.4	2367	5.4
Other	1039	10.9	23	16.7	1062	11.0
Parental asthma or hay fever‡						
Both parents	254	2.5	3	5.3	257	2.5
Father only	984	10.1	15	6.9	999	10.0
Mother only	1261	12.7	29	14.5	1290	12.7
Neither parent	10,579	74.8	236	73.4	10,815	74.8

*Unweighted number. Total for each variable may not add to N due to missing data.

†Weighted to account for probability of selection, nonresponse, and age, sex, and race composition of the United States.

‡Physician-diagnosed asthma or hay fever in subject's parent's lifetime.

diagnosed asthma or hay fever in the child's parent's lifetime. Smoking by anyone in the home and pets in the home were not included in subsequent multivariable models because these variables may be consequences as well as predictors of allergies. Their exclusion did not change the estimated associations between vaccination and any of the allergy variables. Potential confounding variables having χ-square statistics with associated P values >.15 (and sets of binary variables where all P values >.15) were dropped from the initial model. Variables that were deleted were added back into the model one at a time to assess their influence, if any, on the estimated vaccination effect (OR). If the vaccination effect changed by 5% or more with the addition of the previously dropped variable, then the latter variable remained in the model.

Subjects with missing data on vaccination status were excluded from the primary analyses. Comparisons were made between subjects missing vaccination data and subjects not missing vaccination data on predictors of being unvaccinated and on allergy status. Secondary analyses were conducted with certain assumptions to assess the potential effects of missing or misclassified vaccination data on the estimated effects obtained in the primary analyses.

RESULTS

Characteristics of Subjects

Table 1 shows the number and weighted percent of the 13,944 subjects aged 2 months through 16 years by selected variables. Of these, 284 (1.0%) were reported to be unvaccinated (Table 2). Lifetime histories of asthma or hay fever were reported by 1025 and 482 respondents, respectively. Any severe reaction from insect stings or food or having to avoid pets because of allergic reactions was reported by 1030 respondents. Sinusitis or sinus problems during the past 12 months was reported by 1670 respondents; 2920 reported wheezing or whistling in the chest during the past year, and 3902 reported stuffy, itchy or runny nose and watery, itchy eyes (Table 2).

Table 3 shows the number and weighted percent of respondents by vaccination status and category of each potential confounding variable. Unvaccinated persons were more likely to be aged <5 years (63.7% vs 29.5%), nonwhite (37.8% vs 21.9%), at or below poverty level (46.1% vs 24.5%), living with a smoker (45.0% vs 39.0%), and without a pet in the home (65.2% vs 52.2%). Unvaccinated persons were also more likely to live in households with 5 or more members (62.2% vs 43.7%) and with the family reference person having no education beyond high school (76.6% vs 58.1%). Mothers of unvaccinated children aged 11 years or younger were more likely than mothers of vaccinated children to report smoking during pregnancy (35.6% vs 23.3%). Breastfeeding was similar for vaccinated (53.9%) and unvaccinated (51.4%) children aged 5 years or younger. Among the subjects aged 6 through 16 years who received allergy skin tests (N = 4802), vaccinated and unvaccinated persons were almost equally likely to be atopic (49.0% vs 51.0%).

Table 4. *Number and weighted percent of subjects aged 2 months to 16 years from NHANES III, 1988-1994, by type of allergy and DTP or tetanus vaccination status (N = 13,612)*

