
Childhood asthma and measles vaccine response

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Background: Asthmatic patients have a T_H2-predominant milieu that is associated with humoral immunity. However, little is known about whether humoral immune responses to viral antigens differ between asthmatic and nonasthmatic children.

Objective: To determine whether humoral immune response differs in asthmatic patients vs nonasthmatic patients.

Methods: Measles virus specific IgG antibody levels were determined for the Rochester Family Measles Study cohort (n = 876), a convenience sample of healthy children 5 to 12 years of age in Rochester, MN. We conducted comprehensive medical record reviews of 838 children who were eligible for this study. We determined the child's asthma status at the time of determination of antibody levels by applying predetermined criteria for asthma. Comparisons were made using the 2-sample *t* test or χ^2 test.

Results: Of the 838 children, 156 (18.6%) had asthma at the time of the determination of antibody levels and were not taking systemic steroids within 14 days of specimen collection. Among those with a nonequivocal antibody reading, the seropositive response rates were similar in asthmatic patients and nonasthmatic patients (89.7% vs 90.3%, respectively; *P* = .83). However, the equivocal response rates were slightly higher among asthmatic patients than nonasthmatic patients (6.4% vs 4.7%, respectively).

Conclusion: Asthmatic children seem to have similar humoral immune responses to measles vaccine as those without asthma. Although the findings reassure health care practitioners, whether this finding is generalizable to other vaccines and whether asthmatic patients with low antibody levels have normal cell-mediated immunity need to be elucidated in future studies.

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INTRODUCTION

Measles remains a cause of major morbidity and mortality in many developing countries, where more than 30 million people are affected each year by the disease.¹ In 2003, it was estimated that there were 530,000 measles deaths globally.¹ In Western countries, where measles has been largely eliminated, cases imported from other countries remain an important source of outbreaks of measles.^{2–4} Since the measles vaccine was licensed in 1963 in the United States, measles incidence has declined significantly. However, measles outbreaks still occur among children who were vaccinated with 1 dose (18% to 52% of measles cases during outbreak)^{5–7} or even among those vaccinated with 2 doses (1% of cases)^{3,4,6} in the United States and elsewhere in developed countries.^{8,9}

Therefore, measles is still a major public health issue not only in developing but also in developed countries. Vaccination against measles virus is the primary measure to prevent children from acquiring measles, and, thus, it is important to identify possible biological mechanisms that lead to vaccine failure. A previous study suggests a reciprocal counterregulation of immunoglobulin isotype production in T-cell-dependent immune responses (eg, IgG1, IgG2a, and IgE) by interferon- γ (ie, T_H1 cytokine) and interleukin-4 (ie, T_H2

cytokine).¹⁰ Thus, it can be hypothesized that individuals with a T_H2-predominant condition such as asthma may have a different antibody response to microbial antigens (eg, vaccine). In support of this hypothesis, a previous study that compared humoral immunity between asthmatic patients (who were not taking steroids) and healthy individuals showed that 13 (18%) of 74 asthmatic patients and 1 (1.3%) of 74 healthy individuals failed to respond to tetanus toxoid (*P* < .001),¹¹ and another study reported that 10% of patients with atopic dermatitis and none of healthy individuals failed to respond to tetanus toxoid (*P* < .04).¹² In addition, a lower immunoglobulin level among asthmatic patients have been suggested.^{13,14} Furthermore, potential suppression of cellular immunity (which is still important for humoral immunity) by a biased T_H2 response or condition has been demonstrated for both viral^{15–22} and bacterial infections.^{23,24} The mechanism for poor humoral immunity in asthmatic or atopic patients is unclear, although Poland et al^{25–29} have extensively documented the role of HLA type in measles vaccine response. They found that certain HLA class II alleles (eg, *HLA DRB1*03*) were associated with seronegativity. Our recent study and others have reported that *HLA DRB1*03* is associated with childhood asthma.^{30–37} Taken together, it can be hypothesized that asthmatic patients may have a decreased measles vaccine response compared with nonasthmatic patients.

It is important to determine the relationship between measles vaccine response and asthma status in children for 2 main reasons. One is its implications for public health. Measles is

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still responsible for major morbidity and mortality in developing countries; yet, asthma prevalence in developing countries (eg, 10.2% in Africa and 13.4% in Latin America) is not much lower than that of developed countries (13% in Western Europe).³⁸ The other reason is that determining the relationship between measles vaccine response and asthma status in children is likely to advance our understanding of the relationship between asthma status and microbial infections, especially viral infections. Several studies have been conducted to determine the protective effects of prior exposure to measles infection or vaccination on subsequent development of asthma or atopic conditions (ie, the hygiene hypothesis). Some studies supported the findings consistent with the hygiene hypothesis,^{39–42} others disputed it.^{43–48} These studies do not provide clues for the influence of asthma status on measles vaccine response. Rather, evaluation of the impact of asthma status on measles vaccine response helps us interpret the results of such studies. For this reason, we sought to determine the impact of asthma status on measles vaccine response.

