

Vaccines, antibiotics, and atopy[†]

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SUMMARY

Purpose Early exposure to vaccines and antibiotics may increase the risk of developing atopy by protecting against infectious agents and reducing duration and severity of infections (the hygiene hypothesis). It may also shift the developing immune system towards a more allergic response. We assess possible associations in young allergy clinic patients.

Methods We conducted a case-control study of 6- to 16-year-old new allergy clinic patients who were skin tested for inhalant allergens during 1987–2001 and enrolled in KPNW since birth ($n = 1074$). Atopic cases had positive tests for at least one inhalant allergen. Non-atopic controls had negative tests for all inhalant allergens. Using logistic regression analysis, we estimated atopy odds ratios for vaccine and antibiotic exposure variables and associations between vaccine and antibiotic exposures during the first 2 years of life and subsequent new allergy diagnoses.

Results Atopy was not significantly associated with numbers of vaccine and antigen doses, or number of different antigens during the first 2 years of life. Number of antibiotic prescriptions was negatively associated with atopy risk. Neither exposure was significantly associated with risk of new allergy diagnoses in atopic children.

Conclusions Atopy development appears to be unrelated to early vaccine exposure. Frequency of antibiotic prescriptions during early life, a proxy for infection frequency, appears to protect against allergic sensitization. Neither vaccines nor antibiotics appear to induce subsequent allergic reactions in atopic children. Copyright © 2006 John Wiley & Sons Ltd.

KEY WORDS — atopy; vaccines; antibiotics; children; case-control study; allergy clinic patients

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INTRODUCTION

The prevalence of allergic conditions in children has been increasing dramatically over the past two decades in the United States and other developed countries.¹ The hygiene hypothesis proposes that this increase is due to reduced endotoxin or microbial

exposure in childhood. Infections during infancy are postulated to protect against asthma and atopy.^{2–9} By protecting against infectious agents, childhood vaccines may indirectly increase the risk of developing atopy. By preventing infections (prophylaxis) and reducing duration and severity of infections (therapy), antibiotics may indirectly increase the risk of developing atopy. On the other hand, it is possible that vaccines may *decrease* the risk of atopy by protecting against a number of bacterial and viral pathogens (i.e., natural infections) that could weaken the immune system.¹⁰

Some have even speculated that vaccines and antibiotics may directly increase the risk of developing

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atopy. T-lymphocytes that secrete cytokines of the Th2 class are thought to play an etiologic role in allergic asthma and other allergic disorders. Some vaccines or their adjuvants (e.g., aluminum) may shift the immunologic Th1/Th2 balance towards a more allergic response.^{11–17} Live virus vaccines have a different effect on Th1/Th2 balance than component vaccines, and possibly a different effect than even inactivated vaccines.¹⁸ Further, the measles component of MMR may be Th1 stimulating.⁶ The use of antibiotics in early childhood may shift the developing immune system towards a Th2 response by disturbing the flora of the gastrointestinal tract.⁸

Published studies of childhood exposures to vaccines and antibiotics and the development of allergic conditions have reported inconsistent findings.^{19–33} They used a variety of study populations, study designs, case ascertainment methods, vaccine and antibiotic exposure measures, and varied in their ability to control confounding. Previous studies in Kaiser Permanente Northwest (KPNW) found no evidence that vaccines are associated with wheezing conditions in full-term infants or asthma in full-term children.^{27,28}

We investigate the relationships between early childhood exposures to vaccines and antibiotics and the development of atopy. Our analyses controlled for known atopy risk factors and changing patterns of skin testing and diagnosing in KPNW, a large west coast HMO. We are able to look at these patterns and risk factors because KPNW has computerized membership and encounter databases and a comprehensive medical record system. Known risk factors for allergic conditions include family history, race, age, male sex, premature birth, not breast feeding, allergen exposure, exposure to tobacco smoke, and few older siblings.^{34,35} We also investigate whether early exposures to vaccines and antibiotics are associated with the development of allergic conditions (i.e., asthma, allergic rhinitis, atopic dermatitis) in atopic children.

METHODS

Design

We used a case-control design to assess possible associations between atopy and childhood vaccinations and antibiotic use during the first 2 years of life. Study subjects were 6- to 16-year-old new allergy clinic patients who were skin-prick tested during 1987–2001 and continuously enrolled in KPNW since birth. Medically complex children were excluded (i.e., cancer chemotherapy or radiation therapy, HIV infection, major congenital malformations, cystic

fibrosis, an immune deficiency syndrome, or major cardiac disease).

Atopy cases had a positive skin-prick test for at least one inhalant allergen (weeds, grasses, early trees, late trees, dust mites, cats, dogs, or molds) with wheal diameter ≥ 3 mm more than saline control. Non-atopy controls had negative skin-prick tests for all inhalant allergens. The control group included incompletely tested patients who were tested for at least three of the eight allergens and were negative on all tests. Skin-prick test results were abstracted from allergy clinic charts.

We used multiple control groups to adjust for possible confounding by associations between vaccine exposures and the medical conditions that brought children to allergy clinics for skin testing. In addition to comparing all atopy cases to all controls, we compared all atopy cases to controls with clinical diagnoses of asthma, and atopy cases with asthma to controls with asthma.

Measures

We measured atopy or atopic predisposition in early childhood according to skin-prick test results from ages 6–16 years. Vaccine exposure measures were: number of doses of DTP, MMR, HBV, OPV, IPV, HIB, total doses of vaccine antigens received, number of different vaccine antigens received, and age at first HBV dose. Prevnar was not introduced until after the study period. Antibiotic exposure measures were: number of outpatient antibiotic prescriptions dispensed in first and second years of life and age at first antibiotic dispensing. Topical preparations were excluded. We investigated the following covariates: maternal/family history of atopy, age at skin-prick test, gender, race, birthweight, breast feeding, birth order, maternal smoking, household smoking, cats and dogs at home, maternal age at birth, calendar year of allergy skin test, and birth year. Our descriptive tables use approximate tertiles of calendar year of birth, and categories of calendar year of skin test that are based on recommended numbers of vaccinations.