	Vaccinated (N = 13,328)		Unvaccinated (N = 284)		Total (N = 13,612)	
Variable	Number*	%†	Number*	%†	Number*	%†
Asthma‡						
Lifetime history	996	9.5	10	4.5	1006	9.5
No history	12329	90.5	274	95.5	12603	90.5
Hay fever§						
Lifetime history	470	6.2	2	5.2	472	6.2
No history	12858	93.8	282	94.8	13140	93.8
Insect reaction‖						
Lifetime history	347	6.7	0	0.0	347	6.6
No history	6552	93.3	155	100.0	6707	93.4
Food reaction¶						
Lifetime history	310	6.8	3	1.7	313	6.7
No history	6100	93.2	126	98.3	6226	93.3
Allergy shot/test reaction#						
Lifetime history	106	3.3	2	10.9	108	3.4
No history	5405	96.7	92	89.1	5497	96.6
Pet allergy						
Lifetime history	347	4.3	0	0.0	347	4.2
No history	12945	95.7	284	100.0	13229	95.8
Any allergy/allergic reaction						
Lifetime history	2004	20.5	16	10.8	2020	20.4
No history	11282	79.5	268	89.2	11550	79.6
Sinusitis or sinus problems (past 12 months)						
Yes	1632	18.0	15	9.1	1647	17.9
No	11668	82.0	268	90.9	11936	82.1
Wheezing or whistling (past 12 months)						
Yes	2776	19.4	71	18.9	2847	19.4
No	10551	80.7	213	81.1	10764	80.7
Nose and eye symptoms (past 12 months)**						
Yes	3753	31.2	57	15.7	3810	31.0
No	9556	68.8	227	84.3	9783	69.0
Any allergy-related respiratory symptom (past 12 months)††						
Yes	5790	46.8	112	34.4	5902	46.7
No	7519	53.2	172	65.6	7691	53.3
Any lifetime allergy history or 12-month symptoms‡‡						
Yes	6347	51.9	117	37.6	6464	51.7
No	6945	48.1	167	62.4	7112	48.3

*Unweighted number. Total for each variable may not add to N due to missing data.

†Weighted to account for probability of selection, nonresponse, and age, sex, and race composition of the United States.

‡Physician-diagnosed asthma in subject's lifetime.

§Physician-diagnosed hay fever in subject's lifetime.

‖Item included in only phase 1 of NHANES III (1988-1991) (N = 7054).

¶Item included in only phase 2 of NHANES III (1991-1994) (N = 6539).

#Among subjects who received allergy tests or shots (N = 5605).

**Any episodes of stuffy, itchy, or runny nose and watery, itchy eyes during the past 12 months.

††Sinusitis or sinus problems, wheezing or whistling in the chest, or nose and eye symptoms during the past 12 months.

‡‡Any lifetime history of physician-diagnosed asthma or hay fever, or allergic reaction, or sinusitis or sinus problems, wheezing or whistling in the chest, or nose and eye symptoms during the past 12 months.

Table 5. *Estimated crude and adjusted effects (OR and 95% CI) of DTP or tetanus vaccination on specific allergic conditions and allergy-related respiratory symptoms among subjects aged 2 months to 16 years from NHANES III, 1988-1994: Results of binary logistic regression analyses (N = 13,612)*

	Crude Effect		Adjusted Effect*	
Condition	OR	95% CI	OR	95% CI
Asthma†	2.20	0.70-6.84	2.00	0.59-6.74
Hay fever‡	1.21	0.21-6.83	0.82	0.16-4.35
Severe allergic reaction§	2.11	0.42-10.45	1.50	0.33-6.89
Any allergy or allergic reaction‖	2.11	0.81-5.49	1.66	0.67-4.14
Sinusitis or sinus problems¶	2.16	0.77-6.06	1.81	0.69-4.71
Wheezing or whistling#	1.03	0.68-1.57	1.23	0.78-1.95
Nose and eye symptoms**	2.44	1.57-3.78	2.22	1.30-3.77
Any allergy-related respiratory symptom (past 12 months)††	1.68	1.09-2.59	1.63	1.05-2.54
Any lifetime allergy history or 12-month symptoms‡‡	1.79	1.16-2.76	1.69	1.10-2.59

