Vaccination and Allergic Disease: A Birth Cohort Study

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Objectives. We examined the effect of vaccination for diphtheria; polio; pertussis and tetanus; or measles, mumps, and rubella on the incidence of physician-diagnosed asthma and eczema.

Methods. We used a previously established birth cohort in the West Midlands General Practice research database.

Results. We found an association between vaccination and the development of allergic disease; however, this association was present only among children with the fewest physician visits and can be explained by this factor.

Conclusions. Our data suggest that currently recommended routine vaccinations are not a risk factor for asthma or eczema. (*Am J Public Health.* 2004;94:985–989)

An unexplained increase in the prevalence of allergic disease has occurred in the developed world in the past few decades.[1] During the same period, there has been an increase in mass immunization, leading to the hypothesis that certain vaccines may increase the risk of allergic disease. There are 2 proposed mechanisms by which immunization may influence the development of allergic disease. The first is that vaccination could have a direct impact on the immune system, and there is evidence that pertussis vaccine enhances humans' response to histamine[2] and leads to raised immunoglobulin E levels.[3] The second potential mechanism is that vaccination reduces the burden of childhood illness. Children with more older siblings are at a reduced risk of developing atopy and allergic disease.[4] It has been suggested that exposure to infection in childhood reduces a child's risk of developing allergic disease; this is commonly known as the hygiene hypothesis.[5] In addition, there is also evidence that acceptance of vaccination is related to child birth order.[6–11] Evidence to date has both supported and refuted the association between vaccination and allergic disease.[12–23] It is clearly important to gain a detailed understanding of the relationship between vaccination and allergic disease, because a perception that vaccination is harmful may have an adverse impact on the effectiveness of immunization programs.[24]

METHODS

This study used 1988–1999 data from a birth cohort of children identified historically through the West Midlands General Practice Research Database. This database is derived from data collected as part of routine care and is the largest longitudinal primary care data set currently available. The methods we used to establish our cohort have been described in detail elsewhere,[25] and we have previously used these data to investigate the role of infection, antibiotics, and mode of delivery on the incidence of allergic disease.[26,27] Briefly, we identified children who were registered with their general practitioner (GP) (their primary care physician) within 3 months of birth and whose medical history contained at least 1 physician visit at any time, as an indicator that the child was using this GP for medical needs. We then extracted incident diagnoses of asthma/wheeze and eczema from the Oxford Medical Information System (which was derived from the *International Classification of Diseases, 8th Revision*[28]) and Read codes (hierarchical codes commonly used in GP practices in England) and all episodes of vaccination. In this data set there were insufficient data to examine the outcome of hay fever. Because the majority of vaccinations are given in combination, we examined the impact of groups of vaccines rather than individual vaccines, grouping exposures according to recommended administration. The current UK recommendations are that children be given diphtheria, polio, pertussis, and tetanus (DPPT) vaccination at 2, 3, and 4 months and measles, mumps, and rubella (MMR) vaccination between 12 and 15 months. We also extracted data on other vaccines, such as hepatitis B, bacille Calmette-Guérin, meningococcal vaccine, and *Haemophilus influenzae* type B, to allow us to perform an analysis of the impact of the total number of vaccines given. To examine the potential impact of ascertainment bias, we extracted the data on the number of GP consultations in 6-month periods from birth, excluding any consultations for vaccination or any allergic diseases.

Statistical Analysis

The impact of exposure to DPPT and MMR on the incidence of allergic disease was examined initially with Cox regression (Stata version 7.0, Stata Corp, College Station, Tex) as never having or ever having exposure and each of the models was examined to ensure that it satisfied the proportional hazards assumption. We calculated rates of disease from the end of the exposure period, which we defined arbitrarily as the age at which 95% of children had received their third injection of DPPT or, for MMR, the age at which 95% of children had received the first dose of MMR. This means that subjects diagnosed with an allergic disease or lost to follow-up before this time were excluded from the analyses. To examine the effect of the total number of vaccines on the incidence of allergic disease, we modeled the rate of disease from the same point as the MMR vaccine. We also performed an a priori subgroup analysis of the impact of MMR in children who had previously received the DPPT vaccine, to assess the impact of MMR in a population with no apparent bias against vaccination. To examine whether age at vaccination had an effect on the incidence of allergic disease, we divided children who were vaccinated for DPPT or MMR into quartiles by age at vaccination and modeled this variable as an ordered categorical variable. We then used multivariate analyses to determine the potential confounding effects of consulting frequency, parental smoking, parental allergic disease,

