

Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma

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Background: Early childhood immunizations have been viewed as promoters of asthma development by stimulating a T_H2-type immune response or decreasing microbial pressure, which shifts the balance between T_H1 and T_H2 immunity.

Objective: Differing time schedules for childhood immunizations may explain the discrepant findings of an association with asthma reported in observational studies. This research was undertaken to determine whether timing of diphtheria, pertussis, tetanus (DPT) immunization has an effect on the development of childhood asthma by age 7 years.

Methods: This was a retrospective longitudinal study of a cohort of children born in Manitoba in 1995. The complete immunization and health care records of cohort children from birth until age 7 years were available for analysis. The adjusted odds ratio for asthma at age 7 years according to timing of DPT immunization was computed from multivariable logistic regression.

Results: Among 11,531 children who received at least 4 doses of DPT, the risk of asthma was reduced to ½ in children whose first dose of DPT was delayed by more than 2 months. The likelihood of asthma in children with delays in all 3 doses was 0.39 (95% CI, 0.18-0.86).

Conclusion: We found a negative association between delay in administration of the first dose of whole-cell DPT immunization in childhood and the development of asthma; the association was greater with delays in all of the first 3 doses. The mechanism for this phenomenon requires further research. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: DPT combination vaccine, childhood asthma, retrospective birth cohort, administrative health data

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Supported by the Canadian Institutes of Health Research. K.L.M. received studentships from the Western Regional Training Center and the National Training Program for Allergy and Asthma. A.L.K. and L.M.L. are Canadian Institutes of Health Research New Investigators.

Disclosure of potential conflict of interest: K. L. McDonald has received research support from Western Regional Training Center and the National Training Program for Allergy and Asthma. A. B. Becker has received research support from the Canadian Institutes of Health Research, Allergan, and Novartis. The rest of the authors have declared that they have no conflict of interest.

Received for publication September 22, 2006; revised November 11, 2007; accepted for publication November 13, 2007.

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0091-6749/\$34.00

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doi:10.1016/j.jaci.2007.11.034

Abbreviations used

DaPT: Diphtheria, acellular pertussis, tetanus
 DPT: Diphtheria, pertussis, tetanus
 ICD-9: International Classification of Diseases, Ninth Revision
 MIMS: Manitoba Immunization Monitoring System
 MHSP: Manitoba Health Services Insurance Program
 OR: Odds ratio

Childhood asthma is one of the most common childhood diseases in the developed world. The rising prevalence of asthma in many industrialized countries over the last quarter century has occurred alongside improvements in hygienic standards. The hygiene hypothesis postulates that growing up in a more hygienic environment with less microbial exposure may enhance atopic (T_H2) immune responses, whereas microbial exposure would drive the response of the immune system—which is skewed in the atopic T_H2 direction during fetal life—toward a balanced T_H1 and T_H2 immunity. In this context, many early childhood vaccinations have been viewed as promoters of asthma development, directly by stimulating a T_H2-type immune response, or indirectly by decreasing the microbial pressure; both effects would shift the cytokine balance away from T_H1 and T_H2 immunity.^{1,2} What is the evidence that early childhood immunizations promote the development of asthma? An IgE response to vaccine antigens is commonly detectable in the sera of children vaccinated with diphtheria/tetanus, and the IgE response to vaccine antigens is more pronounced among atopic individuals.^{3,4}

The epidemiologic evidence linking diphtheria, pertussis, tetanus (DPT) immunizations to childhood asthma or atopy is mixed, with studies showing an increased⁴⁻⁹ or decreased risk¹⁰⁻¹² of developing asthma, or no association.¹³⁻¹⁹ These studies have primarily addressed the question of whether asthma is more likely to develop in vaccinated versus unvaccinated children. As most children are vaccinated, it is difficult to obtain numbers adequate to examine the vaccination-asthma relationship, and unvaccinated children are usually a highly selected and atypical group.^{20,21}

Recent evidence indicates that the association with childhood asthma is dependent on the timing of exposure to microbes.²² Different schedules for immunization may explain the discrepant findings of an association with asthma reported in observational studies of vaccinated children. This research was undertaken to determine whether timing of DPT vaccination has an influence on the development of childhood asthma by age 7 years.

