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Childhood vaccinations and risk of asthma

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Background. **A few previous studies have suggested that childhood vaccines, particularly whole cell pertussis vaccine, may increase the risk of asthma. We evaluated the suggested association between childhood vaccinations and risk of asthma.**

Methods. **Cohort study involving 167 240 children who were enrolled in 4 large health maintenance organizations during 1991 to 1997, with follow-up from birth until at least 18 months to a maximum of 6 years of age. Vaccinations were ascertained through computerized immunization tracking systems, and onset of asthma was identified through computerized data on medical care encounters and medication dispensings.**

Results. **In the study 18 407 children (11.0%) developed asthma, with a median age at onset of 11 months. The relative risks (95% confidence intervals) of asthma were: 0.92 (0.83 to 1.02) for diphtheria, tetanus and whole cell pertussis vaccine; 1.09 (0.9 to 1.23) for oral polio vaccine; 0.97 (0.91 to 1.04) for measles, mumps and rubella (MMR) vaccine; 1.18 (1.02 to 1.36) for *Haemophilus influenzae* type b (Hib); and 1.20 (1.13 to 1.27) for hepatitis B vaccine. The Hib result was not consistent across health maintenance organizations. In a subanalysis restricted to children who had at least 2 medical care encounters during their first year, the relative risks decreased to 1.07 (0.71 to 1.60) for Hib and 1.09 (0.88 to 1.34) for hepatitis B vaccine.**

Conclusion. **There is no association between diphtheria, tetanus and whole cell pertussis vaccine, oral polio vaccine or measles, mumps and rubella vaccine and the risk of asthma. The weak associations for Hib and hepatitis B vaccines seem to be at least partially accounted for by health care utilization or information bias.**

INTRODUCTION

Asthma is the most common chronic disease of childhood in developed countries, and its prevalence has been increasing.[1, 2] It has been suggested that infant and childhood vaccinations may be contributing to the increasing prevalence of asthma.[3–6] The strongest evidence in support of a possible association between vaccination and asthma comes from a prospective study of a cohort of children born in 1977 in Christchurch, New Zealand.[4] In that study there was no evidence of asthma after 5 to 10 years of follow-up among 23 children who received neither pertussis nor oral polio vaccine, whereas asthma developed in >20% of 1184 children who had been vaccinated. A study of 1934 patients followed from birth to age 12 in a general medical practice in the UK found an ~1.4-fold increased risk of asthma associated with whole cell pertussis vaccination.[7] An association between pertussis vaccination and asthma was also reported in two cross-sectional surveys.[5, 8] No association was found, however, in a Swedish clinical trial involving 669 children.[9]

There are theoretical reasons to suspect a possible association of asthma with vaccination. One possible mechanism is that vaccines or their adjuvants may have direct IgE-potentiating effects.[10–13] Another possibility is that vaccination may shift the immunologic balance toward a more allergenic response.[14] It has also been suggested that vaccination may indirectly affect the tendency to develop allergies and perhaps asthma, by preventing diseases in childhood, such as measles, which may protect against developing allergic conditions later in life.[15, 16] In the case of pertussis the disease has been suggested to increase the occurrence of atopy and asthma, and it may be that the vaccine could have similar effects.[9, 17, 18]

Because vaccination is universally recommended for infants, any association between childhood vaccina-

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tions and the occurrence of a common serious condition such as asthma could be of considerable public health importance. We performed a study using the combined data resources of four large health maintenance organizations (HMOs) to evaluate the associations between vaccines and the occurrence of asthma in childhood. We were primarily interested in associations with diphtheria, tetanus and whole cell pertussis (DTP) and measles, mumps and rubella (MMR) vaccines. For completeness we also evaluated the other routinely recommended childhood vaccines.