Vaccinations and antibiotic dispenses were abstracted from electronic medical records (EMR) and from paper-based medical charts. Covariates were abstracted from allergy clinic charts and from EMR and paper-based general medical charts.

Analysis

We used Chi-square tests to compare prevalence of diagnosed allergic and non-allergic conditions (during

the first 2 years of life and prior to skin testing) in atopy cases and non-atopic controls. Covariate distributions for atopy cases and non-atopic controls were compared using Chi-square statistics for categorical variables and *t*-tests for continuous variables.

We used logistic regression models to estimate adjusted atopy odds ratios for vaccine and antibiotic exposure measures. Covariates associated with atopy at $p < 0.20$ in bivariate analyses were included in the regression models. Logistic regression models were also used to estimate adjusted allergy diagnosis odds ratios for vaccine and antibiotic exposure measures. Separate analyses were conducted for atopy cases and non-atopy controls and for new diagnoses of asthma, eczema/atopic dermatitis, and allergic rhinitis. Missing continuous covariates were imputed by mean values and missing binary (1 = yes/0 = no) covariates by modal values in these models. We performed all statistical analyses using SAS procedures. The KPNW Institutional Review Board approved the study.

RESULTS

Subject characteristics

Of the 1287 continuously eligible children referred to allergy clinics during 1987–2001, 1150 (89%) had records of skin tests. We excluded 14 patients with a skin test because of serious chronic conditions or treatments, which left 1136 study-eligible patients. Eight hundred forty-four (74%) had a positive skin test for at least one allergen and were classified as atopy

cases. Sixty-two of the 292 with no positive skin tests were tested for two or fewer allergens and were excluded from the study as having indeterminate atopy status, leaving 230 non-atopic controls. Atopy cases accounted for 79% (844) of the 1074 eligible study subjects. Controls and cases did not differ much on the number of skin tests. Eighty-five percent of controls were tested for at least six allergens, and 80% were tested for all eight allergens. Among cases, 87% were tested for all eight allergens and 94% were tested for at least six allergens. Only 0.7% of cases were tested for fewer than three allergens.

Compared to non-atopic controls, atopy cases had a higher prevalence of eczema/atopic dermatitis during the first 2 years of life and allergic rhinitis and asthma prior to skin testing. Atopy cases had lower prevalence of sinusitis prior to skin testing. Complete data on clinical diagnoses in the first 2 years of life and prior to the skin test are in Table 1.

Our study population was predominantly white and 55% male, and averaged 10 years of age at skin testing. The average annual number of new skin-tested patients increased from 56 during 1987–1989 to 88 patients during 1998–1999 and then decreased to 56 during 2000–2001. Identification of new allergy clinic patients during 1978–1986 was incomplete. The earliest clinic registration dates in the database (Kare) are for 1985. Abstractors found that some of the 1985 patients had earlier skin tests. The proportion of atopic patients decreased from 83% in 1987–1995 to 71% in 1996–2001.

Maternal/family history of atopy, non-white race, male gender, older age at skin prick test, and younger

Table 1. Number and percentage of atopy cases and controls with clinical diagnoses in first 2 years of life and prior to skin test

	First 2 years			Prior to skin test		
	Cases (<i>n</i> = 844)	Controls (<i>n</i> = 230)	<i>p</i> -value Chi Sq	Cases (<i>n</i> = 844)	Controls (<i>n</i> = 230)	<i>p</i> -value Chi Sq
Allergy						
Asthma	65 (7.7%)	25 (10.9%)	0.124	413 (48.9%)	91 (39.6%)	0.012*
Allergic rhinitis	15 (1.8%)	7 (3.0%)	0.229	496 (58.8%)	111 (48.3%)	0.004*
Eczema/atopic dermatitis	53 (6.3%)	6 (2.6%)	0.030*	109 (12.9%)	21 (9.1%)	0.119
Nonspecific eczema	133 (15.8%)	20 (8.7%)	0.007*	258 (30.6%)	53 (23.0%)	0.026*
Food allergy	20 (2.4%)	4 (1.7%)	0.566	39 (4.6%)	5 (2.2%)	0.097
Any	211 (25.0%)	46 (20.0%)	0.115	722 (85.6%)	169 (73.5%)	0.0001*
Other diagnoses						
Rhinitis (nonallergic/chronic)	39 (4.6%)	8 (3.5%)	0.453	89 (10.6%)	30 (13.0%)	0.285
Food intolerance	6 (0.7%)	0 (0%)	0.351	14 (1.7%)	4 (1.7%)	0.933
Sinusitis	27 (3.2%)	13 (5.7%)	0.082	263 (31.2%)	115 (50.0%)	0.0001*
Urticaria/angioedema	34 (4.0%)	11 (4.8%)	0.613	154 (18.3%)	37 (16.1%)	0.448
Any	97 (11.5%)	27 (11.7%)	0.918	407 (48.2%)	139 (60.4%)	0.001*

*Significant at $p < 0.05$.

maternal age were associated with atopy at $p < 0.05$. Not breast feeding at 2 months, absence of household smoking, and not having a dog appeared to be associated with atopy, but these did not reach statistical significance ($p < 0.20$). Absence of household smoking was associated with atopy among subjects with diagnoses of asthma (data not shown).

The baseline characteristics of cases compared to controls are available in Table 2.

Exposure to vaccines

Compared to controls, atopy cases had fewer antigen doses, fewer different antigens, less exposure to HIB, and fewer doses of HIB, mumps, and rubella vaccines during the first 2 years of life (Table 3). The total number of antigen doses and number of different antigens increased with calendar period of skin testing (Table 3A). There were large increases in the number of antigen doses of and in exposures to HIB, and mumps and rubella vaccines.