METHODS

This was a retrospective longitudinal study of a cohort of children who were born in Manitoba in 1995 and remained in Manitoba until at least age 7 years

(13,980 children). The complete immunization and health care records of cohort children from birth until age 7 were available for analysis. Immunization data were obtained from the Manitoba Immunization Monitoring System (MIMS).

Manitoba Immunization Monitoring System data are collected from (1) physician billing claims, (2) the manual entry of immunization record forms completed by public health nurses, and (3) hospital departments for immunizations that are not billed by physicians. Immunization tariff codes from the billing claims are entered into the children's records. MIMS monitors each record at set intervals (1 year, 2 year, and 6 years of age) to identify which children are behind in their immunization schedules. When this is detected, a letter reminding the child's health care provider of their missed immunizations is mailed out. When children turn 5½ years of age, their parents or legal guardians receive a notification letter of all the immunizations the child should have received and then states the ones that were either missed or MIMS has no record of the child receiving.²³

Health care records included physician visits, hospitalizations, and prescription drugs collected by the Manitoba Health Services Insurance Program (MHSIP) in the provision of universal health insurance to Manitoba residents. Records of physician reimbursement for medical care provided are submitted under a fee-for-service arrangement and contain information on patient diagnosis at the 3-digit level of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) classification system. Discharge abstracts for hospital services include information on as many as 16 ICD-9-CM diagnostic codes, of which the first diagnosis is the primary diagnosis that is most responsible for the hospital stay. Prescription records submitted by retail pharmacies contain data on the date of prescription dispensing, drug name and identification number, dosage form, and quantity dispensed. The MHSIP databases are reliable and valid data sources for describing health care contact for specific conditions and prescriptions dispensed.^{24,25} Linkage among databases is achieved by the use of anonymized personal identifiers. A family registration number present in the MHSIP registry permits linkage of health care data of children with the data of parents and siblings.

The prevalence of asthma in the cohort was identified from health care administrative records. More specifically, a child was defined as an asthma patient if he or she had 1 or more physician visits with an asthma diagnosis code (ICD-9-CM 493), 1 or more hospitalizations with an asthma diagnosis code (ICD-9-CM 493), or at least 1 prescription for any asthma drug (inhaled/oral β -agonists, inhaled corticosteroids or cromones or leukotriene receptor antagonists) in the year preceding his or her seventh birthday. This asthma definition was chosen on the basis of a validation study conducted in a subset of children recruited for clinical assessment by an allergist as part of a nested case-control study.^{26,27} Several health care database definitions of asthma were compared to the gold standard of allergist diagnosis of asthma based on symptoms and history. The positive predictive value of this definition was 88% (95% CI, 77% to 95%), and the specificity was 81% (95% CI, 64% to 92%).

The exposure measure was time of administration of DPT immunizations. It was categorized by months from birth for each dose according to the Manitoba childhood immunization schedule (within 2 days after the recommended period) as follows: first dose (2 months [62 days] or less, between 2 and 3 months [63 to 93 days], between 3 and 4 months [94 to 124 days], and greater than 4 months [125 days or more]); second dose (4 months [124 days] or less, between 4 and 5 months [125 to 155 days], between 5 and 6 months [156 to 186 days], and greater than 6 months [187 days or more]); third dose (6 months [186 days] or less, between 6 and 7 months [187 to 217 days], between 7 and 8 months [218 to 248 days], and greater than 8 months [249 and more]); and fourth dose (18 months [558 days] or less, between 18 and 24 months [559 to 744 days], and greater than 24 months [745 days and over]).

Measures of risk or protective factors for asthma were also derived from health care administrative records.²⁷ These included sex, number of siblings, urban or rural residence, neighborhood income group, number of antibiotic prescriptions (0, 1-2, 3-4, and 5 or more courses), total number of physician visits during the first year of life, and maternal history of asthma (at least 1 physician visit or hospitalization for asthma [ICD-9-CM 493] or 1 prescription for an asthma drug during the birth year). A neighborhood income measure was derived from Statistics Canada Census 1996 public use files. Children were

placed into income quintiles and according to the postal code of residence at birth. These quintiles were derived separately for urban and rural residents.