METHODS

Study population. We analyzed data from the Vaccine Safety Datalink (VSD) project, which has been described previously.[19] Briefly VSD was created in 1991 by the National Immunization Program of the CDC. The project links medical event information, vaccine history and selected demographic information from the automated clinical databases of Group Health Cooperative (GHC) in Seattle, WA; Kaiser Permanente Northwest in Portland, OR; Kaiser Permanente Medical Care Program of Northern California (NCK) in Oakland, CA; and Southern California Kaiser Permanente Medical Care Program (SCK) in Los Angeles, CA. The time periods covered by our study were from 1991 through 1996 for GHC, Kaiser Permanente Northwest and NCK and from 1992 through 1997 for SCK. The study was restricted to children who were enrolled in one of the participating HMOs at birth and remained enrolled until at least 18 months of age.

Ascertainment of vaccination status. We ascertained vaccinations received by children in the study from computerized immunization tracking systems that are maintained by each of the HMOs. Quality control comparisons of the computerized immunization data with information recorded in paper medical records have shown high levels of agreement.[20] For the common infant vaccines administered at each HMO, 85% or more of the vaccinations recorded in the medical records were usually captured by the computerized immunization tracking systems. NCK had nearly perfect agreement (98 to 99%) for all of the vaccines of interest.

Asthma case ascertainment. We identified asthma cases using computerized medical encounter and pharmacy databases. Each of the HMOs maintains computerized databases of prescription medication dispensings and of all hospital discharges and emergency room visits. At GHC and NCK, diagnoses from outpatient clinic encounters also were available in electronic databases for certain years. To be classified as having asthma, a child had to meet one of the following criteria: (1) at least one diagnosis of asthma [International Classification of Diseases, ninth revision (ICD9) Code 493] and at least one prescription for an asthma medication; the first diagnosis and first prescription had to be within a 2-year period. Asthma medications included oral or inhaled beta-agonists, theophyllin, oral or inhaled corticosteroids, cromolyn sodium, adrenergic drugs not elsewhere specified and unclassified asthma medications; (2) at least one prescription for an inhaled beta-agonist and at least one prescription for cromolyn within a 2-year period; (3) at least five prescriptions for asthma medications during a 2-year period.

In addition to one of the above criteria, we also required that the child had to have at least one asthma diagnosis or medication prescription when 1 year of age or older. We defined the asthma incidence date as the earliest of the first asthma diagnosis date or the first date of an asthma medication prescription. A child could have had an asthma incidence date when younger than 1 year of age, but to be classified as a case the child had to have an indication that asthma was still present when he or she was older than 1 year of age. We imposed this requirement because of the difficulty in differentiating between asthma and bronchiolitis in infants.

Statistical analysis. We conducted proportional hazards regression analyses to estimate relative risks of developing asthma according to vaccination status. We used SAS software to perform the analyses (SAS Institute, Cary, NC). The outcome in the regression models was age at asthma incidence. Children were censored when they were first prescribed an asthma medication or received a diagnosis of asthma, disenrolled from HMO membership, or December 31, 1996 (1997 for SCK), whichever occurred first. We modeled vaccination status as a time-dependent variable according to date of first vaccination. We evaluated the following vaccines: DTP; oral polio vaccine (OPV); MMR; *Haemophilus influenzae* type b (Hib); and recombinant hepatitis B. The regression models were stratified by HMO and by month and year of birth. We included gender and low birth weight as covariables in the models, as well as receipt of acellular pertussis vaccine as the first pertussis vaccination.

We performed a subanalysis to evaluate the influence of race and ethnicity and socioeconomic factors on the results. We did not have direct measures of socioeconomic status or information on race and ethnicity. As indirect indicators of these factors, we used the characteristics of the child's Census block group of residence. From the 1990 Census data (US Census Bureau CD-ROM STF-3B), we used the following Census block variables: education (percentage of residents older than 18 years who did not graduate from high school); household income (proportion of households with annual incomes <$25 000); proportion of African-American residents; proportion of Hispanic residents; and proportion of Asian residents. Census block data

TABLE 1. Characteristics of study population by asthma status at follow-up, Vaccine Safety Datalink

	Gender		Birth Wt		Total
	Female	Male	Low	Not low	
Asthma	6893 (37.4)*	11 514 (62.9)	1741 (9.5)	16 666 (90.5)	18 407
Well	74 757 (50.2)	74 076 (49.8)	8096 (5.4)	140 737 (94.6)	148 833
Total	81 650	85 590	9837	157 403	167 240

* Numbers in parentheses, percent.

were available through 1995 at NCK and through 1996 at the other three HMOs.