Exposure to antibiotics

Exposure prevalence during the first 2 years of life was higher for 1981–86 births (88%) and 1987–95 births (85%) than for 1970–80 births (73%). Compared to exposed children born from 1970–80, exposed children born after 1980 received more antibiotic dispenses and were first exposed at younger ages. Among children born after 1980, atopy cases had slightly higher exposure prevalence during the first 2 years of life than controls (88% vs. 83%) but fewer prescriptions per user (4.5 vs. 5.0). Table 4 compares early exposure to antibiotics in atopy cases and controls by calendar period of birth.

Vaccinations and atopy

Total antigen doses, number of different antigens, and number of HIB doses were significantly inversely associated with atopy in Model 1 (Table 5). However, these apparent protective effects are spurious and resulted from the coincidence of a decreasing secular trend in the proportion of positive skin tests with an increasing secular trend in the number of recommended childhood vaccines. Atopy was found to be independent of vaccine exposures when calendar period of skin test was controlled in Model 2. Similar results were found when calendar period of skin test was replaced in Model 2 by year of skin test. We see no evidence in any of the three case-control comparisons that atopy is related to vaccine exposure.

Antibiotics and atopy

There were significant negative associations between atopy and number of antibiotic prescriptions in the first 2 years of life (Table 6). The associations are consistent for comparisons between all cases versus asthma controls and asthma cases versus asthma controls, but did not reach statistical significance for the comparison of all cases versus all controls. Among children with at least one prescription in the first 2 years of life, age at first antibiotic prescription was not associated with atopy.

Vaccinations, antibiotics, and new allergy diagnoses

The number of different antigens prior to 2 years of age appeared from Model 1 to be positively associated with new diagnoses of eczema/atopic dermatitis at more than 2 years of age in atopic children (Table 7). However, when calendar period of birth was controlled in Model 2, the odds ratio confidence interval included 1.0.

Among atopic children exposed to antibiotics, age at first exposure was negatively associated with new diagnoses of allergic rhinitis at more than 2 years of age. Among non-atopic children, the number of antibiotic prescriptions in the first 2 years of life was positively associated with new diagnoses of non-specific eczema at more than 2 years of age.

Atopy risk factors

Atopy risk factors were identified by logistic regression analyses of covariates with bivariate p -values < 0.20 using models that included vaccine exposure variables. The results were consistent across models. Non-white race (OR = 4.22, CI: 1.95–9.12); maternal/family history of atopy (OR = 1.86, CI: 1.34–2.59); male gender (OR = 1.67, CI: 1.23–2.27); and age at skin prick test (OR = 1.09 per year, CI: 1.03–1.15) were independently related to atopy in our entire sample of 1074 allergy clinic patients. Maternal age at birth appeared to be negatively related to atopy, but this association did not reach statistical significance (OR = 0.97 per year, CI: 0.940–1.003). Not significantly associated with atopy were household smoking (OR = 0.70, CI: 0.38–1.28); low birth weight (OR = 0.74, CI: 0.34–1.59); dogs at home (OR = 0.90, CI: 0.66–1.22); and breast feeding at 2 months (OR = 1.00, CI: 0.72–1.39).

For the smaller sample of 504 allergy clinic patients with asthma diagnoses, non-white race (OR = 3.14,

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Table 2. Baseline characteristics of cases and controls

Characteristics	Cases (n = 844)		Controls (n = 230)		Total	p-value
	n	Percent	n	Percent		
Race						
White	742	89.18	207	96.28	1047	0.001*
Non-white	90	10.82	8	3.72		
Missing	12		15			
Maternal/family Hx of Atopy						
Yes	621	80.65	148	76.68	963	0.219
No	149	19.35	45	23.32		
Missing	74		37			
Gender						
Male	487	57.7	106	46.09	1074	0.002*
Female	357	42.3	124	53.91		
Gestational age						
Term	720	90.57	191	90.95	1005	0.864
Pre-term	75	9.43	19	9.05		
Missing	49		20			
Low birth weight						
Yes	32	3.89	10	4.63	1038	0.625
No	790	96.11	206	95.37		
Missing	22		14			
Birth order						
4+	45	5.65	16	7.55	1008	0.234
3	115	14.45	39	18.4		
2	302	37.94	68	32.08		
1	334	41.96	89	41.98		
Missing	48		18			
Smoking during pregnancy						
Yes	32	10.67	9	10.84	383	0.963
No	268	89.33	74	89.16		
Missing	544		147			
Breast feeding at 2 months						
Yes	521	66.97	151	72.95	985	0.101
No	257	33.03	56	27.05		
Missing	66		23			
Household smoking						
Yes	44	25.73	17	35.42	219	0.186
No	127	74.27	31	64.58		
Missing	673		182			
Has cat at test time						
Yes	415	53.55	115	57.5	975	0.317
No	360	46.45	85	42.5		
Missing	69		30			
Has dog at test time						
Yes	384	49.87	112	55.45	972	0.158
No	386	50.13	90	44.55		
Missing	74		28			
Year of Skin Prick test ⁺						
78–86	17	94.44	1	5.56	1074	0.000*
87–89	136	80.95	32	19.05		
90–91	138	90.79	14	9.21		
92–93	109	81.95	24	18.05		
94–95	127	79.87	32	20.13		
96–97	113	71.97	44	28.03		
98–99	135	77.14	40	22.86		
00–01	69	61.61	43	38.39		

Continues

Table 2. (Continued)

Characteristics	Cases (<i>n</i> = 844)		Controls (<i>n</i> = 230)		<i>p</i> -value
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
Age at Skin Prick test	10.28 (2.93)	10 (6–16)	9.60 (2.95)	9 (6–16)	0.002*
Missing	0		0		
Birth weight (grams)	3,515.58 (546.97)	3,542 (1,240–5,460)	3,463.96 (596.22)	3,450 (1,245–5,150)	0.226
Missing	22		14		
Mother's age at birth	28.26 (4.87)	28 (13–42)	29.03 (5.15)	29 (18–46)	0.044*
Missing	46		20		

[†]Row percents.