Multivariable logistic regression models were used to compute the adjusted odds ratio (OR) for asthma at age 7 years according to timing of DPT immunization. Separate models were defined for each DPT dose, with the following periods defined as the reference categories to denote on time administration of dose (within 2 days of the Manitoba childhood immunization schedule): 2 months for the first dose, 4 months for the second dose, 6 months for the third dose, and 18 months for the fourth dose. A sensitivity analysis was conducted by rerunning models after the recategorization of the DPT administration time variable by adding 7 days instead of 2 days to the intervals. All of the models were adjusted for sex, urban/rural location, income quintile, number of siblings, number of antibiotic prescriptions, the number of health care visits during the first year, and maternal history of asthma. Variables were retained in the models at $P < .05$. All of the variables in the model were also tested for collinearity. SAS software (SAS Institute, Cary, NC) was used for all analysis.

This study received approval from both the University of Manitoba Human Research Ethics Committee and Manitoba Health's Health Information Privacy Committee.

RESULTS

Thirty children were excluded from the analysis because they had physician visits for asthma diagnoses before their first immunization. Of the remaining 13,950 children, 11,531 children (82.6%) received at least 4 doses of DPT. These children were primarily immunized with whole-cell pertussis DPT, because the diphtheria, acellular pertussis, tetanus (DaPT) vaccine was phased in throughout the province beginning in November 1997. There were 12,105 children in the 1995 cohort who were immunized with 1 or more doses of DaPT, although the majority of the cohort (80.2%) received only 1 dose of DaPT, typically their fifth dose.

The medical, hospital, prescription, and immunization records of 11,531 children receiving 4 or more doses of DPT were analyzed. The prevalence of asthma among these children was 11.7%. Children with asthma were predominately male (3:2) and lived in urban areas (70.3%). Approximately 25% of children with asthma were from low-income homes. Of the children with asthma, 10.1% had mothers with a history of asthma, whereas 4.7% of the children without asthma had mothers with a maternal history of asthma. Children with more siblings were less likely to develop asthma (children with no siblings had an asthma rate of 15.4%, children with 2 siblings had an asthma rate of 10.4%, and children with 4 siblings had an asthma rate of 8.0%).

There were 4978 children who were immunized with their first dose of DPT by 62 days after birth, of whom 685 developed asthma (13.8%) (Table I). Many of the children were immunized after 62 days following birth, but before 93 days after birth ($n = 5$; 965 children), of whom 614 or 10.3% developed asthma. Only 417 and 171 children had their first dose by 124 days and more than 4 months, respectively. Asthma prevalence rates decreased successively from 13.8% to 5.9% with each month delay in DPT administration.

The adjusted ORs for asthma according to timing of DPT dose are listed in Table II. Children who received their first, second, third, and fourth doses of DPT according to schedule (2, 4, 6, and 18 months after birth) constituted the reference categories for the other groups. Children who were delayed by as long as 1 month in their first dose of DPT were significantly less likely to develop asthma compared with children who received their first dose of DPT by 62 days after birth (OR, 0.84; 95% CI, 0.75-0.95). The likelihood of asthma at age 7 years was halved in children

who received their first dose of DPT at more than 4 months after birth (OR, 0.50; 95% CI, 0.25-0.97). Forty-three children received their first dose before 6 weeks and 1215 children received their first dose before 58 days, before the 6-week to 8-week period recommended by the World Health Organization.²⁸ There was no difference in the likelihood of asthma between children receiving early doses (OR, 1.60; 95% CI, 0.55-4.61 for <45 days; and OR, 1.18; 95% CI, 0.97-1.44 for <58 days) and children receiving their first dose on schedule between 45 and 62 days, providing justification for grouping them together. On switching the reference group in Table II from on time to early administration (<8 weeks), a 2-month or greater delay in the first dose was associated with a similar reduction of asthma risk (OR, 0.56; 95% CI, 0.28-1.11). However, this reduced the sample size of the reference group, and findings were no longer significant.