To evaluate the influence of our case definition, we performed an additional analysis in which we used a different asthma case definition to detect potentially more severe cases of asthma. In that analysis we required a hospital discharge or emergency room visit diagnosis of asthma as part of the case definition plus at least one prescription for an asthma medication.

We also performed subanalyses to evaluate possible medical care utilization bias. We were primarily concerned that children who had no records of receiving recommended vaccines were not actually using the HMO for most of their medical care. Thus we would be missing not only their vaccinations but also their medical care encounters. This would tend to underestimate the risk of asthma in apparently "unvaccinated" children and result in an overestimate of the relative risk associated with vaccination. To minimize this bias, at two HMOs with outpatient encounter data we performed a subanalysis restricted to children who had at least two medical care encounters during their first year of life. To further evaluate the possible influence of medical care utilization bias on the risk associated with hepatitis B vaccine, we also performed a subanalysis restricted to children who had received at least two OPV, two DTP and one MMR vaccine by 18 months of age.

RESULTS

A total of 167 240 children were included in the analysis, of whom 18 407 (11.0%) developed asthma according to our case definition. ~77% (14 237 of 18 407) of the cases met the first criterion (at least one asthma diagnosis and one prescription for an asthma medication). Overall the median age at last follow-up was 28 months, and the asthma cases had a median age of 11 months on their incidence date. Children who developed asthma were more likely to be male and to have had a low birth weight (Table 1).

Vaccination coverage was high in our study population. Only a small proportion of children had no record in the automated immunization tracking systems of receiving DTP, OPV or Hib vaccines (Table 2). Nonetheless the total population was so large that even the small proportion not vaccinated resulted in an absolute number of 6069 children who did not receive DTP vaccine. DTP and OPV were often administered together; only 3400 children (2.0%) had no record of receiving either vaccine. Only 400 children received acellular pertussis vaccine as their first pertussis vaccination. Among the children not vaccinated with OPV, none received inactivated polio vaccine. A relatively large proportion of children apparently did not receive MMR or hepatitis B vaccines. The MMR coverage partially reflects the fact that many of the children had an asthma incidence date before the recommended age for MMR vaccination (12 to 15 months). The first years of our study covered the period when recommendations for universal infant vaccination against hepatitis B were first issued, and the lower hepatitis B vaccination coverage probably reflects delays in implementation of these recommendations.

In the proportional hazards regression analyses, we found that DTP, OPV and MMR were not associated with an increased risk of developing asthma in infancy or childhood (Table 3). The relative risks for Hib and hepatitis B vaccine were 1.18 and 1.20, respectively, with 95% confidence intervals that excluded 1.0. The point estimate of the relative risk for hepatitis B vaccine was >1.0 at each of the HMOs, whereas the Hib relative risk was >1.0 only at NCK and <1.0 at the other HMOs.

We also evaluated the effect of the number of doses of a vaccine and found that after the first dose of each of the vaccines of interest the relative risks were similar to those after a second or subsequent dose of the vaccine (data not shown).

In the subanalysis in which we included additional adjustments for Census block indicators of race, ethnicity and socioeconomic factors, the results were little changed from those presented in Table 3. A total of 116 496 children were included in this subanalysis and the relative risks (95% confidence interval) were 0.96

TABLE 2. Children who did not receive indicated vaccines, Vaccine Safety Datalink

Vaccine	Children Not Vaccinated*
DTP	6069 (3.6)†
OPV	4416 (2.6)
Hib	3605 (2.2)
MMR	12 426 (7.4)
Hepatitis B	18 580 (11.1)

* Before asthma incidence or censoring date.
† Numbers in parentheses, percent.