*Significant at *p* < 0.05.

CI: 1.20–8.21), male gender (OR = 1.60, CI: 0.98–2.62), household smoking (OR = 0.40, CI: 0.17–0.95), and low birth weight (OR = 0.33, CI: 0.13–0.85) were independently related to atopy. Maternal age at birth (OR = 0.967 per year, CI: 0.92–1.02) tended to be negatively related to atopy. Maternal/family history of atopy (OR = 1.45, CI: 0.83–2.55), age at skin prick test (OR = 1.05, CI: 0.96–1.15), dogs at home (OR = 1.19, CI: 0.73–1.95), and breast feeding at 2 months (OR = 0.80, CI: 0.47–1.38) were unrelated to atopy.

DISCUSSION

Among these 6- to 16-year-old allergy clinic patients who were skin-prick tested during 1987–2001, atopy was not significantly associated with total doses of vaccines, number of different vaccine antigens, or

number of doses of specific antigens. Atopy was negatively associated with number of antibiotic prescriptions during the first 2 years of life, but not significantly associated with age at first antibiotic prescription. If frequency of antibiotic prescriptions is a valid proxy for infection frequency, our findings are consistent with the hygiene hypothesis that early infections protect against later allergic sensitization.

HIB and total vaccinations had spurious apparent protective effects on atopy when calendar year of skin test was not controlled. An increasing secular trend in number of recommended vaccines during 1978–2001 coincided with a decreasing secular trend in the skin test positivity rate. Primary care providers managed more allergy patients as improved allergy medications became available and non-allergic patients accounted for increased proportions of allergy clinic referrals.

Table 3. Antigen exposures for atopy cases and all non-atopic controls during the first 2 years of life

Antigen	Cases (<i>n</i> = 844)			Controls (<i>n</i> = 230)			<i>P</i> -value	
	Number of doses		1+ doses	Number of doses		1+ doses		
	Mean	SD	Percent	Mean	SD	Percent	<i>t</i> -test	Chi sq
Diphtheria	3.5	0.87	99%	3.6	0.77	100%	0.273	0.449
Tetanus	3.5	0.87	99%	3.6	0.77	100%	0.273	0.449
Pertussis	3.5	0.88	99%	3.6	0.78	99%	0.621	0.793
Measles	0.9	0.40	84%	0.9	0.34	89%	0.068	0.058
Mumps	0.8*	0.42	81%*	0.9	0.36	88%	0.014	0.015
Rubella	0.8*	0.42	81%*	0.9	0.36	88%	0.024	0.022
OPV	3.2	0.92	98%	3.1	0.72	100%	0.537	0.190
IPV	0.002	0.07	0.1%	0.01	0.20	0.4%	0.192	0.324
HIB	0.4*	1.13	18%*	0.9	1.42	37%	<0.0001	<0.0001
Hep B	0.1	0.59	5%	0.2	0.70	9%	0.181	0.069
Total no. of antigen	16.9*	4.31	100%	17.7	4.06	100%	0.011	0.296
No. of different antigens	6.7*	1.39		7.1	1.25		<0.0001	
Age (months) at 1st HBV [†]	3.7	6.74		3.8	6.27		0.966	

[†]Based on *N* = 46 cases and *N* = 20 controls exposed to HBV.

*Significant at *p* < 0.05.

Table 3A. Antigen exposures for atopy cases and all non-atopic controls stratified by year of skin testing

Antigen	Cases						Controls					
	1978–1993 (<i>n</i> = 400)		1994–1999 (<i>n</i> = 375)		2000–2001 (<i>n</i> = 69)		1978–1993 (<i>n</i> = 71)		1994–1999 (<i>n</i> = 116)		2000–2001 (<i>n</i> = 43)	
	No. of doses	%	No. of doses	%	No. of doses	%	No. of doses	%	No. of doses	%	No. of doses	%
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Diphtheria	3.4 (0.92)	100%	3.6 (0.84)	98%	3.8 (0.57)	100%	3.3 (0.97)	100%	3.7 (0.63)	99%	3.8 (0.59)	100%
Tetanus	3.4 (0.92)	100%	3.6 (0.84)	98%	3.8 (0.57)	100%	3.3 (0.97)	100%	3.7 (0.63)	99%	3.8 (0.59)	100%
Pertussis	3.4 (0.94)	99%	3.6 (0.85)	98%	3.7 (0.62)	100%	3.3 (0.86)	100%	3.6 (0.75)	98%	3.7 (0.62)	100%
Measles	0.8 (0.43)	79%	0.9 (0.36)	88%	0.9 (0.29)	93%	0.9 (0.42)	83%	0.9 (0.32)	91%	0.9 (0.26)	93%
Mumps	0.7 (0.47)	72%	0.9 (0.37)	89%	0.9 (0.29)	93%	0.8 (0.46)	79%	0.9 (0.32)	91%	0.9 (0.26)	93%
Rubella	0.7 (0.46)	73%	0.9 (0.37)	88%	1.0 (0.34)	93%	0.8 (0.46)	79%	0.9 (0.32)	91%	0.9 (0.26)	93%
OPV	3.3 (0.96)	99%	3.1 (0.89)	98%	3.1 (0.75)	99%	3.1 (0.87)	100%	3.2 (0.67)	99%	3.1 (0.59)	100%
IPV	0	0%	0.01 (0.10)	0%	0	0%	0	0%	0.03 (0.28)	1%	0	0%
Hib	0.02 (0.14)	2%	0.6 (1.21)	26%	2.2 (1.86)	71%	0	0%	0.9 (1.26)	46%	2.3 (1.82)	72%
Hep B	0.01 (0.13)	1%	0.13 (0.62)	5%	0.83 (1.25)	32%	0	0%	0.05 (0.32)	3%	0.93 (1.30)	37%
Total antigen	15.9 (4.13)	100%	17.3 (4.25)	99%	20.2 (3.60)	100%	15.5 (4.32)	100%	18.0 (3.07)	100%	20.5 (4.10)	100%
No. of different antigens	6.2 (1.28)		6.9 (1.37)		7.8 (1.12)		6.4 (1.14)		7.2 (1.11)		7.9 (1.24)	
Age (months) at 1st HBV	7.8 (10.84)	<i>n</i> = 4	6.3 (8.17)	<i>n</i> = 20	0.6 (0.85)	<i>n</i> = 22		<i>n</i> = 0	13.0 (8.83)	<i>n</i> = 4	1.4 (2.37)	<i>n</i> = 16