There were 4238 children who received their second dose of DPT by 124 days (4 months), 5909 children who received their second dose between 4 and 5 months after birth, 839 children who received their second dose between 5 and 6 months, and 545 children who received their second dose more than 6 months after birth (Table I). Children who received their second dose according to schedule had asthma rates of 13.5%, and these rates declined successively with each delay in DPT administration to 6.8%. Only children with the greatest delay in administration of the second DPT dose had an adjusted OR that was statistically significant (Table II). They were 59% as likely to have asthma in comparison with children who were immunized with their second dose of DPT by 4 months after birth.

There were 3799 children who received their third dose of DPT by 6 months after birth, of whom 506 developed asthma (13.3%; Table I). More children were immunized between 6 to 7 months after birth (5383), of whom 615 developed asthma (11.4%). There were also 1162 children who were immunized with their third dose of DPT between 7 and 8 months after birth and 1187 who were immunized with their third dose of DPT after this period. These children had asthma rates of 11.0% and 8.3% respectively. In comparison with children who were immunized with their third dose of DPT by 6 months after birth, the likelihood of asthma was significantly reduced (OR, 0.73; 95% CI, 0.58-0.94) only in children who received their third DPT immunization after 8 months following birth (Table II).

Finally, there were 1785 children who were immunized with their fourth dose of DPT by 18 months after birth, of whom 246 developed asthma (13.8%; Table I). The majority of cohort children (n = 8935) were immunized with their fourth dose of DPT between 18 and 24 months after birth. These children had an asthma prevalence rate of 11.4%. Among the 811 children who were immunized with their fourth dose of DPT after 24 months following birth, 82 of them developed asthma (10.1%). None of the adjusted ORs were statistically significant (Table II).

The sensitivity analysis, which involved extending the intervals for DPT administration to 7 days postschedule, yielded similar findings. More than 2-month delays in the administration of DPT doses resulted in the following reduced risk for asthma: OR, 0.41, 95% CI, 0.19-0.90 for the first dose; OR, 0.56, 95% CI, 0.37-0.83 for the second dose; and OR, 0.75, 95% CI, 0.59-0.95 for the third dose. This reduction in asthma risk was of greater magnitude than for the ORs obtained by using the 2-day postschedule allowance.

Among children with greater than a 2-month delay in receiving the first dose, 88% experienced the same delay in the second dose, and 86% had delays in all 3 doses. The percent of children with

TABLE I. Number of children by months after birth in which they received their doses of DPT and the corresponding asthma rates

	Total no. of children	No. with asthma	Asthma rate (%)
First DPT dose			
2 Mo after birth	4978	685	13.8
3 Mo after birth	5965	614	10.3
4 Mo after birth	417	38	9.1
More than 4 mo after birth	171	10	5.9
Second DPT dose			
4 Mo after birth	4238	570	13.5
5 Mo after birth	5909	661	11.2
6 Mo after birth	839	79	9.4
More than 6 mo after birth	545	37	6.8
Third DPT dose			
6 Mo after birth	3799	506	13.3
7 Mo after birth	5383	615	11.4
8 Mo after birth	1162	128	11.0
More than 8 mo after birth	1187	98	8.3
Fourth DPT dose			
18 Mo after birth	1785	246	13.8
24 Mo after birth	8935	1019	11.4
More than 24 mo after birth	811	82	10.1
Total	11,531	1347	11.7

asthma in the latter group was 5%, in comparison with 12% in the remainder of the cohort. The likelihood of asthma among children with greater than 2-month delays in all 3 doses of DPT was 0.39 (95% CI, 0.18-0.86). Reductions in asthma likelihood subsequent to greater than 2-month delays in the administration of the second and third doses were observed in children who had received the first dose on schedule (Table III). However, these reductions were not statistically significant.