METHODS

Study Design and Setting

The study was a retrospective cross-sectional study. Rochester, MN, has an excellent epidemiologic setting and advantage in conducting a retrospective cohort study, because medical care is virtually self-contained within the community, and a unified medical record system has been maintained among 2 medical centers for the past 90 years. This dossier-type medical record contains all inpatient and outpatient data that have been indexed in an automated form since 1935.⁴⁹

Study Participants

The study protocol was approved by the institutional review boards at both the Mayo Clinic and the Olmsted Medical Center. Study participants were obtained from a previously assembled study designed to examine the relationship between HLA type and measles vaccine response in a convenience sample of children who were enrolled in the Rochester Family Measles Project.²⁶ Briefly, the original cohort of this study was 876 healthy school children ages 5 to 12 years who had been immunized with the measles-mumps-rubella (MMR) II vaccine (Merck, West Point, PA) at approximately 15 months of age. At the time of the original study in 1990, routine administration of a second MMR vaccine before school entry was not recommended by the American Academy of Pediatrics.⁵⁰ All participants resided in a geographic area with no circulating measles virus; therefore, the presence of measurable measles antibody could reasonably be attributed to the single dose of vaccine. The original study participants were identified through the school district, and after obtaining informed consent from parents and assent from the participants, serum samples were collected from the children. A variety of information on these children was obtained from parental self-administered questionnaires from the original study and medical records. For this study, 838 patients were

included. Of the 37 patients who were excluded, 24 parents denied research authorization for access to their children's medical records. Thirteen additional children did not have the necessary data for analysis and were excluded from the analysis. Only 1 child took a systemic steroid within 14 days before the specimen collection and was excluded from the analysis, although a short period of systemic steroid administration has little influence on humoral immune response. Because inhaled corticosteroid has been found not to affect humoral immune responses, children who were taking inhaled corticosteroid were included in the analysis.^{51,52}

Dependent Variable

The dependent variable in this study was measles virus vaccine specific IgG level. The detailed procedures of measurement of antimeasles antibodies were described previously.²⁶ Briefly, circulating measles virus vaccine specific IgG antibody levels in the participants' serum samples were determined by an IgG whole-virus specific enzyme immunoassay (MeaslesELISA, BioWhittaker, Walkersville, MD). Tests were performed in duplicate, and the mean value was used for the analyses. The coefficient of variation for this assay in our laboratory was 6.63%. According to the manufacturer, optical density readings of less than 0.8 index unit are negative, 0.8 to 1.0 are equivocal, and 1.0 or greater are positive. Subclass of measles virus specific IgG was not determined in this study. Because the clinical nature of equivocal response to measles vaccine (ie, whether it is a suboptimal level for protection from measles infection is not known), we excluded equivocal responders (n = 42) from part of our analysis.

Independent Variables

The main independent variable (ie, predictor variable) in this study was asthma status. The criteria for identifying incident asthma cases have been previously described⁵³ and are detailed in Table 1. Briefly, the medical records of all study participants were comprehensively reviewed to determine whether they met predetermined criteria for asthma, and their index date of asthma was abstracted. These asthma criteria have been used in previous literature on asthma epidemiology research.^{54,53,55–61} In this study, we combined both definite and probable asthma as incident asthma cases, because most (43/66) of the probable asthma cases became definite asthma over time.⁵³

In addition to demographic variables and asthma status, we also obtained pertinent clinical variables to childhood asthma, including family history of asthma or atopy. For family history of asthma or atopy of the participants and their first-degree relatives, we reviewed medical records of the first-degree relatives of the study participants when the study participants' medical records did not indicate the status. We applied the same criteria, outlined in Table 1, for asthma to first-degree relatives to ascertain whether the first-degree relatives of the study participants have asthma. We determined atopy status (ie, allergic rhinitis, hay fever and atopic dermatitis) of the first-degree relatives of the study partici-