TABLE 3. Relative risk* of developing asthma associated with childhood vaccinations, by vaccine and HMO, Vaccine Safety Datalink

Vaccine	HMO				Total (n = 167 240)
	GHC (n = 9813)	NWK (n = 10 732)	NCK (n = 74 610)	SCK (n = 72 085)	
DTP	1.09 (0.44–2.66)†	1.75 (0.66–4.62)	0.89 (0.80–0.99)	1.02 (0.73–1.41)	0.92 (0.83–1.02)
OPV	1.19 (0.65–2.19)	0.57 (0.28–1.14)	1.04 (0.90–1.20)	1.35 (0.98–1.86)	1.09 (0.96–1.23)
MMR	1.04 (0.73–1.49)	0.88 (0.60–1.29)	0.91 (0.84–0.99)	1.12 (0.98–1.28)	0.97 (0.91–1.04)
Hib	0.71 (0.29–1.75)	0.78 (0.32–1.88)	1.30 (1.10–1.54)	0.88 (0.65–1.20)	1.18 (1.02–1.36)
Hepatitis B	1.07 (0.82–1.38)	1.31 (0.94–1.84)	1.20 (1.12–1.28)	1.23 (1.05–1.43)	1.20 (1.13–1.27)

* Adjusted relative risk estimated from a proportional hazards regression model stratified by HMO and month and year of birth, and adjusted for gender, low birth weight status and all vaccines listed in the table plus acellular pertussis vaccine as the first pertussis vaccination.

† Numbers in parentheses, 95% confidence interval.

(0.85 to 1.10) for DTP, 1.00 (0.92 to 1.08) for MMR, 1.14 (0.97 to 1.35) for Hib and 1.16 (1.08 to 1.25) for hepatitis B vaccine.

In the subanalysis in which we used a case definition intended to identify more severe cases of asthma, the relative risks were not materially different from the results of our main analysis. In this analysis, which required a hospital discharge or emergency room visit diagnosis of asthma as part of the case definition, the number of cases decreased to 4164 (from 18 407 in the main analysis). The largest change in the relative risk was for DTP vaccine, which decreased to 0.77 (0.63 to 0.94) compared with 0.92 (0.83 to 1.02) in the main analysis. The relative risks for Hib and hepatitis B vaccines remained elevated at 1.32 (0.99 to 1.76) and 1.15 (1.03 to 1.29), respectively.

To assess the influence of medical care utilization, we performed a subanalysis according to number of medical care encounters during the first year of life. This analysis required availability of computerized outpatient clinic encounters data, which were only completely available at GHC from 1992 through 1996 and at NCK for 1995 and 1996. Among the entire group of 17 949 children included in this subanalysis, regardless of number of encounters, the relative risks for all of the vaccines (Table 4) were generally similar to the results of the main analysis (Table 3). When the analysis was restricted to the 17 740 children at NCK and GHC who had at least 2 medical encounters during their first year of life, the relative risks for both Hib and hepatitis B vaccines, as well as OPV, decreased and the relative risks for the other vaccines were unchanged (Table 4).

In the subanalysis restricted to children who had received at least two doses of OPV, two doses of DTP and one dose of MMR by age 18 months, the relative risk of asthma among children who also received hepatitis B vaccine compared with those who had not received hepatitis B vaccine was 1.12 (1.05 to 1.20).

TABLE 4. Relative risk* of developing asthma associated with childhood vaccinations, by number of medical care encounters at GHC and NCK, Vaccine Safety Datalink

Vaccine	No. of Medical Encounters in First Year of Life	
	2 or more (n = 17 740)	Any or none (n = 17 949)
DTP	0.87 (0.61–1.24)†	0.84 (0.59–1.19)
OPV	0.85 (0.63–1.15)	1.10 (0.74–1.38)
MMR	0.80 (0.61–1.04)	0.81 (0.63–1.05)
Hib	1.07 (0.71–1.60)	1.20 (0.80–1.81)
Hepatitis B	1.09 (0.88–1.34)	1.17 (0.95–1.44)

* Adjusted relative risk estimated from a proportional hazards regression model stratified by HMO and month and year of birth, and adjusted for gender, low birth weight status and all vaccines listed in the table plus acellular pertussis vaccine as first pertussis vaccination.