DISCUSSION

In a complete birth cohort of 11,531 children who were immunized with at least 4 doses of DPT, we have uncovered an association between timing of DPT administration and onset of asthma at age 7 years. Delayed administration of the first dose of DPT of more than 2 months from the recommended 2-month period was associated with a reduced risk of childhood asthma by 50%. Sensitivity analyses that varied the interval for DPT immunization demonstrated that our findings are robust. Very few studies have published on the timing of childhood immunizations and childhood asthma. Bremner et al²⁹ documented a reduced risk for hay fever among children with delayed completion of the third DPT vaccination. On the other hand, McKeever et al⁶ did not find an association between asthma onset and age at first injection of diphtheria, polio, pertussis, and tetanus vaccine in their database study of 29,000 children. To our knowledge, we are the first to report that delay in administration of the first dose of DPT immunization is significantly associated with a reduced risk of developing asthma in childhood.

We also found a decreased likelihood of childhood asthma after delays in the administration of the second and third doses of DPT. Consistent with immunization guidelines, the majority of these delays were in children with delays in their first dose. Our data indicate that the reduction in asthma risk for the second and third doses was primarily a result of the delay in the first dose, because no statistically significant differences in asthma risk were seen

TABLE II. Adjusted* ORs (OR, 95% CI) for asthma at age 7 years by month of DPT dose administration (n = 11,531)

Months after birth	DPT dose							
	1		2		3		4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
2	Reference†							
3	0.84	0.75-0.95						
4	0.81	0.56-1.16	Reference†					
5	0.50	0.25-0.97	0.93	0.82-1.06				
6			0.90	0.69-1.17	Reference†			
7			0.59	0.41-0.85	0.95	0.83-1.08		
8					1.04	0.83-1.29		
9					0.74	0.58-0.94		
10								
11								
12								
18							Reference†	
24							0.92	0.78-1.07
More than 24							0.91	0.69-1.20

*Adjusted for sex, maternal history asthma, urban/rural location, household income, number of siblings, number of courses of antibiotics, and number of health care visits.

†Reference groups are children receiving DPT doses according to schedule.

TABLE III. Adjusted* ORs (OR, 95% CI) for asthma at age 7 years by month of DPT administration for dose 2 and dose 3 in children receiving dose 1 on schedule (n = 11,360)

Months after birth	DPT dose			
	2		3	
	OR	95% CI	OR	95% CI
4	Reference			
5	0.94	0.83-1.06		
6	0.90	0.69-1.17	Reference	
7	0.68	0.45-1.01	0.95	0.83-1.08
8			1.06	0.85-1.32
9			0.79	0.62-1.02

*Adjusted for sex, maternal history asthma, urban/rural location, household income, number of siblings, number of courses of antibiotics, and number of health care visits.

with delays in the second and third doses in the absence of delays in the first dose. However, among children with delays in all 3 doses, the likelihood of asthma was further reduced to 60%.

The majority of studies investigating the effect of vaccination on the development of asthma have compared vaccinated and unvaccinated children. Because unvaccinated children have environmental exposures that may protect against asthma in known and unknown ways,³⁰ the strength of our study is that the comparison group consisted of children vaccinated with at least 4 doses of DPT. Having said this, children with delayed DPT immunization may differ from other children in several ways. Some of the previous vaccine-asthma associations have been explained by ascertainment bias,⁶ whereby asthma has been reported to be less prevalent in unvaccinated children with a low frequency of physician visits. Similarly, even among vaccinated children, it is possible that families who consult their general practitioner less often would be less likely to attend for routine vaccination on time, and less likely to present their child with asthma symptoms.³¹ In addition, children from larger families are less likely to complete their vaccinations on time, and having a greater number of older or younger siblings is strongly protective of asthma.³² Low family socioeconomic status is another risk factor for delayed childhood vaccinations that has been associated with childhood asthma.³³ To address these 3

potential sources of bias, analyses were adjusted for the frequency of health care contact, the number of siblings, and income quintile. These adjustments had no effect on our findings. The association between delayed administration of vaccination and decreased onset of asthma was independent of these factors.