*Estimated effects (odds ratios) controlling for the following variables by outcome. Asthma: age (<5 years, 5-10 years, 11-16 years), sex (male, female), poverty status (poverty income ratio ≤1, >1), and parental history of physician-diagnosed asthma or hay fever (yes, no); hay fever: age, area of residence (metropolitan/suburban, nonmetro/rural), parental history of physician-diagnosed asthma or hay fever, and household size (<5 members, ≥5 members); severe allergic reaction: age, parental history of physician-diagnosed asthma or hay fever, education level of family reference person (≤12 years, ≥13 years), and household size; lifetime history of asthma, hay fever, or severe allergic reaction: age, sex, parental history of physician-diagnosed asthma or hay fever, and household size; sinusitis or sinus problems: race (white, nonwhite), age, geographic region (northeast, midwest, south, west), parental history of physician-diagnosed asthma or hay fever, education level of family reference person, household size, and parents' birthplace (one or both parents born outside United States, both parents born in United States); wheezing or whistling in the chest: race, age, geographic region, parental history of physician-diagnosed asthma or hay fever, poverty status, household size, and parents' birthplace; nose and eye symptoms: race, age, area of residence, geographic region, parental history of physician-diagnosed asthma or hay fever, poverty status, education level of family reference person, household size, and parents' birthplace; any allergy-related respiratory symptom: race, age, geographic region, parental history of physician-diagnosed asthma or hay fever, education level of family reference person, household size, and parents' birthplace; and any lifetime allergy history or 12-month symptoms: race, age, geographic region, parental history of physician-diagnosed asthma or hay fever, household size, and parents' birthplace.

†Physician-diagnosed asthma in subject's lifetime.

‡Physician-diagnosed hay fever in subject's lifetime.

§Severe reaction (eg, itching all over, trouble breathing, flushing, hives, or swelling of the face, hands, or feet) within an hour after being stung by an insect (phase 1 of NHANES III only) or after eating something (phase 2 of NHANES III only), or after receiving allergy shots or allergy tests, or having to give up or avoid a pet because of allergies.

‖Lifetime history physician-diagnosed asthma or hay fever, or history of severe reaction from insect sting, food, allergy shots or tests, or pets.

¶Sinusitis or sinus problems during the past 12 months.

#Wheezing or whistling in chest at any time in the past 12 months.

**Any episodes of stuffy, itchy, or runny nose and watery, itchy eyes during the past 12 months.

††Sinusitis or sinus problems, wheezing or whistling in the chest, or nose and eye symptoms during the past 12 months.

‡‡Any lifetime history of physician-diagnosed asthma or hay fever, or allergic reaction, or sinusitis or sinus problems, wheezing or whistling in the chest, or nose and eye symptoms during the past 12 months.

Table 4 shows the number and weighted percent of respondents by vaccination status and type of allergy. Vaccinated persons were more likely to have lifetime histories of asthma (9.5% vs 4.5%), hay fever (6.2% vs 5.2%), and histories of allergies or allergic reactions (20.5% vs 10.8%). Vac-

Table 6. *Number, weighted percent, and estimated age-specific effects (OR and 95% CI) of DTP or tetanus vaccination on specific allergic conditions and allergy-related respiratory symptoms among subjects aged 2 months to 16 years from NHANES III, 1988-1994, by type of allergy and age group: Results of binary logistic regression analyses*

Variable	Age category (y)	Vaccinated		Unvaccinated		Age-specific effect	
		Number*	%†	Number*	%†	OR	95% CI
Asthma‡	<5	379	5.4	8	6.4	0.84	0.26-2.67
	5-16	617	11.2	2	1.1	5.99	1.68-21.33
Hay fever‡	<11	269	4.1	1	1.0	3.95	0.52-29.81
	11-16	201	10.3	1	19.6	0.47	0.05-3.97
Severe allergic reaction§	<11	678	8.8	3	0.8	10.08	3.59-28.33
	11-16	333	15.4	2	21.9	0.65	0.09-4.82
Any allergy/allergic reaction‖	<5	711	10.9	12	8.6	1.29	0.51-3.27
	5-10	688	21.7	2	3.0	6.11	1.11-33.53
	11-16	605	27.6	2	21.9	1.36	0.19-9.77
Sinusitis or sinus problems (12 months)¶	<11	1122	14.3	12	4.6	3.43	1.73-6.81
	11-16	510	25.0	3	24.7	1.02	0.16-6.43
Wheezing or whistling (12 months)#	<5	1761	24.6	65	27.7	0.85	0.56-1.30
	5-16	1015	17.1	6	3.4	4.65	2.02-10.73
Nose and eye symptoms (12 months)**	<5	1905	30.1	49	20.4	1.68	1.08-2.61
	5-16	1848	31.7	8	7.4	5.73	2.49-13.17
Any allergy-related respiratory symptom	<5	3093	47.5	99	40.5	1.33	0.97-1.83
(past 12 months)††	5-10	1551	44.3	6	10.6	6.65	2.75-16.07
	11-16	1146	48.9	7	31.7	2.06	0.43-9.93
Any lifetime allergy history or 12-month	<5	3283	49.9	103	45.2	1.21	0.89-1.64
symptoms‡‡	5-10	1745	50.3	7	12.3	7.16	2.68-19.12
	11-16	1319	55.3	7	31.7	2.66	0.56-12.74

