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Asthma Status and Waning of Measles Antibody Concentrations after Measles Immunization

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Abstract

Background—Asthmatics have increased risks of common and serious microbial infections including vaccine preventable diseases. Little is known about whether asthma influences waning of humoral immunity. We assessed whether asthma status influences waning of anti-measles virus antibody concentrations over time.

Methods—The study utilized a cross-sectional study cohort of healthy children who had been immunized with one-dose of MMR-II at age approximately 15 months. Between 5 and 12 years of age, measles vaccine virus-specific antibody (IgG) values were measured by EIA and considered seropositive if the EIA index unit was ≥ 1. The medical records were reviewed to determine asthma status during the first 18 years of life by applying predetermined criteria for asthma. A least squares regression model was used to evaluate the effect of asthma status on the relationship between measles antibody titer and time elapsed between the initial measles vaccination and measurement of measles antibody concentrations.

Results—Of the 838 eligible children, 281 (34%) met criteria for asthma. Measles antibody waned over time (r=-0.19, p<0.001), specifically more rapidly in asthmatics (r=-0.30, p<0.001, a

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decrease of -0.114 unit per year) than non-asthmatics (r=-0.13, p=0.002, a decrease of -0.046 unit per year) (p-value for interaction=0.010). This differential waning rate resulted in a lower mean (SD) measles antibody concentration [1.42 (0.67) vs. 1.67 (0.69), p=0.008] and lower seropositivity rate (73% vs. 84%, p=0.038) in asthmatics than non-asthmatics starting around 9.3 years after the initial measles vaccination.

Conclusion—Asthma status is associated with waning kinetics of measles antibody among children.

Keywords

Asthma; epidemiology; humoral immunity; waning; measles

Introduction

In 2010 there were 139,000 deaths due to measles globally.[1] Despite the effectiveness of the vaccine, measles outbreaks continue to occur throughout the world. There were 222 measles cases in the US reported from 31 states in 2011 and more than 30,567 measles cases reported in the WHO European Region.[2] Five European countries (France, Italy, German, Spain and Romania) accounted for 90% of these cases.[3]

Despite the reported long lasting humoral immunity against measles (25 years to life-long),[4,5] there are some concerns about waning or decay of measles vaccine-induced humoral immunity in terms of the potential for re-emergence of measles in developed countries[6,7] and the possible impediment to the eradication of measles,[7,8] A few studies have predicted the difficulty of sustaining complete elimination of measles due to waning of immunity based on mathematical models (or even primary vaccine failure).[8,9] Research efforts concerning identification of factors potentially associated with waning of measles vaccine virus-specific antibody are limited. A few previous studies have reported general subject characteristics (sociodemographic or serologic features) in relation to waning of measles antibody.[8-11] To date, no study has been conducted to assess the impact of prevalent immune-mediated chronic conditions such as asthma on waning of measles vaccine virus-specific antibody. This concern becomes especially relevant considering asthma has been reported to be associated with an increased risk of microbial infections[12-14] and suboptimal innate[15] and adaptive immune functions.[16-18] Also, a few recent papers demonstrated evidence of waning of pertussis, mumps, and measles vaccine-induced immunity in children and its potential impact on public health.[8, 19,20] Despite the public health concerns over the outbreaks of vaccine preventable diseases in the United States and elsewhere, currently there are scant data about factors influencing waning of vaccine-induced humoral immunity.

We explored whether asthma status affects waning of adaptive immunity and hypothesized that asthmatics have a more rapid waning of measles antibody than non-asthmatics. To test this hypothesis, we compared waning of measles antibody between children with and without a history of asthma using subjects from a previous cross-sectional community vaccine study.

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Methods

Study design and subjects

The study utilized a cross-sectional cohort of healthy children residing in Olmsted County, Minnesota who had been enrolled in a previous vaccine study.[21,22] Study subjects of this present study were obtained from the original study designed to examine seroprevalence of measles vaccine virus-specific antibody in 1993 (n=876). Briefly, the original study cohort (n=876) included healthy children, ages 5-12 years, who had been immunized with one-dose of MMR-II vaccine (Merck, West Point, PA) at approximately age 15 months between 1981-1992 (MMR vaccination status was confirmed by medical record documentation).[21,22] The original study cohort was identified through the school district using a population-based stratified sampling. Although a two-dose MMR vaccine policy in the US was started in 1989, at the time of the original study conducted, study subjects had received only one dose of MMR vaccine (none of study subjects had received two doses of MMR). Although a majority of subjects had received the first MMR vaccine around 15 months as shown in the table below, some subjects (8%) had received it at >24 months of age. Since all subjects resided in a geographic area with no circulating measles virus, the presence of measurable measles antibody could reasonably be attributed to the single dose of vaccine.[23,24]