When skin test positivity at 6–16 years of age was used as a proxy for atopy or atopic predisposition early in life, we found that vaccine exposures of atopic children during the first 2 years of life were not significantly associated with risk of new diagnoses of allergic conditions between the second birthday and the date of skin testing. We controlled for the duration of time during which new allergic conditions could have been diagnosed and for secular trends in diagnostic practice by including age-at-skin-test and calendar period of birth as covariates in the logistic regressions. Children born during 1987–1995 tended to be diagnosed with asthma and eczema/atopic dermatitis more often than children born during 1970–1980. Non-atopic children born during 1987–1995 were less likely to be diagnosed with allergic rhinitis than non-atopic children born during 1970–1980. We were unable to control for frequency of medical care encounters at which diagnoses could have been made.

Vaccines

Our findings of no significant associations between atopy and the number of doses of DTP or tetanus vaccines are consistent with the NHANES III findings of no association between skin test positivity and some or no exposure to these vaccines.²⁵ Our study had too few children with no exposure to DTP or tetanus vaccination to make a direct comparison. Hurwitz speculates from NHANES III findings that the effect of DTP on inducing subsequent allergic reactions may be influenced by underlying atopy or atopic predisposition.²⁵ Our findings do not support his speculation, but their atopy proxy was family history, whereas our proxy was skin test positivity at ages 6–16 years and we controlled for family history. Our 79% skin-test-positivity rate among 6- to 16-year-old allergy clinic patients is considerably higher than the 50% rate for 6- to 16-year-old NHANES III respondents. Even if all 62 of our patients with incomplete skin-prick testing were classified as non-atopic, our positivity rate would be 74%.

A randomized pertussis vaccine trial provides strong evidence that pertussis vaccines are unrelated to skin-prick test positivity.²¹ Selection factors and recall bias may have confounded the positive associations between pertussis vaccine and asthma or hay fever reported by a cross-sectional survey of persons traced through La Leche League International¹⁹ and a mailed survey of households concerned about vaccine safety.²⁹ A cross-sectional study of anthroposophic (Steiner) and neighboring schools in Sweden reported that exposure to MMR increased the risk of atopy, but

Table 4. Early exposure to antibiotics in atopy cases and controls by calendar period of birth

	1970–80		1981–86		1987–95	
	Case (<i>n</i> = 272)	Control (<i>n</i> = 54)	Case (<i>n</i> = 348)	Control (<i>n</i> = 59)	Case (<i>n</i> = 224)	Control (<i>n</i> = 117)
Any use in 1st year						
<i>n</i>	149	35	245	44	172	83
%	55%	65%	70%	75%	77%	71%
Any use in 2nd year						
<i>n</i>	155	30	254	38	168	85
%	57%	56%	73%	64%	75%	73%
Any use in 1st 2 years						
<i>n</i>	198	41	307	51	196	95
%	73%	76%	88%	86%	88%	81%
Age (months) at first use						
Range	0–23	0–20	0–23	0–22	0–22	0–23
Median	7	7	7	6	6	6
Mean	8.19	7.54	7.52	6.61	6.68	6.75
SD	5.66	5.01	5.33	5.35	4.27	4.76
No. of prescriptions per user in 1st year						
Range	0–10	0–10	0–13	0–8	0–11	0–12
Median	1	1	1	2	2	2
Mean	1.44	1.54	2.00	2.42	2.47	2.42
SD	1.97	2.02	2.19	2.28	2.52	2.72
No. of prescriptions per user in 2nd year						
Range	0–11	0–9	0–12	0–11	0–11	0–12
Median	1	1	1	1	2	2
Mean	1.42	1.33	2.15	2.36	2.59	2.73
SD	1.90	1.79	2.33	2.78	2.57	2.61
No. of prescriptions per user in 1st 2 years						
Range	0–16	0–12	0–16	0–16	0–16	0–16
Median	2	2	3	3	4	4
Mean	2.86	2.87	4.15	4.78	5.06	5.15
SD	3.40	3.02	3.78	4.54	4.29	4.49

did not control for confounding by lifestyle and other selection factors.³⁰

Antibiotics

While our finding that antibiotic prescriptions were negatively associated with atopy seems consistent with the hygiene hypotheses, studies of antibiotic use and atopy have reported mixed results. Early childhood use of antibiotics was found to be positively associated with medical record diagnoses of asthma, hay fever, or eczema;⁸ parental reports of asthma;³⁶ and positive skin tests in certain subgroups of children.³⁷ However, a prospective study of children with a parental history of atopy monitored since birth found no associations between antibiotic use in the first year of life and asthma, recurrent wheezing, allergic rhinitis, or eczema at age 5 years.³⁴ In addition, studies have found that fevers before age 1 decrease the risk of allergic sensitization at age 6–7 years.⁹ Further, studies have found that childhood infections have a weak protective effect on asthma at

age 6–7 years in children who had not used antibiotics in the first year of life.³² Finally, a UK study found that early childhood use of antibiotics increased the risk of allergic rhinitis in atopic children.³⁸ That study used parental hay fever to identify children who are predisposed to atopic immune responses.