TABLE 1—Rate and Age at Onset of Disease After Immunizations: West Midlands, England, 1988–1999

	No. of Diagnoses	Total Person-Years	Rate[a]	Mean Age at Onset, y (Range)
Population for DPPT analyses				
Asthma (n = 23 483)	3814	77 922	4.89	2.12 (0.72–9.43)
Eczema (n = 21 489)	4559	68 026	6.70	1.93 (0.72–10.29)
Population for MMR analyses				
Asthma (n = 16 470)	1753	69 602	2.52	3.30 (1.75–9.43)
Eczema (n = 14 353)	1884	59 520	3.17	3.00 (1.75–10.29)

Note. DPPT = diphtheria, polio, pertussis, and tetanus vaccination; MMR = measles, mumps, and rubella vaccination.
[a]Per 100 person-years.

maternal age, number of older siblings, use of antibiotics early in life, year of birth, and GP practice. We also examined the data for effect modification where appropriate.

RESULTS

Our cohort contained 29 238 children aged between 0 and 11 years and had slightly more males (n = 14 597, 51%) than females.[25] The median age at vaccination for DPPT was 0.39 years (95% centile: 0.72) and for MMR was 1.17 years (95% centile: 1.75). A total of 27 701 (96%) children were recorded as having received DPPT, and 20 845 (71.3%) children were recorded as having received MMR vaccination. The characteristics of disease onset for each of the cohorts are described in Table 1.

Our univariate analysis showed that exposure to DPPT was associated with an increased risk of developing asthma (hazard ratio [HR] = 14.0; 95% confidence interval [CI] = 7.3, 26.9) and eczema (HR = 9.40; 95% CI = 5.92, 14.92) (Tables 2 and 3). However, these relations were dependent on consulting frequency: 83% of children not recorded as vaccinated were in the lowest quartile of consulting frequency for the first 6 months. When the analysis was stratified by consulting frequency, it became clear that there was a strong association between DPPT and asthma in the lowest quartile of consulting frequency, and that this association was reduced considerably in the next higher category of consulting frequency. We were unable to calculate an association in the highest 2 categories, because too few children in these categories were unvaccinated (Table 2). The effects showed a similar pattern for eczema, and here we had enough data to perform a test for interaction. We found a significant interaction between vaccination exposure and consulting frequency ($P < .001$) (Table 3).

For MMR, the univariate analysis showed a strong association between MMR vaccination and risk of asthma and eczema, but again this association was confined to children in the lowest category of consulting frequency (Tables 2 and 3). Examining the impact of MMR in only those children who also received the DPPT vaccine, we found no increase in the risk of developing asthma after adjusting for consulting frequency (adjusted HR = 1.42; 95% CI = 0.96, 2.11); for eczema, an association was limited to the lowest level of consulting frequency (HR = 4.62; 95% CI = 1.57, 15.4) and was no longer significant at higher consulting frequencies: 7 to 10 visits (HR = 0.92; 95% CI = 0.80, 4.65), 11 to 16 visits (HR = 2.27; 95% CI = 0.94, 5.49), or 16 or more visits (HR = 1.15; 95% CI = 0.89, 5.19).

There was no relation between the age at first injection of either DPPT or MMR and the risk of asthma or eczema. The total number of vaccines given also showed no association with the incidence of allergic disease. Exposure to vaccinations did not affect the strong birth-order effects seen within this cohort, and other than consulting frequency, no other covariates investigated—including parental smoking, parental allergic disease, maternal age, number of older siblings, use of antibiotics early in life, year of birth, and GP practice—confounded or modified the estimates of the vaccine effect.

DISCUSSION

In this observational study analyzing computerized primary care records, we found an association between MMR and DPPT vaccination and the incidence of asthma and eczema, but these associations appeared to be limited to the minority of children who rarely seek care from a GP. This limited association is more likely to be the result of bias than a biological effect.

The case definitions we used for this study were based on physician-diagnosed disease and thus were dependent on the child's being taken to the doctor and receiving a recorded diagnosis. We have shown this definition to be valid for a number of established risk factors for allergic disease, including parental smoking, parental allergic disease, and number of older siblings. However, when we examined the impact of vaccination, consulting frequency was a major consideration. Children who are not taken to the doctor are less likely to be vaccinated and also have less of an opportunity to have a diagnosis of allergic disease recorded. Our data are in keeping with the ascertainment bias, showing the impact of vaccination occurs only in children who rarely consult a physician.