A second study based on this cohort was conducted between 2002 and 2006 to ascertain asthma status of the original vaccine study cohort and compared measles vaccine virus-specific antibody values based on a single M-M-R vaccination between asthmatic and non-asthmatics.[22] This second study included 838 eligible subjects from the original study cohort (n=876) after excluding 38 subjects (n=24 for no research authorization for additional research studies and n=14 for insufficient information for determining asthma status). This present study was based on the second study cohort

Dependent variable

The dependent variable in this study was measles vaccine virus-specific IgG concentrations measured by an IgG whole virus-specific enzyme immunoassay (EIA) (MeaslesELISA, BIoWhittaker, Walkersville, MD).[21] According to the manufacturer, readings of the EIA index units ≥1.0 are “positive”.

Independent variables

The main independent variable was asthma status during the first 18 years of life as defined by the criteria as delineated below. The criteria was used to ascertain asthma status in the previous study mentioned above[22] which have been extensively used in epidemiologic investigations for asthma and found to have high degree of reliability.[25,26] We divided asthma status into two categories (asthmatics vs. non-asthmatics regardless of asthma status at the time of enrollment or measurement of measles antibody) and three categories (asthmatics at the time of enrollment vs. asthmatics who developed asthma after enrollment or measurement of measles antibody vs. non-asthmatics). We combined both definite and probable asthma as asthma cases because most of the probable asthma cases became definite asthma over time[26]

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Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma and/or if each of the following three conditions were present, and they were considered to have *probable* asthma if only the first two conditions were present:[26]

1. History of cough with wheezing, and/or dyspnea, 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 disturbance by nocturnal cough and wheeze
    - Nonsmoker (14 years or older)
    - Nasal polyps
    - Blood eosinophilia higher than 300/uL
    - Positive wheal and flare skin tests OR elevated serum IgE
    - History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to allergen
    - Pulmonary function tests showing one FEV_1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV_1 of higher70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
    - Favorable response to bronchodilator (e.g., improvement of symptoms, peak flow meter, or FEV1 in spirometry (≥12%) after bronchodilator therapy)

Statistical Analysis

The time elapsed between the initial measles vaccination and measurement of measles antibody titers were evaluated in two ways: 1) as a continuous measurement in years, and 2) as deciles. To determine the deciles, the elapsed time intervals for all subjects were ordered from shortest to longest and the subjects were classified into 10 groups with an equal number of subjects (roughly 84) in each group, with the first decile consisting of subjects with the shortest time interval.

We adopted an analytic approach for assessing the effect of time since vaccination on effectiveness of vaccine using regression methods similar to the approach proposed by Nicolai et al.[27] Ordinary linear least squares regression methods were applied given that the distribution of measles antibody concentrations, overall and within asthmatics and non-asthmatics, followed a Gaussian distribution upon visual inspection of the normal probability plot and the Kolmogorov-Smirnov normality test. We assessed whether the impact of elapsed time since vaccination on measles antibody (waning) varied depending on asthma status and included asthma status, elapsed time since vaccination, and its interaction term in the model reflected in Equation 1.

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$$y=\alpha+\beta 1(elapsed\ time\ since\ vaccination)+\beta 2(asthma)+\beta 3(asthma*elapsed\ time\ since\ vaccination)+\varepsilon \quad \text{(Equation 1)}$$

where y is the estimated measles antibody values, α is an intercept (average of measles antibody), β1 is parameter estimate for elapsed time since vaccination, β2 is a parameter estimate for asthma status, β3 is a parameter estimate for the interaction term between asthma status and elapsed time since vaccination, and ε is an error term (residual). Separate models were fit considering the elapsed time since vaccination in years and in deciles, respectively. Significance of the interaction term between asthma and elapsed time since vaccination directed whether to carry out stratified analyses of waning of measles antibody by asthma status. A second model, equation 2, was then fit separately for asthmatics and non-asthmatic.