Although parental and clinician factors influence the decision to refer children to allergy clinics for skin testing, our findings that non-white race, maternal/family history of atopy, and male gender are independent atopy risk factors in the total sample of allergy patients are consistent with previous studies.^{35,36} The negative association between household smoking and atopy in allergy clinic patients with asthma may be attributable to higher prevalence of non-atopic asthma among children in smoking households. Children in smoking households are at increased risk of asthma symptoms and may be more likely to be referred to allergy clinics for skin testing.

The literature on breast feeding and atopy is sparse. The duration of breast feeding less than 6 months has

VACCINES, ANTIBIOTICS, AND ATOPY

Table 5. Adjusted atopy odds ratios for vaccine exposure variables

Comparison	Exposure variable	Model 1*		Model 2 [#]	
		Adj OR	95% CI	Adj OR	95% CI
All cases versus all controls 844 cases, 230 controls	Tot antigen doses	0.966	0.929–1.004	0.999	0.960–1.039
	No. of different antigens	0.785	0.687–0.898	0.887	0.774–1.017
	No. of pertussis doses	0.999	0.837–1.193	1.060	0.885–1.271
	No. of measles doses	0.753	0.501–1.132	0.848	0.557–1.291
	No. of OPV doses	1.057	0.889–1.255	1.015	0.848–1.216
	No. of HIB doses	0.796	0.707–0.897	0.933	0.808–1.077
	No. of HBV doses	0.885	0.704–1.113	1.145	0.882–1.487
All cases versus asthma controls 844 cases, 91 controls	Tot antigen doses	0.925	0.871–0.983	0.975	0.917–1.036
	No. of different antigens	0.702	0.563–0.875	0.873	0.706–1.080
	No. of pertussis doses	0.904	0.690–1.183	0.978	0.739–1.293
	No. of measles doses	0.662	0.359–1.220	0.802	0.420–1.533
	No. of OPV doses	1.006	0.782–1.294	0.935	0.710–1.231
	No. of HIB doses	0.721	0.617–0.842	0.880	0.726–1.066
	No. of HBV doses	0.769	0.580–1.020	1.044	0.754–1.445
Asthma cases versus asthma controls 413 cases, 91 controls	Tot antigen doses	0.924	0.869–0.983	0.967	0.907–1.031
	No. of different antigens	0.702	0.561–0.879	0.835	0.664–1.049
	No. of pertussis doses	0.876	0.655–1.171	0.954	0.707–1.286
	No. of measles doses	0.611	0.325–1.148	0.694	0.356–1.354
	No. of OPV doses	0.934	0.705–1.238	0.907	0.672–1.225
	No. of HIB doses	0.745	0.629–0.882	0.880	0.721–1.075
	No. of HBV doses	0.763	0.560–1.041	1.045	0.730–1.497

*Model 1 controls for age at skin test, gender, race, maternal/family history of atopy, low birth weight, maternal age at birth, breast feeding at 2 months, household smoking, dogs in home.

[#]Model 2 includes calendar period of skin test (1978–93, 1994–99, 2000–01) as an additional control.

been reported to increase the risk of atopic dermatitis among small-for-gestational-age babies at 3.5 years of age.³⁶ Breast feeding at 2 months, our only measure, was unassociated with atopy at ages 6–16 years in our total study population. We did not stratify on gestational age. We found that atopy risk decreased

with maternal age at birth and increased with child's age at skin testing, but this finding may be confounded by different thresholds for bringing children to allergy clinics for skin testing.

The hygiene hypothesis would appear to predict that atopy is negatively associated with low birth weight

Table 6. Adjusted atopy ratios for antibiotic exposure variables

Comparison	Exposure variable	Model 1*		Model 2 [#]	
		Adj OR	95% CI	Adj OR	95% CI
All cases versus all controls 844 cases, 230 controls	No. of Rx in 1st year	0.951	0.892–1.013	0.968	0.907–1.033
	No. of Rx in 2nd year	0.958	0.901–1.020	0.978	0.918–1.042
	No. of Rx in 1st 2 years	0.969	0.934–1.005	0.981	0.945–1.019
	Age at first Rx	1.024	0.990–1.060	1.018	0.983–1.054
	No. of Rx in 1st year	0.889	0.816–0.968	0.909	0.832–0.992
All cases versus asthma controls 844 cases, 91 controls	No. of Rx in 2nd year	0.880	0.810–0.956	0.896	0.823–0.976
	No. of Rx in 1st 2 years	0.918	0.873–0.965	0.930	0.883–0.980
	Age at first Rx	1.063	1.007–1.122	1.055	0.997–1.116
	No. of Rx in 1st year	0.919	0.838–1.009	0.930	0.845–1.024
	No. of Rx in 2nd year	0.906	0.827–0.992	0.914	0.832–1.004
Asthma cases versus asthma controls 413 cases, 91 controls	No. of Rx in 1st 2 years	0.937	0.887–0.990	0.944	0.893–0.999
	Age at first Rx	1.051	0.994–1.110	1.052	0.993–1.114

*Model 1 controls for age at skin test, gender, race, maternal/family history of atopy, low birth weight, maternal age at birth, breast feeding at 2 mos, household smoking, dogs in home.

[#]Model 2 includes calendar period of skin test (1978–93, 1994–99, 2000–01) as an additional control.