Table 1. Asthma Criteria

Patients were considered to have <i>definite</i> asthma if a physician had made a diagnosis of asthma and/or if each of the following 3 conditions were present. They were considered to have <i>probable</i> asthma if 2 of the following conditions were present: 1. History of cough, dyspnea, and/or wheezing OR history of cough and/or dyspnea plus wheezing on examination 2. Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and 3. Two or more of the following: • Sleep disturbed by nocturnal cough and wheeze • Nonsmoker (14 years or older) • Nasal polyps • Blood eosinophilia $>300/\mu\text{L}$ • Positive wheal-and-flare skin test results OR elevated serum IgE levels • History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen • Pulmonary function tests showing one FEV_1 or FVC $<70\%$ predicted and another with at least 20% improvement to an FEV_1 of $>70\%$ predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1 • Favorable clinical response to bronchodilator Patients were excluded from the study if any of these conditions were present: • Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity • Tracheobronchial foreign body at or about the incidence date • Hypogammaglobulinemia (IgG <2.0 mg/mL) or other immunodeficiency disorder • Wheezing occurring only in response to anesthesia or medications The following diseases excluded the patient from study if they occurred before the incidence date: • Bullous emphysema or pulmonary fibrosis on chest radiograph • α_1-antiprotease phenotype ZZ α_1-antitrypsin • Cystic fibrosis • Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

Abbreviations: FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity.

pant by using physician diagnoses in medical records. We identified patients with single wheezing episodes who had not met the criteria for asthma.

Statistical Analysis

Demographic and clinical characteristics were compared between participants with a seronegative vs seropositive measles vaccine response using the χ^2 test, Wilcoxon rank sum test, and 2-sample t test, as appropriate. Among those with a nonequivocal antibody reading, the seropositive response

rates were compared between asthmatic patients and nonasthmatic patients with the χ^2 test. The mean measles virus specific IgG level was compared between asthmatic patients and nonasthmatic patients using the 2-sample t test. All calculated P values were 2-sided, and $P < .05$ was considered statistically significant. The poststudy statistical power to detect an odds ratio of 0.85 (eg, 16% vs 13.9%) was 10%. The analysis was performed using SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

Of the 838 children who had undergone measurement of measles virus specific IgG levels and met the inclusion criteria for this study, 50.7% were male and 93% were white. The mean and median age at the time of enrollment in the original study was 8.8 and 9.0 years, respectively. The demographic and clinical characteristics of the study participants and their relation to measles vaccine responses are summarized in Table 2. Overall, 42 children (4.8%) had an equivocal measles vaccine response. Of the children with a nonequivocal response, 718 (90.2%) had a seropositive response. The mean time from immunization to blood draw was significantly shorter for the children who had a seropositive response ($P = .009$). In addition, there was a tendency for children with a seropositive response to be more likely to have a mother with a higher education level ($P = .06$) and to be less likely to have a family history of atopy ($P = .09$).

The results of the relationship between measles virus specific IgG levels and asthma status are summarized in Table 3. A total of 156 children (18.6%) met the criteria for either definite or probable asthma by the time of measurement of measles vaccine response. The median and mean age at index date for asthmatic patients was 4 and 3.9 years, respectively. The median follow-up period was 13 years. Both measles virus specific IgG levels and the proportion of measles vaccine responders were not different between asthmatic and nonasthmatic patients. Of 156 asthmatic children, 10 (6.4%) had an equivocal response, compared with 32 (4.7%) of the nonasthmatic children. Among those with a nonequivocal antibody reading, the seropositive response rates were similar in asthmatic patients and nonasthmatic patients (89.7% vs 90.3%, respectively). The mean antibody level in asthmatic children was not different from those in nonasthmatic children (mean [SD], 1.79 [0.83] vs 1.83 [0.78], respectively; $P = .55$).

DISCUSSION

Our study results suggest that asthmatic children seem to have normal antibody response to the first measles virus vaccine administered at approximately 15 months of age despite the speculation that asthmatic patients may have a different humoral and cellular immune response to microbial antigens. Also, the underlying genetic factors reflected in a family history of asthma or atopy did not seem to affect the antibody response either. Also, it clarifies that the positive association between exposure to measles infection and sub-

Table 2. Demographic and Clinical Characteristics and Measles Virus Vaccine Response*

