The relationship between vaccine refusal and self-report of atopic disease in children

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Background: In the last 3 decades, there has been an unexplained increase in the prevalence of asthma and hay fever.
Objective: We sought to determine whether there is an association between childhood vaccination and atopic diseases, and we assessed the self-reported prevalence of atopic diseases in a population that included a large number of families not vaccinating their children.
Methods: Surveys were mailed to 2964 member households of the National Vaccine Information Center, which represents people concerned about vaccine safety, to ascertain vaccination and atopic disease status.
Results: The data included 515 never vaccinated, 423 partially vaccinated, and 239 completely vaccinated children. In multiple regression analyses there were significant ($P < .0005$) and dose-dependent negative relationships between vaccination refusal and self-reported asthma or hay fever only in children with no family history of the condition and, for asthma, in children with no exposure to antibiotics during infancy. Vaccination refusal was also significantly ($P < .005$) and negatively associated with self-reported eczema and current wheeze. A sensitivity analysis indicated that substantial biases would be required to overturn the observed associations.
Conclusion: Parents who refuse vaccinations reported less asthma and allergies in their unvaccinated children. Although this relationship was independent of measured confounders, it could be due to differences in other unmeasured lifestyle factors or systematic bias. Further research is needed to verify these results and investigate which exposures are driving the associations between vaccination refusal and allergic disease. The known benefits of vaccination currently outweigh the unproved risk of allergic disease. (J Allergy Clin Immunol 2005;115:737-44.)

Key words: *Immunization, asthma, allergic rhinitis, eczema, prevalence, cross-sectional survey*

Abbreviations used
DTP: Diphtheria, tetanus, and pertussis
HiB: *Haemophilus influenzae* B
MMR: Measles, mumps, and rubella
NVIC: National Vaccine Information Center
RR: Rate ratio

Asthma is a chronic disease that causes substantial disability, death, and economic burden.[1] Hay fever, which is more common than asthma, is not life-threatening, but the costs of care and treatment are high.[2] Asthma, hay fever, and eczema are separate but related atopic diseases. Over the last 20 to 30 years, the prevalence of these 3 atopic diseases in westernized countries has increased.[3] Recent surveys of self-reported asthma prevalence in the United States and Canada suggest rates of 11% to 17%.[4,5] In developed societies, between 25% and 32% of children typically report allergic rhinitis.[5,6]

Previous studies examining the relationship between asthma and vaccinations have yielded inconsistent results.[7-15] Presently, nearly all children receive vaccinations, and published studies have included few completely unvaccinated children. This study examines the association between vaccinations and atopic disease in a large number of unvaccinated children.

METHODS

Population

Nonimmunized children include families that intended to use immunizations but have not yet done so and a distinct, smaller population of families that consciously refuse immunizations because of religious, philosophical, or safety concerns.[16] This study sampled the mailing list of the National Vaccine Information Center (NVIC), the members of which choose to refuse vaccination. Families might join the NVIC because they believe vaccinations have caused or contributed to their child's illness, frequently autism. The organization focuses on immunization issues, but its members embrace diverse alternative health care philosophies.

Any selected household in the NVIC with children aged 3 to 18 years was eligible to participate in the study. The NVIC assigned a unique study identification number to each selected household to ensure participant anonymity. Thus the investigators never knew participant identities nor had access to information that could be used to identify households. The Institutional Review Board of the University of Illinois at Chicago reviewed and approved the study protocol.

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Five hundred households received a pilot survey in October 2002. New households (n = 2464) plus nonresponding households (n = 336) from the pilot mailing were contacted in March 2003 and received a reminder postcard 2 weeks later. Households not responding to this mailing received the survey and reminder postcard again in May 2003. The response rate to the survey was 41%, which was calculated by dividing the total number of eligible responses by the estimated total number of eligible households (American Association for Public Opinion Research formula number 3[17]).

Survey instrument

The mailed survey packet included a cover letter that briefly described the study as a survey of allergic disease and invited households to return the survey or an enclosed postcard indicating they were either ineligible to participate (no children aged 3-18 years) or chose not to participate in the survey. The NVIC leadership reviewed the survey before distribution. The survey could not ask, for example, why the family initially joined the organization nor could it collect zip codes. Parents answered questions regarding their eligible children's vaccination history, family medical history, early and current home environment, and their current and cumulative experience of symptoms of hay fever or asthma.

The survey asked ''Has this child ever received an immunization or vaccination?'' and ''Did this child receive all vaccinations as recommended by your health care provider?'' Each child was then classified as refusing all vaccines, refusing some vaccines, or completely vaccinated. From additional questions, children were further classified by exposure to individual vaccines. Parents were instructed to refer to written immunization records, and as vaccine activists, they were likely to know their children's vaccination status.