Table 7. Adjusted allergy diagnosis odds ratios (95%CI) for vaccine and antibiotic exposure variables, by atopy status

Status	Diagnosis	Vaccine exposure				Antibiotic exposure			
		Model 1*		Model 2#		Model 1		Model 2	
		Tot antigen doses	No. of different antigens	Tot antigen doses	No. of different antigens	Age at 1st use	No. of prescriptions	Age at 1st use	No. of prescriptions
Atopic	Asthma	Adj OR 95%CI	Adj OR 95%CI	Adj OR 95%CI	Adj OR 95%CI	Adj OR 95%CI	Adj OR 95%CI	Adj OR 95%CI	Adj OR 95%CI
		0.988	0.983	0.982	0.956	0.990	1.017	0.990	1.014
		0.954–1.023	0.884–1.094	0.947–1.017	0.854–1.070	0.960–1.021	0.979–1.056	0.960–1.021	0.975–1.054
		1.076	1.284	1.061	1.201	1.007	1.027	1.013	1.016
		0.998–1.161	1.004–1.643	0.983–1.145	0.935–1.543	0.953–1.064	0.957–1.102	0.958–1.071	0.945–1.092
	Eczema	1.026	1.112	1.022	1.099	1.001	1.016	1.002	1.013
		0.978–1.076	0.955–1.294	0.973–1.073	0.937–1.289	0.961–1.042	0.966–1.069	0.962–1.044	0.962–1.066
		1.008	0.988	1.003	0.965	0.960	1.034	0.962	1.032
		0.967–1.050	0.868–1.125	0.961–1.047	0.839–1.109	0.927–0.996	0.986–1.083	0.928–0.997	0.984–1.083
		1.013	1.012	0.990	0.941	0.943	1.071	0.949	1.062
Non-atopic	Asthma	0.932–1.102	0.769–1.331	0.906–1.082	0.709–1.249	0.878–1.013	0.996–1.151	0.883–1.020	0.987–1.143
		1.071	1.439	1.072	1.505	0.879	1.090	0.867	1.088
		0.909–1.262	0.785–2.639	0.903–1.272	0.752–3.012	0.753–1.026	0.970–1.224	0.736–1.022	0.966–1.225
	Eczema	0.998	1.046	0.978	0.973	0.950	1.095	0.945	1.097
		0.898–1.109	0.749–1.462	0.876–1.091	0.693–1.367	0.870–1.036	1.008–1.190	0.863–1.033	1.006–1.196
		1.003	0.937	1.024	0.979	0.992	1.046	0.988	1.063
	Allergic rhinitis	0.933–1.079	0.737–1.191	0.946–1.108	0.758–1.266	0.932–1.057	0.980–1.117	0.927–1.053	0.994–1.137

*Model 1 controlled for age at skin test, gender, race, maternal age at birth, low birth weight, breast feeding at 2 months, and household smoking.

#Models 2 included calendar period of birth (1970–80, 1981–86, 1987–95) as an additional control.

(LBW), since LBW is a known risk factor for childhood infections.^{39,40} The association was significant (OR = 0.33, CI: 0.13–0.85) among asthma patients but not among all allergy clinic patients (OR = 0.74, CI: 0.34–1.59).

Limitations

Our power to detect atopy effects of vaccine and antibiotic exposures was limited by the small number of controls relative to the number of atopy cases. Only 21% of allergy patients with skin tests were classified as non-atopic controls. Limited variation in vaccine exposure variables also reduced our power to detect atopy effects of vaccines. When calendar period of skin test was controlled, coefficients of variation ranged from 0.14 to 0.28 for total antigen doses; number of different antigens; and doses of specific vaccines, except for HIB and HBV. Coefficients of variation for HIB and HBV doses ranged from 0.8 to 7.0 and from 1.4 to 13.0, respectively. We had greater power to detect atopy effects of antibiotic exposures than vaccine exposures. Coefficients of variation of numbers of antibiotic prescriptions in the first and second years of life ranged from 0.94 to 1.37 and from 0.96 to 1.34, respectively, when calendar period of birth was controlled. Although study power was reduced by relatively small numbers of non-atopic controls and by limited variation in exposure measures, we controlled confounding by using allergy clinic patients and multiple control groups, and by adjusting odds ratios for known atopy risk factors and for secular trends in skin testing, diagnostic, and antibiotic dispensing practices.

Although the atopic status of some controls with incomplete skin prick testing may have been misclassified, the scope for misclassification was limited. Our results show that controls and cases did not differ much on the number of skin tests. Although the study population reflects the gender and racial distributions of the KPNW membership, the use of allergy clinic patients may limit the generalizability of our findings to all children.

Our analyses of new allergy diagnoses were limited to diagnoses made after the second birthday. We did not attempt to analyze time relationships between allergy diagnoses and vaccine and antibiotic exposures prior to the second birthday since prevalence is low (2% for allergic rhinitis, 5.5% for eczema/atopic dermatitis, and 8.4% for asthma) and onset dates are uncertain.

Although frequencies of antibiotic prescriptions are expected to be highly correlated with diagnosed infections, our hygiene hypothesis interpretation

would be stronger if we directly measured the association between infection frequency and atopy. We unfortunately did not have the considerable resources required to accomplish this. We attribute our finding of a weak negative association between age at first antibiotic prescription and risk of new allergic rhinitis diagnoses in atopic children to residual confounding by frequency of care encounters. We controlled for the duration of time during which new allergic conditions could be diagnoses (from the second birthday to the date of skin testing) but were unable to control for frequency of medical care encounters at which diagnoses could have been made. High use of antibiotics and younger age at first antibiotic prescription would be expected to be associated with high frequency of care encounters.