Characteristics	Seronegative (n = 78)	Seropositive (n = 718)	P value
Time from immunization to blood draw, y			.009
No. of subjects	77	714	
Mean (SD)	8.4 (2.3)	7.7 (2.2)	
Median	8.7	7.7	
Tertile (tertile 1–tertile 3)	6.6–10.5	5.8–9.5	
Sex, No. (%)			.51
Male	37 (47.4)	369 (51.4)	
Female	41 (52.6)	349 (48.6)	
Race, No. (%)			.51
Asian	2 (2.6)	16 (2.2)	
Black	0 (0)	5 (0.7)	
White	74 (94.9)	667 (92.9)	
Native Indian	0 (0)	1 (0.1)	
Other	2 (2.6)	29 (4)	
Education of mother, No. (%)			.06
Unknown	27	305	
Less than high school	1 (2)	3 (0.7)	
High school	8 (15.7)	50 (12.1)	
Some college	27 (52.9)	181 (43.8)	
College degree	15 (29.4)	179 (43.3)	
Family history of asthma, No. (%)			.64
Unknown	12	98	
No	40 (60.6)	394 (63.5)	
Yes	26 (39.4)	226 (36.5)	
Family history of atopy, No. (%)			.09
Unknown	14	110	
No	31 (48.4)	361 (59.4)	
Yes	33 (51.6)	247 (40.6)	

* Children with an equivocal measles virus vaccine reading (n = 42) were excluded from the analysis.

Table 3. Relationship Between Asthma Status and Measles Virus Vaccine Response

	Nonasthmatic (n = 682)	Asthmatic (n = 156)	P value
Proportions of measles vaccine responders, No. (%)			.83
Seronegative	63 (9.7)	15 (10.3)	
Seropositive	587 (90.3)	131 (89.7)	
Equivocal	32	10	
Measles virus specific IgG level, mg/dL*			.55
Mean (SD)	1.83 (0.78)	1.79 (0.83)	
Median	1.79	1.75	
Tertile (tertile 1–tertile 3)	1.31–2.32	1.12–2.28	

* If the children with an equivocal reading are removed from the analysis, the results are as follows: nonasthmatic children: mean (SD), 1.87 (0.77); median, 1.83; tertile 1 to 3, 1.37 to 2.35; asthmatic children: mean (SD), 1.85 (0.83); median, 1.82; tertile 1 to 3, 1.21 to 2.37; *P* = .69.

sequent development of asthma status is not mediated through a reduced antibody response to measles virus among asthmatic children.

Our data indicate that mean $\pm$ SD measles virus specific IgG level (1.78 ± 0.83) and the proportion of measles vaccine responders (89.7%) in asthmatic patients is not different from those of nonasthmatic children (1.83 ± 0.77 and 90.3%, respectively). However, there is a tendency for asthmatic children to have higher seronegative or equivocal responses (16.0%) to measles vaccine compared with those (13.9%) of nonasthmatic children, although this finding is not statisti-

cally insignificant (*P* = .26). In addition, children with a family history of atopy have a similar tendency (a higher seronegative response, 11.8%) compared with those without a family history of atopy (7.9%) (*P* = .09). If we assume that equivocal response to measles vaccine is a suboptimal protective level from measles infection, considering our study's statistical power to detect a small effect, a large-scale study may be needed to determine the influences of these tendencies on susceptibility to measles infection. At any rate, despite previous speculation on the potential decreased humoral immune response in asthmatic patients mediated through

HLA type (ie, association of *HLA DRB1*03* with both seronegativity of measles vaccine response and childhood asthma), our study does not support such speculation. However, our study findings still raise a few important immunologic questions. Can our study findings be applied to humoral immune response to other vaccines or microbial antigens? Do children with vaccine failure have normal cell-mediated immunity, because almost 16% of our study participants had subprotective antibody levels?

For the first question, the literature suggests that antibody responses to vaccines in asthmatic patients have been heterogeneous; thus, our study findings may not be generalizable to other microbial antigens. For example, Grove et al^{11,12} reported that 18% and 10% of patients with asthma or atopic dermatitis failed to respond to tetanus toxoid, respectively, but almost all asthmatic patients showed a normal antibody response to *Salmonella typhi*. This poor antibody response to tetanus toxoid in asthmatic patients, who were not receiving systemic steroid therapy, was supported by another study, although the study did not include a control group.¹⁴ On the other hand, Hamilos et al¹⁴ reported that all asthmatic patients (n = 9) showed normal antibody responses to pneumococcal antigens (3, 7F, 9N, and 14) except 1 asthmatic patient who failed to respond to 7F. This study finding was supported by others.⁶² However, little is known about the impact of asthma status on antibody response to viral antigens. A few previous studies suggest that asthmatic patients had compatible antibody response to influenza A^{51,63} and varicella vaccine⁵² but had a decreased antibody response to influenza B vaccine, perhaps due to steroid intake. In addition to microbial factors, host factors also play a significant role in determining humoral immune response to microbial antigens. For example, a genetic factor such as HLA type plays a significant role in humoral immune response to measles virus antigens.^{25,64,65} Also, poor antibody response to a vaccine among asthmatic patients has been attributed to systemic steroid intake or high-dose inhaled corticosteroid, although it may be a surrogate indicator for severe asthma, and, thus, it may be difficult to discern the impact of severe asthma on humoral immune response.^{13,51} Our study is limited in addressing this concern. Therefore, although our study finding suggests normal humoral immune response to measles virus vaccine, it may not be generalizable to other microbial antigens, because heterogeneity of host (eg, severity of asthma or genetics) and microbial factors (eg, antigenic structure and properties)^{29,66} may elicit different humoral immune responses. Given the heterogeneity of humoral immune responses to microbial antigens among asthmatic patients, we urge caution when using seroprevalence of an antibody as a marker for exposure to microbial infections in relation to subsequent development of asthma unless the nature of the humoral immune response to a specific microbial antigen is clearly understood.