*Unweighted number.
†Weighted percent.
‡Physician-diagnosed in subject's lifetime.
§Severe reaction (eg, itching all over, trouble breathing, flushing, hives, or swelling of the face, hands, or feet) within an hour after being stung by an insect (Phase 1 of NHANES III only) or after eating something (Phase 2 of NHANES III only), or after receiving allergy shots or allergy tests, or having to give up or avoid a pet because of allergies.
‖Lifetime history physician-diagnosed asthma or hay fever, or history of severe reaction from insect sting, food, allergy shots or tests, or pets.
¶Sinusitis or sinus problems during the past 12 months.
#Wheezing or whistling in chest at any time in the past 12 months.
**Any episodes of stuffy, itchy, or runny nose and watery, itchy eyes during the past 12 months.
††Sinusitis or sinus problems, wheezing or whistling in the chest, or nose and eye symptoms during the past 12 months.
‡‡Any lifetime history of physician-diagnosed asthma or hay fever, or allergic reaction, or sinusitis or sinus problems, wheezing or whistling in the chest, or nose and eye symptoms during the past 12 months.

cinated persons were also more likely to have sinusitis or sinus problems in the past 12 months (18.0% vs 9.1%) and allergy-related respiratory symptoms, including wheezing or whistling in the chest (19.4% vs 18.9%) and stuffy, itchy, or runny nose and watery, itchy eyes (31.2% vs 15.7%).

Subjects with missing data on vaccination status were similar to the nonmissing subjects with respect to smoking in the home (38.7% vs 39.0%) and parental asthma or hay fever (26.0% vs 25.2%). However, they were somewhat more likely to be aged <5 years, nonwhite, and living at or below poverty level. They were also more likely than (reported) unvaccinated subjects to have lifetime histories of allergies and episodes of allergy-related respiratory symptoms in the past year.

Effects of Vaccination on Asthma and Other Allergies

Table 5 shows the estimated crude and adjusted effects of vaccination on each type of allergy and allergy-related respiratory symptom. The estimated adjusted effects of vaccination were attenuated somewhat from the crude effects. The odds of having a lifetime history of physician-diagnosed asthma was twice as great among vaccinated subjects than among unvaccinated subjects (Table 5). Vaccinated children had more than 1.8 times greater odds of having sinusitis or sinus problems in the past 12 months and more than twice the odds of having episodes of stuffy, itchy, or runny nose and watery, itchy eyes than did unvaccinated children. Vaccination status was minimally associated with physician-diagnosed hay fever or with wheezing or whistling in the chest in the past 12 months (Table 5). The odds of having a lifetime history of allergies or allergy-related respiratory symptoms in the past 12 months was 69% greater among vaccinated subjects than unvaccinated subjects. Among children and adolescents aged 6 through 16 years, no association was detected between vaccination status and atopy (OR, 0.91; 95% CI, 0.29 to 2.84). However, allergy history or 12-month symptoms were reported in 59% of subjects aged 6 through 16 years who were both vaccinated and skin-test reactive compared with 46% of children who were either vaccinated or atopic and less than 2% who were neither vaccinated nor atopic.