CONCLUSION

We conclude that early vaccine exposures do not appear to be associated with risk of developing atopy and that early vaccine exposures of atopic children do not appear to be associated with risk of allergy diagnoses. Consistent with the hygiene hypothesis, early antibiotic exposures appear to decrease risk of developing atopy. Finally, this study showed weak associations between antibiotic exposure measures and risk of allergy diagnoses, which were probably confounded by frequency of health care encounters.

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KEY POINTS

- Vaccine exposures during the first 2 years of life do not appear to be associated with risk of developing atopy.
- Antibiotic exposures during the first 2 years of life appear to decrease risk of developing atopy.
- Early exposures of atopic children to vaccines and antibiotics do not seem to affect the risk of allergy diagnoses.

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APPENDIX 1: ICD-9-CM CODES AND WRITTEN DIAGNOSES

Electronic medical record codes		Diagnoses from paper chart
Code	Codebook definition	Clinical terms used
Allergy diagnoses:		
	Asthma	
493.0	Extrinsic asthma	'Extrinsic asthma [with status asthmaticus]'
493.00A*	Asthma, exercise-induced	'Exercise-induced asthma'
493.1	Intrinsic asthma	'Intrinsic asthma [with status asthmaticus]'
		'viral triggered asthma,' 'nonallergic asthma'
493.2	Chronic obstructive asthma	'Asthmatic bronchitis'
493.9	Asthma—unspecified	'Asthma,' 'allergic asthma,' 'possible asthma,'
		'suspected asthma,' 'allergic bronchitis,'
		'RAD (reactive airway disease)'
493.90A*	Asthma—mild intermittent	'Mild intermittent asthma'
493.90B*	Asthma—mild persistent	'Mild persistent asthma'
493.90C*	Asthma—moderate persistent	'Moderate persistent asthma'
493.90D*	Asthma—severe persistent	'Moderate severe asthma'
493.90E*	Cough variant asthma	'Cough variant asthma'
	Allergic rhinitis	
477.0	Allergic rhinitis due to pollen	'Pollenosis,' 'pollen-induced rhinitis'
477.8	Allergic rhinitis due to other allergen	'Allergic rhinitis (NEC)'
477.9	Allergic rhinitis cause unspecified	'Allergies-[seasonal or perennial]' 'SAR,' 'PAR,'
		'hay fever,' 'allergic nose'
	Eczema/atopic dermatitis (specific)	
691.8	Other atopic dermatitis and related conditions	'Atopic dermatitis'
692.5	Dermatitis due to food in contact with skin	
692.9A*	Nummular dermatitis	'Nummular dermatitis'
693.8A*	Eczema-atopic	'Atopic eczema'
		'Atopic keratoconjunctivitis,' 'dyshidrotic eczema,'
		'keratosis pilaris'
	Nonspecific eczema/atopic dermatitis	
692.9	Contact dermatitis and other eczema, unspecified cause	'Dermatitis NOS,' 'Contact dermatitis NOS,'
		'Eczema NOS'
	Food allergy	
693.1B*	Dermatitis due to food	'Food allergies'
V15.0	Allergy other than to medicinal agents	
V15.01	Allergy to peanuts	'Allergy, peanuts'
V15.02	Allergy to milk products	'Allergy, milk products'
V15.03	Allergy to eggs	'Allergy, eggs'
V15.04	Allergy to seafood	'Allergy, seafood'
V15.15	Allergy to other foods	'Allergy, other foods'
Other diagnoses:		
	Rhinitis (nonallergic/chronic)	
472.0	Rhinitis-chronic	'Irritant rhinitis,' 'viral triggered rhinitis,' 'NARES,'
		'vasomotor rhinitis'
472.0A*	Rhinitis medicamentosa	
472.0B*	Rhinitis-non allergic	'[Chronic] nonallergic rhinitis'
472.0	Rhinitis-chronic	'Irritant rhinitis,' 'viral triggered rhinitis,' 'NARES,'
		'vasomotor rhinitis'
	Food intolerance	
271.3	Intestinal disaccharidase deficiencies and disaccharide malabsorption	'Lactose intolerance or malabsorption (congenital)'
271.3A*	Lactase deficiency, lactose intolerance	'Lactase deficiency,' 'lactose intolerance'
564.1	Irritable bowel syndrome	'Irritable bowel syndrome (IBS)'

Continues

APPENDIX 1: (Continued)

Electronic medical record codes		Diagnoses from paper chart
Code	Codebook definition	Clinical terms used
579.8	Other specified intestinal malabsorption Sinusitis	'Food intolerance, milk intolerance'
461.0	Acute sinusitis—maxillary	'Maxillary sinusitis'
461.1	Acute sinusitis—frontal	'Frontal sinusitis'
461.2	Acute sinusitis—ethmoidal	'Ethmoid sinusitis'
461.3	Acute sinusitis—sphenoidal	'Sphenoid sinusitis'
461.9	Acute sinusitis—unspecified	'Acute sinusitis'
473.0	Sinusitis—maxillary	'Maxillary sinusitis'
473.1	Sinusitis—frontal	'Frontal sinusitis'
473.2	Sinusitis—ethmoidal	'Ethmoid sinusitis'
473.3	Sinusitis—sphenoidal	'Sphenoid sinusitis'
473.8	Other chronic sinusitis	'Pansinusitis'
473.9	Unspecified sinusitis (chronic) Urticaria/angioedema	'[Chronic] sinusitis'
277.6	Other deficiencies of circulating enzymes	'Enzyme deficiency-circulating'
708.0	Allergic urticaria	'Allergic urticaria'
708.1	Idiopathic urticaria	'Idiopathic urticaria'
708.3	Dermatographic urticaria	'Dermatographic urticaria'
708.8	Other specified urticaria	'Chronic urticaria'
708.9	Urticaria, unspecified	'[Acute/chronic] hives,' '[Acute] urticaria'
995.1	Angioneurotic edema	'Angioedema'

*Special NW Kaiser Epic code.