For cell-mediated immunity in children with vaccine failure, most healthy children who had measles virus vaccine failure had normal cellular immunity, which plays a protective role in seronegative individuals.^{67,68} Is it true for asth-

matic children? This may be an important question to address, because we found a significant proportion of asthmatic patients with vaccine failure (9.6%) or equivocal vaccine response (6.4%). However, this may be a difficult question to answer, because the inverse relationship between cell-mediated immunity and atopic disorder has been reported.^{11,12,69} For example, a previous study reported that 8 (9.2%) of 87 asthmatic children and adults and 1 (1.2%) of 86 healthy individuals failed to mount delayed-type hypersensitivity response ($P < .02$)¹¹ and 45% of patients with atopic dermatitis and 27% of healthy individuals failed to show delayed-type hypersensitivity response ($P < .001$).¹² In support of this speculation, potential suppression of cell-mediated immunity by a biased T_H2 response has been demonstrated for both viral¹⁵⁻²² and bacterial infections.^{23,24} Also, measles virus vaccination itself results in suppression of lymphoproliferative response (ie, cell-mediated immunity) and T_H2 -predominant cytokine responses (ie, increased production of interleukin-4).⁷⁰ This issue is further complicated by a recent study finding that suggested that the cytokine responses after measles virus vaccine are associated with genetic factors such as HLA class II genes.⁷¹ Therefore, we have only circumstantial evidence that asthmatic children who have measles vaccine failure may have much more severe disease or higher mortality when they acquire measles compared with nonasthmatic children with vaccine failure. This speculation may explain the study findings on the inverse relationship between measles infection during childhood and subsequent development of asthma due to increased disease severity or mortality to measles among asthmatic children, leading to a selection bias with another postulated mechanism (ie, defect in interferon- β ⁷² and interferon- γ ^{73,74} in asthmatic patients).

The strengths of our study include the epidemiologic advantage of our study environment (ie, unified medical record system in self-contained health care environment), elimination of confounding effect of systemic steroids on the study findings, and ascertainment of asthma status by predetermined criteria. However, there are also inherent limitations in our study because of its retrospective design. Because our study population is predominantly white (93%), our results may not be generalizable to populations of other races or ethnicity. However, at cost of external validity, internal validity can be enhanced (ie, minimizing the confounding effect of ethnicity or race on measles vaccine responses).⁶⁴

In conclusion, our study results suggest that asthmatic children seem to have normal antibody response to measles virus vaccine. This finding should reassure public health officials, practitioners, and parents and clarifies that the previously reported relationship between exposure to measles infection and subsequent asthma status is not mediated through a reduced antibody response among asthmatic children. However, whether the study findings can be applied to other vaccines and whether asthmatic patients with vaccine failure have normal cell-mediated immunity need further study.