There is inconsistent evidence for a relation between vaccination and the development of allergic disease. Because most children are vaccinated, and therefore do not develop allergic disease, it is difficult to obtain numbers adequate to examine the vaccination–allergic disease relationship, and unvaccinated children are a highly selected and probably atypical group. Such was found to be the case in a study conducted by Kemp et al.[12] that examined 1265 children born in 1977 and followed them with annual examinations. Only 23 children had not received routine vaccinations, and none of these children had recorded allergic diagnoses; the authors concluded that this finding was evidence for an association between allergic disease and vaccination, although their results showed no statistically significant relation. They also found that children who were not immunized tended to belong to lower social classes and be from minority backgrounds, which could have confounded their findings, especially because the information about disease was col-

TABLE 2—Effect of Vaccination With DPPT or MMR on Incidence of Asthma: Crude, Adjusted, and Stratified Results

	No. GP Consults	Vaccination Status	No. With Asthma	Person-Years	Hazard Ratio (95% Confidence Interval)
		DPPT			
Crude		Not vaccinated	9	2 487	1.00
		Vaccinated	3805	75 435	14.0 (7.3, 26.9)
Adjusted for consulting frequency		Not vaccinated	9	2 487	1.00
		Vaccinated	3805	75 435	10.33 (5.36, 19.91)
Stratified by consulting frequency in first 6 mo					
	0–3	Not vaccinated	7	2 256	1.00
		Vaccinated	829	23 450	11.5 (5.46, 24.20)
	4–6	Not vaccinated	2	168	1.00
		Vaccinated	1378	29 155	4.00 (1.00, 15.99)
	7–8	Not vaccinated	0	29	[a]
		Vaccinated	626	11 498	
	>8	Not vaccinated	0	34	
		Vaccinated	902	11 333	[a]
		MMR			
Crude		Not vaccinated	28	4 006	1.00
		Vaccinated	1725	65 597	3.51 (2.42, 5.11)
Adjusted for consulting frequency		Not vaccinated	28	4 006	1.00
		Vaccinated	1725	65 597	2.20 (1.50, 3.21)
Stratified by consulting frequency in first 18 mo					
	0–6	Not vaccinated	5	2 843	1.00
		Vaccinated	165	12 462	7.18 (2.95, 17.49)
	7–10	Not vaccinated	7	425	1.00
		Vaccinated	351	17 522	0.95 (0.45, 2.01)
	11–16	Not vaccinated	8	452	1.00
		Vaccinated	601	20 693	1.36 (0.68, 2.73)
	>16	Not vaccinated	8	286	1.00
		Vaccinated	608	14 920	1.21 (0.60, 2.43)

Note. DPPT = diphtheria, polio, pertussis, and tetanus vaccination; MMR = measles, mumps, and rubella vaccination; GP = general practitioner.
[a]Insufficient data to calculate hazard ratio.

lected from medical diary cards given to the mother to complete.

In a study that was similar in design to ours, Farooqui and Hopkin[13] collected data from 1934 individuals in an Oxfordshire general practice and found a weak positive association between exposure to pertussis vaccination and the development of allergic disease (odds ratio [OR]=1.76; 95% CI=1.39, 2.23), even after adjustment for the number of visits to the family doctor in early childhood. In our study, the relationship remained significant after we controlled for consulting frequency; it was not until the relation was stratified according to consulting frequency that we discovered the full extent of the bias involved in this relation. The study by Farooqui and Hopkin also found no association between measles vaccination and the development of allergic disease.

A cross-sectional study conducted by Alm et al.[14] of 2 anthroposophic schools (also called Steiner or Waldorf schools, offering a curriculum emphasizing human development) demonstrated a positive association between measles vaccination and allergic disease. These investigators found that children who were not immunized to MMR had a decreased risk of allergen skin sensitization (OR=0.67; 95% CI=0.46, 0.99). Other factors of the anthroposophic lifestyle reduced the risk of developing allergic disease, and the authors admitted that because of strong correlations among variables associated with this lifestyle, they were unable to determine the independent effects of the various exposures; thus, the relation that was shown could have owed to an aspect of the anthroposophic lifestyle that was not studied.

In a letter to the *Journal of the American Medical Association,* Odent et al.[15] presented results from a cross-sectional study that suggested that immunized children were more likely to develop asthma (risk ratio=5.43; 95% CI=1.93, 15.30). The authors were unable to find confounding factors to explain this finding, though little detail was given about the study design and the types of confounders investigated. In light of our results, many of the positive findings of previously published studies could be explained by ascertainment bias.