† Numbers in parentheses, 95% confidence interval.

DISCUSSION

Prior evidence of a possible association between vaccination and asthma was limited primarily to whole cell pertussis vaccine. The strongest association was found in a large, prospective study in New Zealand, in which none of the unvaccinated children developed asthma by age 10 years compared with nearly one-fourth of the vaccinated children.[4] The study was limited, however, by the small number of unvaccinated children (n = 23) and uncertainty about differences in medical care utilization between the two groups. A record review of 1934 patients registered from birth until at least 12 years of age in one general medical practice in the UK found a statistically significant relative risk of developing asthma of 1.44 associated with whole cell pertussis vaccine.[7] Another study of 448 English children found that 10.7% of the 243 who had received pertussis vaccine had asthma compared with 2.0% of the 203 children who had not been immunized.[5] This study was retrospective and subject to recall bias. An analysis of data from the Third National Health and Nutrition Examination Survey, involving 13 944 children, found that children who had received DTP or tetanus vaccination had a 2-fold in-

creased risk of asthma compared with unvaccinated children.[8] This cross-sectional survey also was subject to recall bias. As part of a large randomized clinical trial of the efficacy of whole cell pertussis and acellular pertussis vaccines in Sweden, 669 children were evaluated for development of atopic disease, including asthma, from age 2 months to 2.5 years.[9] The incidence of asthma, as well as other atopic diseases, was similar in the groups of children who received whole cell pertussis vaccine, acellular pertussis vaccines and no pertussis vaccine (i.e. diphtheria-tetanus). Methodologically this was the strongest study, but the sample size was relatively small and follow-up was only to age 2.5 years. A recently reported longitudinal study from England found no association between pertussis vaccination and wheezing illnesses.[21]

A hypothesis has been developed that asthma is caused by an immunologic imbalance in the antigen-stimulated cytokine response of two classes of T helper cells (Th1 and Th2) in favor of the Th2 response.[16, 22] Some studies suggest that early infections with certain respiratory pathogens may shift the Th1/Th2 balance toward Th2 cells,[23, 24] whereas infections that stimulate predominantly a Th1 response (e.g. mycobacteria, measles) may decrease atopic manifestations.[15, 25] This theory, however, is probably overly simplistic, and its applicability to human exposure to vaccine antigens is uncertain. Current laboratory evidence on the effect of vaccines in general and pertussis-containing vaccines in particular on Th1/Th2 balance is inconclusive. Alum, an adjuvant in vaccines against pertussis, may stimulate induction of a Th2-like response.[26, 27] Pertussis toxin itself can act as an adjuvant, but it seems to stimulate a mixed Th1 and Th2 cytokine response.[28] More recent studies suggest that whole cell pertussis vaccine stimulates primarily a Th1 response.[29, 30]

MMR was the only vaccine, other than pertussis, for which we had any *a priori* suspicion of a possible association with asthma. A study in Guinea Bissau[15] found that children who contract clinical measles may be less likely to develop atopy than children who do not contract measles (usually because they have been vaccinated). Thus measles in infancy may be protective against developing atopic conditions, including asthma, and by preventing measles disease, measles vaccine may indirectly increase the risk of asthma or atopy. These epidemiologic conclusions conflict with a recent large study in Finland, which found a positive association between measles and atopic conditions.[31] A study in a general medical practice in the UK did not find an association between measles vaccination and atopy or asthma.[7] The immune responses to measles and measles vaccine are complex, involving both Th1 and Th2 responses.[32–34] Our results indicate that children vaccinated with MMR are not at increased risk of developing asthma compared with unvaccinated children.

In our main analysis we found that Hib and hepatitis B vaccines were associated with 18 and 20% increases in asthma risk, respectively. The Hib results, however, were not consistent by HMO. An increased risk was evident only at NCK, and at the other HMOs the relative risks associated with Hib were <1.0. The Hib vaccines used at NCK were also used at the other HMOs; thus we do not have a ready explanation for the idiosyncratic Hib results at NCK and suspect that they are probably a random chance finding.