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REFERENCES

1. World Health Organization. Measles Fact Sheet. Geneva, Switzerland: World Health Organization; 2005.
2. Centers for Disease Control and Prevention. Measles, mumps, and rubella—vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 1998;47(No. RR-8):1–57.
3. Centers for Disease Control and Prevention. Postexposure prophylaxis, isolation, and quarantine to control an import-associated measles outbreak—Iowa, 2004. *MMWR Morb Mortal Wkly Rep.* 2004;53:969–971.
4. Centers for Disease Control and Prevention. Measles outbreak in a boarding school—Pennsylvania, 2003. *MMWR Morb Mortal Wkly Rep.* 2004;53:306–309.
5. Centers for Disease Control and Prevention. Measles—Duval County, Florida, 1991–1992. *MMWR Morb Mortal Wkly Rep.* 1993;42:81–83.
6. Centers for Disease Control and Prevention. Measles outbreak—Southwestern Utah, 1996. *MMWR Morb Mortal Wkly Rep.* 1997;46:766–769.
7. Centers for Disease Control and Prevention. Measles outbreak among school-aged children—Juneau, Alaska, 1996. *MMWR Morb Mortal Wkly.* 1996;45:777–780.
8. Centers for Disease Control and Prevention. Measles epidemic attributed to inadequate vaccination coverage—Campania, Italy, 2002. *MMWR Morb Mortal Wkly Rep.* 2003;52:1044–1057.
9. Centers for Disease Control and Prevention. Measles outbreak—Netherlands, April 1999. *MMWR Morb Mortal Wkly Rep.* 1999; 49:299–303.
10. Snapper WM. Interferon- γ and B cell stimulatory factor-1 reciprocally regulate Ig isotype production. *Science.* 1987;236:44.
11. Grove D, Burston T, Wellby M, Ford M, Forbes I. Humoral and cellular immunity in asthma. *J Allergy Clin Immunol.* 1975;55: 152–163.
12. Grove D, Reid JG, Forbes A. Humoral and cellular immunity in atopic asthma. *Br J Dermatol.* 1975;92:611–618.
13. Berger W, Pollock J, Kiechel F, Dunning M, Pearlman DS. Immunoglobulin levels in children with chronic severe asthma. *Ann Allergy.* 1978;41:67–74.
14. Hamilos DL, Young RM, Peter JB, Agopian MS, Ikle DN, Barka N. Hypogammaglobulinemia in asthmatic patients. *Ann Allergy.* 1992;68:472–481.
15. van Den Broek J, Bachmann M, Kohler G, et al. IL-4 and IL-10 antagonize IL-12-mediated protection against acute vaccinia virus infection with a limited role of IFN- γ and nitric oxide synthetase 2. *J Immunol.* 2000;164:371–378.
16. Graham MB, Braciale VL, Braciale TJ. Influenza virus-specific CD4⁺ T helper type 2 T lymphocytes do not promote recovery from experimental virus infection. *J Exp Med.* 1994;180: 1273–1282.
17. Moran TM, Isobe H, Fernandez-Sesma A, Schulman JL. Interleukin-4 causes delayed virus clearance in influenza virus-infected mice. *J Virol.* 1996;70:5230–5235.
18. Mahon BP, Katrak K, Nomoto A, Macadam AJ, Minor PD, Mills KH. Poliovirus-specific CD4⁺ Th1 clones with both cytotoxic and helper activity mediate protective humoral immunity against a lethal poliovirus infection in transgenic mice expressing the human poliovirus receptor. *J Exp Med.* 1995; 181:1285–1292.
19. Fischer JE, Johnson JE, Kuli-Zade RK, et al. Overexpression of interleukin-4 delays virus clearance in mice infected with respiratory syncytial virus. *J Virol.* 1997;71:8672–8677.
20. Clerici M, Shearer GM. The Th1-Th2 hypothesis of HIV infection: new insights. *Immunol Today.* 1994;15:575–581.
21. Clerici M, Shearer GM. A TH1→TH2 switch is a critical step in the etiology of HIV infection [see comment]. *Immunol Today.* 1993;14:107–111.
22. Barker E, Mackewicz CE, Levy JA. Effects of TH1 and TH2 cytokines on CD8⁺ cell response against human immunodeficiency virus: implications for long-term survival. *Proc Natl Acad Sci U S A.* 1995;92:11135–11139.
23. Kincy-Cain T, Clements JD, Bost KL. Endogenous and exogenous interleukin-12 augment the protective immune response in mice orally challenged with *Salmonella dublin*. *Infect Immun.* 1437;64:1437–1440.
24. Talbot T, Hartert TV, Arbogast PG, et al. Asthma as a risk factor for invasive pneumococcal disease. *N Engl J Med.* 2005; 352:2082–2090.
25. Jacobson R, Poland G, Vierkant R, et al. The association of class I HLA alleles and antibody levels after a single dose of measles vaccine. *Human Immunol.* 2003;64:103–109.
26. Poland G, Ovsyannikova I, Jacobson R, et al. Identification of an association between HLA class II alleles and low antibody after measles immunization. *Vaccine.* 2002;20:430–438.
27. Ovsyannikova IG, JK, Naylor S, Muddiman DC, Poland GA. Naturally processed measles virus peptide eluted from class II HLA-DRB1*03 recognized by T lymphocytes from human blood. *Virology.* 2003;312:495–506.
28. Ovsyannikova IG, Johnson KL, Naylor S, Muddiman DC, Vierkant RA, Poland GA. Identification and characterization of novel, naturally processed measles virus class II HLA-DRB1 peptides. *J Virol.* 2004;78:42–51.
29. Ovsyannikova IG, Poland GA, Easler NJ, Vierkant RA. Influence of HLA-DRB1 alleles on lymphoproliferative responses to a naturally processed and presented measles virus phosphoprotein in measles immunized individuals. *Human Immunol.* 2004; 65:209–217.
30. Lara-Marquez M, Yunis J, Layrisse Z, et al. Immunogenetics of atopic asthma: association of DRB1*1101 DQA1*0501 DQB1 haplotype with *Dermatophagoides* spp.-sensitive asthma in a sample of the Venezuelan population. *Clin Exp Allergy.* 1999; 29:60–71.
31. Torio A, Sanchez-Guerrero I, Muro M, et al. Analysis of the phenotypic distribution of HLA class I and class II in atopic and non-atopic asthma patients. *Eur J Immunogenet.* 2000;27:81–85.
32. Stephan V, Schmid V, Frischer T, et al. Mite allergy, clinical atopy, and restriction by HLA class II immune response genes. *Pediatr Allergy Immunol.* 1996;7:28–34.
33. Aron Y, Desmazes-Dufeu N, Matran R, et al. Evidence of a strong, positive association between atopy and the HLA class II alleles DR4 and DR7. *Clin Exp Allergy.* 1996;26:821–828.
34. Di Somma C, Charron D, Deichmann K, Buono C, Ruffilli A. Atopic asthma and TNF-308 alleles: linkage disequilibrium and association analyses. *Hum Immunol.* 2003;64:359–365.