$$y=\alpha+\beta i\ (elapsed\ time\_\ i)+\varepsilon \quad \text{(Equation 2)}$$

where y is estimated measles antibody values, α is an intercept (average of measles antibody), βi is the parameter estimate (slope or regression coefficient) for each decile (i= 1 to 10, i.e., elapsed time since vaccination), and ε is an error term (residual). In this model, the referent group is the group of children whose elapsed time since vaccination was the shortest (i.e., elapsed time_1). Then, based on the parameter estimates (βi) for elapsed time since vaccination in deciles, we identified the cut-off decile at which waning of measles antibody started becoming significant compared to the referent group whose elapsed time since vaccination was the shortest. Within each subset, we compared measles antibody titers between the two or three asthma categories using the two-sample t-test or an F-test from a one-way ANOVA, and we compared seropositivity rates between the asthma categories using a chi-square test. Correlation coefficients were estimated using the Pearson correlation coefficient. All statistical significance was tested at a two-sided alpha error of 0.05. We did not apply adjustments for multiple comparisons since the analysis was based on *a priori* hypothesis testing. The SAS version 9.2 (SAS Institute, Cary, NC) was used for analysis.

Results

Study cohort

Of the eligible 838 children for the present study, 425 (50.7%) were male, 778 (92.8) were Caucasian, 157 met asthma criteria prior to enrollment, and 124 met asthma criteria after enrollment (Table 1). The mean (SD) age at index date for asthma was 8.1 (5.1) years based on all 281 asthmatics. Only one asthmatic child took a systemic steroid within 14 days prior to the specimen collection and there were only three asthmatic children who took either a burst-course of systemic corticosteroid or inhaled corticosteroids, or both within 3 months of antibody measurement (two subjects took both medications). The measles antibody values for these 3 subjects were within the range of antibody concentrations for the rest of the 154 subjects who were asthmatic prior to enrollment without systematic corticosteroid therapy. The mean (SD) age at the time of measurement of measles antibody was 9.3 (2.1) years. There were 67 subjects (8.0%) who had received the first MMR vaccination older than 2 years of age. The proportions of these subjects did not differ by asthma status (9.0% for non-asthmatics, 5.7% for asthmatics before enrollment, and 6.5% for asthmatics after enrollment,

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p=0.33). Among the 67 who received their MMR at later age, the mean (SD) measles antibody value was 1.85 (0.67) compared to 1.82 (0.80) for the 771 who received their MMR vaccine prior to age 24 months (two-sample t-test, p=0.77). The mean (SD) measles antibody titers was 1.82 (0.79), the median (IQR) was 1.79 (1.25, 2.31), and the distribution was sufficiently normally distributed (Kolmogorov-Smirnov normality test for a Gaussian distribution, p=0.306). None of these subject characteristics varied significantly across the ordered deciles (p=0.26 for male vs. female, p=0.28 for Caucasian vs. non-Caucasian, p=0.22 for HLA DR3 allele presence vs. absence, except an increase in the mean age at index date of asthma across the ordered deciles (p=0.026).

Waning of measles vaccine virus-specific antibody values and asthma status

There was a significant interaction between the elapsed time since vaccination and asthma status, suggesting that the relationship between the elapsed time since vaccination and measles antibody concentrations varies depending on asthma status (Supplemental Digital Content 1, Table). When we entered ages at the first MMR vaccination as a continuous variable and a categorical variable (<24 months vs. ≥ 24 months) in the regression model, it was not significant in predicting measles antibody values (p=0.51) and all parameter estimates in the model including the interaction term between asthma and elapsed time virtually remain unchanged (data not shown). Therefore, subsequent analyses were stratified by asthma status. The overall correlation coefficient for measles antibody values and the elapsed time since vaccination in years and in deciles was r= -0.19 (p<0.001) and r= -0.19 (p<0.001), respectively. Using the elapsed time since vaccination in years, the differential waning of measles antibody between asthmatics and non-asthmatics is illustrated in Supplemental Digital Content 2, Figure, showing a more rapid waning of measles antibody in asthmatics (r= -0.30, p<0.001) than non-asthmatics (r= -0.13, p=0.002) and this difference was statistically significant (p=0.010). The change in measles antibody in the EIA index unit per year is a decrease of -0.114 among asthmatics and -0.046 among non-asthmatics. Comparing the three groups of asthma status (no asthma, asthma prior to enrollment, and asthma after enrollment), we found similar trends of more rapid waning of measles antibody in asthmatics regardless of asthma status at enrollment (Supplemental Digital Content 3, Figure; r= -0.32, p<0.001 for asthmatics before enrollment and r= -0.27, p=0.003 for asthmatics after enrollment; p=0.82 for the comparison of the two correlations). As summarized in Supplemental Digital Content 1, Table, the p-values for the comparison of the correlation between asthmatics before enrollment vs. non-asthmatics were 0.015-0.025 depending on elapsed time in deciles or years, respectively. The p-values for the comparison of the correlation between asthmatics after enrollment vs. non-asthmatics were 0.05-0.1. Supplemental Digital Content 4, Figure shows the trends of mean of measles antibody values in EIA index units in deciles.