We are not aware of any previous studies of asthma risk after hepatitis B vaccination or of any data suggesting an association between hepatitis B disease and asthma. The hepatitis B vaccine may contain residual brewers yeast antigens from the production process, but we are not aware of any association between brewers yeast and asthma. The immunologic response to the hepatitis B surface antigen used in the vaccine appears to be predominantly Th1.[35, 36] Hepatitis B vaccine, however, is the one vaccine that in the US is often administered at birth. Because it has been shown that Th2 cells dominate at birth in children who develop atopy,[37, 38] we performed a subanalysis to assess whether vaccination at birth (i.e. up to 14 days of age) carried a different risk than administering the first dose of hepatitis B vaccine at later ages, but we did not find any difference (data not shown).

Potential limitations of our study included possible misclassification of asthma status, incomplete information on potential confounding factors and relatively short follow-up. Relying on computerized information, we used several criteria to identify children with asthma. A previous study using asthma prescription criteria similar to those of ours showed that they have high sensitivity and positive predictive value for asthma.[39] We performed additional analyses in which we used different asthma case definitions, and the results were not materially different from those of the main analysis. We were able to adjust for gender and date of birth and for the racial, ethnic and socioeconomic characteristics of area of residence, but we did not have information on family history of asthma and other asthma risk factors. The few increased relative risks that we found were all <1.3 and could be highly subject to possible confounding by factors on which we did not have information.

The ages of the children in our study (18 months to 6 years) may have been too young to fully evaluate asthma risk. Recent studies, however, indicate that most children with asthma are diagnosed by the age of 5 years and that symptoms usually first appear in infancy and early childhood.[40, 41] In the New Zealand study differences in asthma prevalence were apparent by age 5 years.[4] That $>10\%$ of the children in our study

developed asthma also suggests that the age of the children was not a major limitation.

It was critically important in our study that children for whom no vaccinations were identified in the computerized immunization tracking systems were actually not vaccinated. To have a complete vaccination history from birth is the main reason that we restricted the analysis to children who became HMO members at birth. Nonetheless it is possible that some of the children who had no immunization record in the automated immunization tracking systems actually had been vaccinated. For example some children may have had dual health plan coverage and, although enrolled in one of the VSD HMOs, received most of their medical care through another health care provider. In this case we would not have data on their immunizations or on their medical care visits, including any for asthma. Including such children in the analysis would result in a biased lower apparent risk of asthma among "unvaccinated" children.

To evaluate the magnitude of possible medical care utilization bias, we performed a subanalysis restricted to children whom we knew were using two of the VSD HMOs (GHC and NCK) for their health care because they had made at least two medical care visits during their first year of life. In this subanalysis the relative risks for almost all of the vaccines of interest decreased, including those for Hib and hepatitis B. In another subanalysis in which we tried to reduce possible health care utilization bias by restricting the analysis to children who had received at least two OPV, two DTP and one MMR, the relative risk of asthma associated with hepatitis B vaccine was less than that found in the main analysis. We conclude from these findings that the results of our main analysis are probably biased upward and tend to overestimate the relative risks associated with vaccination.

In conclusion medical care utilization bias did seem to influence the results for Hib and hepatitis B vaccines, for which we found weak associations with asthma. Despite a similar bias that would favor finding an increased risk, we found that DTP, OPV and MMR vaccines did not increase a child's risk of developing asthma.

APPENDIX

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Announcement

SEVENTH INTERNATIONAL SYMPOSIUM ON PERTUSSIS: GENOME, PATHOGENESIS, AND IMMUNITY. The American Society for Microbiology and the Wellcome Trust are cosponsoring a symposium on pertussis, to be held September 18 to 22, 2002, at the Wellcome Trust Hinxton Conference Center, near Cambridge, UK. The conference is limited to 300 participants. Information on the scientific program, abstract submission, and registration procedure can be found at the ASM Conferences website: www.asmusa.org/mtgsrc/conferences.htm.