Among the studies that have found no association between immunization and allergic disease, ecological studies have been unable to explain between-country differences in the prevalence of allergic disease by differences in immunization rates[16]; 1 study could not account for the increase in wheezing in children in Leicestershire between 1990 and 1998 by changes in vaccination rates.[17] In a recent analysis of the third National Health and Nutrition Survey in the United States, Hurwitz and Morgenstern[18] examined the effect of DPPT on up to 12 different allergic outcomes and in general found no association between vaccination and allergic disease. Two case–control studies of asthma/wheezing found no significant associations between disease and administration of different types of vaccines after adjustment for potential confounders.[19,20] In a large prospective study, no relationship was shown between administration of the pertussis vaccination and development of allergic disease.[21] The strongest evidence against such an association is from the Swedish Pertussis Vaccine Efficacy Trial 1, a double-blinded

TABLE 3—Effect of Vaccination With DPPT or MMR on Incidence of Eczema: Crude, Adjusted, and Stratified Results

	No. GP Consults	Vaccination Status	No. With Eczema	Person-Years	Hazard Ratio (95% Confidence Interval)
		DPPT			
Crude		Not vaccinated	18	2 434	1.00
		Vaccinated	4541	65 592	9.40 (5.92, 14.92)
Adjusted for consulting frequency		Not vaccinated	18	2 434	1.00
		Vaccinated	4541	65 592	7.51 (5.27, 10.70)
Stratified by consulting frequency in first 6 mo					
	0–3	Not vaccinated	8	2 228	1.00
		Vaccinated	1134	20 180	15.80 (7.88, 31.7)
	4–6	Not vaccinated	6	146	1.00
		Vaccinated	1692	25 242	1.67 (0.75, 3.71)
	7–8	Not vaccinated	1	32	1.00
		Vaccinated	761	9 888	2.61 (0.37, 18.5)
	>8	Not vaccinated	3	28	1.00
		Vaccinated	954	10 281	0.91 (0.30, 2.82)
		MMR			
Crude		Not vaccinated	27	3 868	1.00
		Vaccinated	1857	55 651	4.61 (3.15, 6.74)
Adjusted for consulting frequency		Not vaccinated	27	3 868	1.00
		Vaccinated	1857	55 651	3.50 (2.38, 5.15)
Stratified by consulting frequency in first 18 mo					
	0–6	Not vaccinated	6	2 768	1.00
		Vaccinated	244	10 625	10.4 (4.61, 23.29)
	7–10	Not vaccinated	7	402	1.00
		Vaccinated	457	14 293	1.57 (0.75, 3.32)
	11–16	Not vaccinated	9	400	1.00
		Vaccinated	601	17 427	1.36 (0.71, 2.64)
	>16	Not vaccinated	5	297	1.00
		Vaccinated	555	13 306	2.21 (0.92, 5.33)

Note. DPPT = diphtheria, polio, pertussis, and tetanus vaccination; MMR = measles, mumps, and rubella vaccination; GP = general practitioner.

trial of 9289 children; no associations were found between vaccination to pertussis and development of wheezing, eczema, or hay fever.[22,23]

In summary, although our results in an observational cohort study demonstrated a positive association between vaccination and allergic disease, this association can be explained by ascertainment bias. These data, together with other published evidence, suggest that current vaccination practices do not have an adverse effect on the incidence of allergic disease. ■

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This article was accepted March 6, 2003.

Contributors

C. Smith was responsible for the retrieval and management of data and preparation of the article. T. McKeever was involved in the design of the study, conducted the statistical analyses, and prepared successive drafts of the article. S. Lewis and R. Hubbard were involved in the design of the study and provided overall supervision of the analyses and preparation of this article.

Acknowledgments

We are grateful to the Department of Medicines Management, Keele University, for providing access to the West Midlands General Practice Research Database for use in this project.

Human Participant Protection

The study protocol was reviewed and approved by the General Practice Research Database ethics committee (scientific and ethical advisory board).

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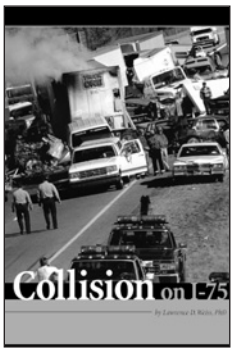
Subject codes 7, 12, 17, 56, 83



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