35. Jeal H, Draper A, Jones M, et al. HLA associations with occupational sensitization to rat lipocalin allergens: a model for other animal allergies? *J Allergy Clin Immunol.* 2003;111:795–799.
36. Moffatt MF, Schou C, Faux JA, et al. Association between quantitative traits underlying asthma and the HLA-DRB1 locus in a family-based population sample. *Eur J Hum Genet.* 2001;9:341–346.
37. Juhn Y, Kita H, Poland G, Amy Weaver, Pankratz S, Jacobson R. HLA genotype and childhood asthma. *Eur Respir J.* 2005;26:694s.
38. Asher MI, Weiland SK. The International Study of Asthma and Allergies in Childhood (ISAAC). *Clin Exp Allergy.* 1998;28:52–66.
39. Shaheen S, Aaby P, Hall AJ, et al. Measles and atopy in Guinea-Bissau. *Lancet.* 1996;347:1792–1796.
40. Lewis SA, Britton JR. Measles infection, measles vaccination and the effect of birth order in the aetiology of hay fever. *Clin Exp Allergy.* 1998;28:1493–1500.
41. Wickens KL, Crane J, Kemp TJ, et al. Family size, infections, and asthma prevalence in New Zealand children. *Epidemiology.* 1999;10:699–705.
42. Bodner C, Godden D, Seaton A. Family size, childhood infection and atopic diseases. *Thorax.* 1998;53:28–32.
43. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax.* 1998;53:927–932.
44. Kuyucu SSY, Tuner A, Sackesen C, Adahoglu G, Sumbuloglu V, Sekerel BE. Determinants of atopic sensitization in Turkish school children: effects of pre- and post-natal events and maternal atopy. *Pediatr Allergy Immunol.* 2004;15:62–71.
45. Paunio M, Heinonen O, Virtanen M, Leinikki P, Patja A, Peltola H. Measles history and atopic diseases: a population-based cross-sectional study. *JAMA.* 2000;283:343–346.
46. Bager PWT, Rostgaard K, Hjalgrim H, Melbye M. Age at childhood infections and risk of atopy. *Thorax.* 2002;57:379–382.
47. Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: historical follow up by record linkage. *BMJ.* 1997;314:1003–1008.
48. Olesen AB JS, Thestrup-Pedersen K. Atopic dermatitis is increased following vaccination for measles, mumps and rubella or measles infection. *Acta Derm Venereol.* 2003;83:445–450.
49. Kurland L, Molgaard CA. The patient record in epidemiology. *Sci Am.* 1981;245:54–63.
50. Advisory Committee on Immunization Practices. Recommendation for childhood immunization schedule. *MMWR Morb Mortal Wkly Rep.* 1995;44:1–9.
51. Hanania NA, Sockrider M, Castro M, et al. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. *J Allergy Clin Immunol.* 2004;113:717–724.
52. Verstraeten T, Jumaan AO, Mullooly JP, et al. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. *Pediatrics.* 2003;112(2):e98–103.
53. Yunginger J, Reed CE, O'Connell EJ, Melton J, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma: incidence rates, 1964–1983. *Am Rev Respir Dis.* 1992;146:888–894.
54. Yawn B, Yunginger JW, Wollan P, Reed CE, Silverstein M, Harris A. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clin Immunol.* 1999;103:54–59.
55. Silverstein M, Reed CE, O'Connell EJ, Melton L, O'Fallon W, Yunginger JW. Long-term survival of a cohort of community residents with asthma. *N Engl J Med.* 1994;331:1537–1541.