One of the main reasons for delayed immunization is the presence of fever or an infection in the child.³¹⁻³⁴ Fever during the first year of life has been shown to decrease the likelihood of childhood asthma and atopy.²² Attendance at day care, especially during the first 6 months of life, causes more frequent infections, but protects against asthma at age 6 years.³⁵ Bremner et al²⁹ proposed that delay in immunization because of current infection was the most plausible explanation for their findings of an association with decreased risk of hay fever. However, their analysis of the monthly infection rate did not show a graded relation with vaccination delay. In our analysis, the OR was adjusted for the number of antibiotic prescriptions, which are excellent proxy measures for respiratory tract infections.³⁶ Further, we are certain of the integrity of the MIMS database, and we have used a database definition for childhood asthma that has been validated by pediatric allergist assessment in a subset of children.

Whole-cell pertussis DPT is no longer used in many countries, but our study generates some interesting hypotheses for the biological mechanisms behind early childhood vaccination and the development of asthma. The acellular pertussis vaccine was developed because of high rates of adverse reactions for the whole-cell vaccine, such as neurological disorders and high fever.^{37,38} Fevers result from the release of inflammatory cytokines by cells involved in the innate immunity response to infections and have been proposed as markers for the intensity of innate immune system stimulation and early skewing toward the T_H1 phenotype during infancy.³⁹ At birth, the newborn immune system has a limited ability to produce T_H1 cytokines, but levels increase over the period of the next 6 months.^{40,41} Similar to the fever-asthma association reported by Williams et al,²² a high fever response elicited by the cellular pertussis vaccine in later infancy potentially has a greater effect in stimulating the innate immune response than a fever response in early infancy. An alternate interpretation of our findings is that vaccine stimulation of IgE levels at a later time during infancy, when the T_H1 immune system gains

more prominence, may have little effect in promoting T_H2 skewing.⁴² Our study would need to be repeated in a later birth cohort to assess the effect of the acellular pertussis vaccine because the DaPT vaccine has been found to be less reactogenic, with a lower incidence of adverse events.³⁴

It is premature to make recommendations until these findings have been confirmed with the DaPT vaccine, and the benefits of altering immunization schedules need to be weighed against the risks. North American childhood immunization schedules, which normally include 2-month, 4-month, and 6-month intervals, were introduced in the 1950s to increase overall immunization rates. The rationale for continuing to use this schedule is to provide protection in early infancy as quickly as possible to the greatest number of infants.²⁸ However, immunization schedules vary by country subsequent to differences in infectious disease prevalence, public demand, and the level of health care. The childhood immunization schedule in Japan recommends that children be immunized with 3 doses of DaPT between 6 to 9 months after birth; first doses can be given no earlier than 3 months.⁴³ It is interesting to note that between 1975 and 1988, Japan did not recommend immunizing children under 2 years of age.³⁸ In 1982, Japan's asthma prevalence rate in children was approximately 3.2%, and by 2002 it was 6.5%. Although these statistics represent a doubling of asthma over a period of 20 years, these prevalence rates are well below those seen in North America.⁴⁴ However, the administration of pertussis vaccine in Japan to children after 2 years of age resulted in higher rates of pertussis than in children given the vaccine at an earlier time.^{38,45}

Asthma in children is a significant contributor to morbidity and health care costs.⁴⁶⁻⁴⁸ Our study offers hypotheses regarding the timing of immunization and the development of this common childhood disease. Although we believe that antibiotic use is a sufficient adjustment for existing infection, further analyses are required to refute the issue of early-life infections as an explanation for the association between delayed immunization and protection against the development of asthma. For example, children hospitalized for respiratory syncytial virus are more likely to have delayed pertussis immunization, yet respiratory syncytial virus is associated with an increased risk of asthma.⁴⁹ Moreover, further study is vital to gain a detailed understanding of the relationship between vaccination and allergic disease, because a perception that vaccination is harmful may have an adverse effect on the effectiveness of immunization programs.

This research was conducted by using the Population Health Research Data Repository at the Manitoba Centre for Health Policy, Winnipeg, Canada. The results and conclusions are our own, and no official endorsement by Manitoba Health is intended or should be inferred. We acknowledge the computer analysis support of Matthew Dahl.

Clinical implications: These findings suggest a protective role for vaccine-induced fever response in early life in the development of childhood asthma but need to be confirmed with further studies of acellular DPT combination vaccines.

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