Differential waning kinetics for measles vaccine virus-specific antibody values in asthmatics

In the regression model for non-asthmatics, none of the parameter estimates (βi) for waning of measles antibody titers were significant (Supplemental Digital Content 5, Table). However, the waning of measles antibody titers in asthmatics became much more rapid

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during the 8th (9.3-10.0 years from the measles vaccination) thru 10th (more than 10.7 years from the measles vaccination) deciles, compared to the 1st thru 7th deciles.

Comparisons of measles vaccine virus-specific antibody values by asthma status

We compared measles antibody values and seropositivity before and after the cutoff (i.e. before and after the 8th decile) identified for significant waning of measles antibody values between asthmatics and non-asthmatics (Table 2). There were no significant differences in measles antibody values and seropositivity between asthmatics and non-asthmatics before significant waning of measles antibody values (1-7th deciles). However, asthmatics had a lower mean (SD) measles antibody value [1.67 (0.69) vs. 1.42 (0.67); p=0.008] and lower seropositivity rate (83.7 vs. 72.5%, p=0.038) than non-asthmatics after significant waning of measles antibody values (8-10th deciles). When we divided asthma into two categories, asthma before and after enrollment, we found similar results.

Discussion

This is the first study demonstrating evidence for the potential negative impact of asthma on a more rapid waning of measles antibody. After a differential waning of measles antibody occurred, asthmatics had lower antibody values and lower seropositivity (72.5% vs. 83.7%) than non-asthmatics (Table 2). We believe 10% difference in seropositivity between asthmatics and non-asthmatics is significant considering that the main rationale for the ACIP's two-dose recommendation for measles vaccine in 1989 was to reduce vaccine failure after the first dose of vaccine (up to 5%).[28]

Systemic corticosteroids are unlikely to account for the waning of measles antibody in asthmatics in our study because only one and three asthmatic children took either a burst-course of systemic steroid or inhaled corticosteroid, or both within 14 and 90 days of enrollment, respectively and their antibody values were within the range of antibody values for the rest of the 154 subjects who were asthmatic prior to enrollment without systematic corticosteroid therapy. In addition, burst-course or inhaled corticosteroids have a minimal impact on immune response.[29-33] None of the potential covariates including HLA DR3 allele (associated with seronegativity of measles antibody)[21] accounted for our study findings (data not shown). Although a previous study reported that age at the first MMR vaccination was an important factor associated with risk of measles,[34] it was not significantly associated with antibody values and did not affect the influence of asthma on waning of antibody value over time. Overall, asthma is associated with a more rapid waning of measles antibody leading to a lower seropositivity of measles antibody among asthmatics than non-asthmatics. Alternatively, waning of measles antibody may be a previously unrecognized immunologic feature of asthma. A previous study reported that a significant proportion of asthmatics aged 1.6-17 years, who had received two doses of MMR, became seronegative for measles (40-43%) and mumps (25-39%) immunity.[35] Children who developed asthma after enrollment of the study (i.e., measurement of measles antibody) had a more rapid waning of measles antibody than non-asthmatics (slope, -0.117 vs. -0.046; p=0.025) and their degree of waning was similar to that for those who developed asthma prior to enrollment (slope= -0.107) as shown in Figure 1 and 2. These results suggest that

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mechanisms related to the development of asthma are likely to underlie the association between asthma and waning of measles antibody. Our study results are reminiscent of recent study findings on impaired lung function among newborns[36] and increased susceptibility to bacterial colonization in newborns *prior to* development of asthma.[37] One noteworthy finding was an initial trend of slightly higher values of antibody during the first 7 deciles among asthmatics (which might be a reason for positive β-coefficient for asthma in the regression model in Supplementary Table 1) followed by the subsequent more rapid waning of antibody in asthmatics between 8th and 10th deciles as shown in Figure 2 and 3. Vos et al reported early and brief exposure (4 hours) of B cells to IL-4 enhanced a subsequent immunoglobulin secretory response but the continued presence of IL-4 during B cell stimulation suppressed antibody responses in a mouse model.[38] Whether our study findings are related to the results reported by Vos et al needs to be studied in the future.