Primary outcomes were defined by answers to a single question. For example, questions included ''Has a doctor ever said this child has asthma?,'' ''Has this child ever had hay fever (seasonal or environmental allergies)?,'' and ''Has a doctor ever said this child has eczema?'' Additional questions asked about current symptoms of atopic disease.

Parents were asked to identify a single ''primary source of medical care.'' In adjusted models any family that reported using an MD or a DO was classified as exposed to traditional medicine, regardless of their concurrent use of alternative health care providers.

Statistical methods

Subjects were characterized by asthma status and vaccine exposure. The Pearson χ^2 statistic tested the significance of differences between groups for all covariates. Preliminary analyses included calculating rate ratios (RRs) stratified by all available covariates to assess the potential for confounding and effect modification.

Multiple logistic regression models adjusted for confounding variables (age, sex, source of medical care, antibiotic use, and family clustering). Age was entered as a continuous variable, and sex (male/female), source of medical care (see traditional MD/only alternative provider), and exposure to antibiotics in the first year of life (ever/never) were dichotomous variables. Statistically significant ($P < .05$) terms for effect modifiers were included in models and were not the same for all examined outcomes. The model for asthma included interaction terms for family history of asthma and exposure to antibiotics during infancy. Family history of hay fever was the only effect modifier for the association between vaccine refusal and hay fever. There were no effect modifiers for eczema or current wheeze.

Mixed-effects multiple logistic regression models adjusted for familial clustering of observations by estimating both a model intercept and a random intercept for each family cluster to account for covariance. Estimates for random intercepts and predictive variables were calculated through iterative marginal maximum likelihood calculations.[18] When calculating estimated prevalence rates, parameter estimates were transformed to represent the average family cluster by using the method outlined by Neuhaus et al,[19] and calculations used the study average values for age, sex, exposure to antibiotics, source of medical care, and family history of asthma or allergies (eczema and current wheeze only). The prevalence RR is presented with a 95% CI. The *P* value for trend was calculated by entering vaccine refusal as an ordinal variable in the mixed-effects multiple logistic regression models.

We performed a sensitivity analysis to assess the potential effect of nonrandom error caused by response bias and differential misclassification. The prevalence of asthma was 20.3%, 11.8%, and 15% among fully vaccinated, partially vaccinated, and ever-vaccinated children, respectively. Because of the high prevalence of asthma among fully vaccinated children, we hypothesized that NVIC member families with fully vaccinated children might be more likely to respond to the survey if their children had asthma. If true asthma prevalence among fully vaccinated children in the NVIC was 15%, then there could be a response bias as high as 30%. Differential misclassification was also possible because vaccine-refusing families were more likely to use alternative health care and therefore might not receive diagnoses. Similarly, families that vaccinate despite concerns might be less tolerant of symptoms and more likely to seek diagnosis. For example, the children of vaccine refusers who reported current wheezing were 2.6 times less likely than wheezing vaccinated children to report an asthma diagnosis.

Detailed methods for sensitivity analysis have been published by Greenland.[20] Briefly, the analysis dichotomized vaccine exposure (ever/never) and assumed up to 50% differential misclassification bias by multiplying (dividing) observed prevalence rates by a combined total of up to 0.5 and reapplying the adjusted prevalence rate to vaccinated (unvaccinated) marginal totals. The RR was multiplied by 0.7 to assess the potential effect of response bias. Because modifications were made to summary counts, there is no adjustment for confounding in the sensitivity analysis.

Analyses were performed with SAS version 8.0 (Cary, NC), Mixor version 2.0 (Chicago, Ill), and EpiInfo version 3 (Atlanta, Ga).

RESULTS

Table I characterizes respondents demographically by self-reported asthma status. Children with asthma were older, more frequently male, and more likely to report a family history of asthma. Children with asthma were also less likely to see chiropractors, had less educated mothers, and were more likely to be exposed to cigarette smoke, formula feedings, and vaccines. Table II provides data by vaccination refusal: 515 children received no vaccines, 423 received some vaccines, and 239 were fully vaccinated. Among the partially vaccinated children, 92 (20%) had received no vaccines in the first year of life, and overall, 69% were exposed to diphtheria, tetanus, and pertussis (DTP) vaccine; 56% were exposed to measles, mumps, and rubella (MMR) vaccine; and 77% received polio vaccine (not shown). Parents who refused vaccines had younger children, higher maternal education, less exposure to cigarettes, were more likely breast-fed, and had a lower prevalence of a family history of asthma, had less exposure to antibiotics, had more contact with alternative health