Among the 5843 children with shot records and reported DTP or tetanus vaccinations, 7.4% and 5.7% had been diagnosed with asthma or hay fever, respectively. A total of 9.6% reported severe allergic reactions compared with 1 asthma diagnosis, no hay fever, and no severe allergic reactions among the 22 subjects with available shot records and no

reported DTP or tetanus vaccinations. Episodes of sinusitis, wheezing or whistling, and nose and eye symptoms in the past 12 months were reported by 17%, 19.4%, and 33%, respectively, of the vaccinated group compared with none, 8.9%, and 14.8%, respectively, of children with available shot records and no reported DTP or tetanus vaccinations.

The associations between vaccination and allergies appear to be modified by age (Table 6). Crude associations between vaccination and severe allergic reactions and sinusitis or sinus problems were detected only among children aged 10 years or younger, whereas vaccination was associated with asthma, wheezing or whistling in the chest and nose, and eye symptoms only among children aged ≥5 years. The estimated crude associations of vaccination with lifetime allergy history or allergy-related respiratory symptom in the past 12 months were greater among subjects aged 5 through 10 years than among subjects younger than 5 years or older than 10 years. Controlling for each potential confounder one at a time in separate logistic models did not result in effects appreciably different from the crude age-specific effects. Similarly, smoking while pregnant and breastfeeding status did not change the estimated effects of DTP or tetanus vaccination when these variables were included in analyses with populations restricted to subjects aged ≤11 years and subjects aged ≤5 years (data not shown).

Because subjects with missing data on vaccination status were more likely to be aged <5 years, nonwhite, and living at or below poverty level (predictors of being unvaccinated) and because they were more likely to have allergies than unvaccinated subjects, the exclusion of subjects with missing vaccination data may have biased the estimated effects. Under the assumption of 0% vaccination among subjects with missing vaccination data, the effect estimates were consistent with those obtained from the primary (nonmissing) analyses, albeit attenuated toward the null for 5 of the 6 specific allergy outcomes. For asthma, the adjusted OR was 1.58 (95% CI, 0.69 to 3.63); hay fever, 0.97 (95% CI, 0.36 to 2.63); severe allergic reaction, 1.40 (95% CI, 0.65 to 3.01); sinusitis or sinus problems, 1.76 (95% CI, 0.92 to 3.34); wheezing or whistling in the chest, 1.36 (95% CI, 1.02 to 1.83); and nose and eye symptoms, 1.31 (95% CI, 0.85 to 2.01).

DISCUSSION

DTP or tetanus vaccination in US children is associated with lifetime history of asthma or other allergies and allergy-related symptoms in the past 12 months. This study, to our knowledge, provides the most comprehensive assessment of the effects of DTP or tetanus vaccination on allergies and allergy-related respiratory symptoms. Evidence was also presented showing that vaccination may be associated with different types of allergies at different ages. The vaccination may be associated with severe allergic reactions and sinusitis or sinus problems among younger children, and with asthma, wheezing and whistling, and nose and eye symptoms among older children and adolescents. The associations between the vaccination and subsequent allergies and symptoms were greatest among children aged 5 through 10 years.

The consistency of the estimated effects on both lifetime prevalence of allergic reactions and 12-month prevalence of allergy-related respiratory symptoms and the finding of effects for conditions requiring health-care usage and symptoms not requiring doctor visits suggest that the DTP or tetanus vaccine itself has potential long-term adverse consequences that cannot be explained by differences in health or health-care usage between vaccinated and unvaccinated children. The NHANES III data, however, do not allow for the identification of the immunologic mechanisms or specific vaccine components that may be responsible for the link between vaccination and the development of allergic disorders. There was little difference in skin test reactivity between vaccinated and unvaccinated children and adolescents aged 6 through 16 years, suggesting that vaccination did not induce atopy (and providing assurance that vaccinated subjects were probably not more likely to be atopic before vaccination). However, the effect of DTP on inducing subsequent allergic reactions may be influenced by underlying atopy or atopic predisposition, supported by the relatively greater prevalence of allergies among subjects aged 6 through 16 years who were both vaccinated and atopic.