56. Hunt W, Silverstein M, Reed CE, O'Connell EJ, O'Fallon W, Yunginger JW. Accuracy of the death certificate in a population-based study of asthmatic patients. *JAMA.* 1993;269:1947–1952.
57. Beard M, Yunginger JW, Reed CE, O'Connell EJ, Silverstein MD. Interobserver variability in medical record review: an epidemiological study of asthma. *J Clin Epidemiol.* 1992;45:1013–1020.
58. Bauer B, Reed CE, Yunginger JW, Wollan P, Silverstein MD. Incidence and outcomes of asthma in the elderly: a population-based study in Rochester, MN. *Chest.* 1997;111:303–310.
59. Silverstein MD, Yunginger JW, Reed CE, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol.* 1997;99:466–474.
60. Juhn YJ, Sauve JS, Katusic SK, Vargas D, Weaver A, Yunginger J. The influence of neighborhood environment on the incidence of childhood asthma: a multilevel approach. *Soc Sci Med.* In press.
61. Juhn Y, Weaver A, Katusic S, and Yunginger J. Mode of delivery at birth and development of asthma: a population-based cohort study. *J Allergy Clin Immunol.* 2005;116:510–516.
62. Lahood N, Emerson SS, Kumar P, Sorensen RU. Antibody levels and response to pneumococcal vaccine in steroid-dependent asthma. *Ann Allergy.* 1993;70:289–294.
63. McIntosh K, Foy H, Modlin JF, Boyer KM, Hilman BC, Gross PA. Multicenter two-dose trials of bivalent influenza A vaccines in asthmatic children aged six to 18 years. *J Infect Dis.* 1977;136(suppl):S645–S647.
64. Poland G, Jacobson R, Colbourne A, et al. Measles antibody seroprevalence rates among immunized Inuit, Innu and Caucasian subjects. *Vaccine.* 1999;17:1525–1531.
65. Poland G. Immunogenetic mechanisms of antibody response to measles vaccine: the role of the HLA genes. *Vaccine.* 1999;17:1719–1725.
66. Kovarik J, Martinez X, Pihlgren M, et al. Limitations of in vivo IL-12 supplementation strategies to induce Th1 early life responses to model viral and bacterial vaccine antigens. *Virology.* 2000;268:122–131.
67. Wu VH, McFarland H, Mayo K, Hanger L, Griffin DE, Dhib-Jalbut S. Measles virus-specific cellular immunity in patients with vaccine failure. *J Clin Microbiol.* 1993;31:118–122.
68. Ruckdeschel JC, Graziano KD, Mardiney MR Jr. Additional evidence that the cell-associated immune system is the primary host defense against measles (rubeola). *Cell Immunol.* 1975;17:11–18.
69. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science.* 1997;275:77–79.
70. Ward BJ, Griffin DE. Changes in cytokine production after measles virus vaccination: predominant production of IL-4 suggests induction of a Th2 response. *Clin Immunol Immunopathol.* 1993;67:171–177.
71. Ovsyannikova IG, Jacobson RM, Ryan JE, et al. HLA class II alleles and measles virus-specific cytokine immune response following two doses of measles vaccine. *Immunogenetics.* 2005;56:798–807.
72. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial

-
- epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med*. 2005;201:937–947.
73. Warner JA ME, Jones AC, Quint DJ, Colwell BM, Warner JO. Is deficiency of interferon gamma production by allergen triggered cord blood cells a predictor of atopic eczema? *Clin Exp Allergy*. 1994;24:423–430.
74. Campbell DE, Kemp AS. Measles and atopy in African children [comment]. *Lancet*. 1996;348:825.

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