The DTP or tetanus vaccination may induce immediate allergic reactions in certain susceptible individuals, a subset of whom are then sensitized to other allergens, or the vaccine may sensitize the person to related or unrelated allergens, resulting in hypersensitivity reactions after exposure to these allergens. The latter hypothesis is supported by findings from 2 studies showing that 63% of subjects who did not have previous reactions to tetanus toxoids had immediate hypersensitivity reactions to subsequent tetanus toxoids.[28] Pain, erythema, and swelling have been noted in 1% to 80% of persons receiving booster doses of tetanus toxoid,[25-27] whereas up to 27% of adults receiving diphtheria vaccinations have local hypersensitivity reactions.[44-47] The finding of stronger associations between vaccination and severe allergic reactions at younger ages than older ages and stronger associations between vaccination and allergy-related symptoms among older children and adolescents suggests that the vaccination or related allergic reaction may sensitize atopic subjects to subsequent antigenic stimuli. NHANES III did not ask about immediate hypersensitivity reactions associated with the DTP or tetanus shot; thus whether children who had immediate allergic reactions were also more likely to have subsequent generalized allergic hypersensitivity develop cannot be determined.

Rook and Stanford[20] hypothesize that vaccinations, by preventing natural infections during childhood, prevent the switch to Th1 activity that typically occurs by age 5.[48] The vaccine "may deprive the immune system of the learning experience that it would have derived from clearing established infection with a Th1-mediated pathway."[20] Vaccination in combination with stress, which also induces Th2 activity, may be associated with allergic disorders by way of stress-related release of cortisol and consequent IgE.[49] Because of age-related changes in immune system development and in response to stress, the age at which children are vaccinated may be a critical determinant in the magnitude of effect. Th2

responses are known to predominate in utero and in early childhood.[50,51] Environmental factors during the first few years of life cause T-cell responses to become Th1 with a steady decline in Th2 responses and an increase in the Th1 cytokine interferon γ production, which inhibits Th2 cell growth.[50,51] Vaccination with DTP or tetanus may prevent the Th2-to-Th1 shift, resulting in inhibition of Th1 activity and dysregulated Th2 activity in susceptible children. This may occur because of the Th2-inducing effect of the vaccine itself or because of the lack of Th1 stimulus of natural infection. Because NHANES did not ask the age of first dose of vaccine, occurrence of childhood infections, or about exposure to stressors that may be related to immediate or subsequent responses, we cannot address these alternative hypotheses.

Six studies have recently addressed the association between pertussis or DTP immunizations and allergy-related disease.[33-36,52,53] Our results are similar to findings reported from 3 retrospective cohort studies.[34-36] Odent et al[34] asked parents of 448 children (aged >4 years) and adolescents if their children had "ever been diagnosed as asthmatic." Twenty-six (10.7%) of the 243 pertussis-immunized children had been diagnosed as asthmatic versus 4 (2%) of the 203 nonimmunized children (risk ratio, 5.43; 95% CI, 1.93 to 15.30). Kemp et al[35] conducted a study of 1265 children born in New Zealand in 1977 and observed them until they were aged 16 years and found 2 cases of asthma and 1 consultation for other allergies among the 23 children who did not receive DTP or polio immunizations. Conversely, asthma cases and other allergy consultations were reported in 33.5% and 43.3%, respectively, of the immunized group (risk ratio for asthma, 2.9; 95% CI, 0.8 to 23.6; risk ratio for other allergy consultations, 5.6; 95% CI, 1.0 to 222.6). Using public health and medical record data from 1934 children born in England from 1975 to 1984 and observed for at least 12 years, Farooqi and Hopkin[36] performed multivariable logistic regression analysis and found whole-cell pertussis immunization to be a predictor of subsequent diagnosis of asthma, hay fever, or eczema (adjusted OR, 1.76; 95% CI, 1.39 to 2.23).

The pertussis immunization-atopic disorder associations observed by Farooqi and Hopkin[36] were less in children younger than 5 years than in older children, findings consistent with the relatively smaller vaccination-asthma and vaccination-allergy symptom associations estimated for this age group in this study. The suggestion of effect modification by age may explain the mostly negative results reported by the authors of recent prospective studies of children observed until the age of 2½ years[33,52] or until 3½ years of age.[53] Nilsson et al[52] found little evidence that acellular or whole-cell DTP vaccines increase the risk of wheezing, itching, or sneezing relative to DT vaccine alone. The risk of atopic disease during the first 2½ years of life in children randomly assigned to receive to acellular DTP vaccine was only approximately 10% greater than the risk among children randomly assigned to receive whole-cell DTP vaccine.[33] Henderson et al[53] found no evidence in support of a link between pertussis vaccination and wheezing symptoms during the first 4 years of life among children enrolled in the Avon Longitudinal Study of Pregnancy and Childhood. Planned observation of these populations will be helpful in further elucidating the potential influence of age on vaccination-allergy associations.

Limitations of our study included the cross-sectional design, reliance on self-reports for vaccination status, allergies, and allergy-related respiratory symptoms, missing data on vaccination status for 2.4% of all subjects, lack of information about the clinical nature (eg, allergic vs nonallergic) and age at onset of the asthma and other allergic conditions, and possible confounding by unknown factors. Proxy respondents of children with allergic disorders may have been more likely than proxy respondents of children without allergic disorders to report inaccurately that their children had been vaccinated. In addition, subjects with missing vaccination data may have been more likely to have been unvaccinated and to have allergies than were subjects with vaccination data. Although parental recall is an imperfect measure of vaccination status,[54,55] data obtained from parents who refer to shot records have been shown to have fair to good agreement with medical records.[56,57] Despite the small number (22) of unvaccinated children with available shot records, the associations of vaccination with each type of allergy among children with available shot records were consistent with the associations estimated in the total sample (based primarily on parental recall). Furthermore, the observed effects did not change appreciably under the assumption of 100% nonvaccination among the missing. There is no reason to expect the association between vaccination and allergies would be different between respondents who gave the vaccination status of their child and those who did not.

Proxy respondents for vaccinated children may have been more likely to have sought care and thus more likely to have been diagnosed with asthma or hay fever. However, this cannot explain the associations detected between vaccinations and severe allergic reactions, sinusitis, and episodes of allergy-related nose and eye symptoms in the past year, which do not depend on health care use. Analyses restricted to children of at least one US-born, college-educated parent or guardian yielded similar associations between vaccination and allergies to those estimated from the total sample. Although we could not control for unknown confounders, logistic regression modeling was used to control for all known risk factors that may have confounded the vaccination effects.

CONCLUSION

Asthma and other allergic hypersensitivity reactions and related symptoms may be caused, in part, by the delayed effects of DTP or tetanus vaccination. One or more vaccine components may be responsible for a portion of the increased prevalence of asthma and allergies in US children. Given the consistency of the estimated effects for many types of allergies and allergic reactions, the control of confounding by known risk factors for asthma and other allergies, the observation of effects for both diagnosed asthma and reported allergy-related symptoms, and the observation

of effects for both lifetime and 12-month prevalence of allergic reactions and symptoms, it is unlikely that misclassification and selection biases and confounding are responsible for the observed effects. However, the study design and the small number of unvaccinated children preclude definitive causal inferences.

Because the proportion of US children who have received at least 1 dose of DTP vaccine approaches 100%, the number of allergies and allergy-related conditions attributable to DTP or tetanus vaccination in the United States may be very high. For example, assuming that the estimated vaccination effect is unbiased, 50% of diagnosed asthma cases (2.93 million) in US children and adolescents would be prevented if the DTP or tetanus vaccination was not administered. Similarly, 45% of sinusitis cases (4.94 million) and 54% of allergy-related episodes of nose and eye symptoms (10.54 million) in a 12-month period would be prevented after discontinuation of the vaccine. The well-documented public health benefits of the DTP and tetanus vaccines must be considered in light of these potential long-term risks, which should be addressed in future studies.

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