Only a few studies have reported general characteristics of subjects in relation to waning of measles antibody[8-11] and there is no literature with which we can compare our study results. Amanna et al reported duration of humoral immunity to common viral and vaccine antigens including humoral immunity against measles virus based on 45 subjects who were followed for a period of up to 26 years.[4] They reported four different profiles of longitudinal decays of antibodies. They described one profile that all antibody values decreased at relatively similar rates acknowledging “unknown host-specific factors” affecting waning of antibody.[4] Interestingly, this profile with relatively short-lived antibody values belonged to an asthmatic (Subgroup analysis on waning of antibody by asthma status. Correspondence with Dr. Mark Slifka, Rochester, Minnesota, 2012).

This result may be consistent with what we observed in our study results. Children with house-dust mite (HDM) sensitization had lower pneumococcal surface protein A titers at three years of age as well as lower anti-P6 antibody for *H. influenza*[16] and lower pneumococcal antibody titers. [30,39] We recently reported that HDM-stimulated IL-5 secretion was inversely correlated with pneumococcal antibody values in asthmatics.[39]

The mechanisms underlying our study findings are unknown. The potential mechanisms for differential plasma cell lifespan and the duration of humoral immunity have been proposed and multiple mechanisms are likely to be involved.[40] Clinical and public health significance of our study findings remains to be determined. The waning of measles antibody titers in asthmatics 9-10 years after one M-M-R vaccination in our study may be noteworthy historically. These children would be in grades 6-9, when their titers were low and in the late 1980’s, the measles outbreaks occurred often in children in middle schools and high schools in the United States.[41] Although measles outbreaks did not occur in our study setting, one may speculate that asthma-associated waned measles antibody (9-10 years after one M-M-R vaccination) might be at least a partial explanation for measles outbreaks when all children in the US received only one M-M-R vaccine.

The strength of this study was the ability to determine index date of asthma and predetermined criteria for asthma of subjects during their first 18 years of life. Another strength of our study is the epidemiologic advantages of our self-contained health care environment and the availability of the nearly entire medical record of all subjects. There

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were no measles outbreaks during the original study period ensuring that all antibody titers were acquired from vaccination. Also, our study has the inherent limitations of being a retrospective study. As the first exploratory study on the study question we did not address other immunologic parameters such as avidity of measles antibody and cell-mediated immunity. Also, given the unknown protective measles antibody value, the difference in measles antibody values in EIA between asthmatics and non-asthmatics needs to be further studied in relation to protectivity from measles infection. Our study results were based on one-dose of measles vaccine but the results provide an important insight into the nature of asthma in relation to durability of vaccine-induced humoral immunity. Given the reported waning of measles antibody after two doses of measles vaccine which may delay waning by 5-10 years,[42] whether our study findings are germane to children who received two doses of measles vaccine needs to be determined. Our study was designed as a cross-sectional study and our study findings need to be replicated in a longitudinal prospective study. In our study subjects, asthmatics appear to be over-represented. However, based on the number of children with asthma at the time of enrollment of the original study (n=157), asthma prevalence was 18.7% which is close to asthma prevalence by a physician diagnosis of asthma (17.6%) among children in grades kindergarten through 12th grade in our community.

In conclusion, asthma status is associated with waning of measles antibody among children and this influence takes place prior to onset of clinical asthma. Waning of measles antibody may be an important unrecognized immunologic feature of asthma. The study findings need to be replicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of subjects by asthma status.

Characteristic	Non-asthmatics (N=557)	Asthmatics	
		Met asthma criteria prior to enrollment (N=157)	Met asthma criteria after enrollment (N=124)
Male, n (%)	274 (49.2%)	98 (62.4%)	53 (42.7%)
Age at MMR vaccination (months)			
Mean (SD)	19.1 (10.9)	18.2 (11.3)	18.6 (10.1)
Median (IQR)	15.9 (15.2, 18.2)	15.6 (15.2, 17.5)	15.9 (15.1, 17.5)
Age at enrollment (years)			
Mean (SD)	9.4 (2.1)	9.4 (2.2)	9.1 (2.0)
Median (IQR)	9.4 (7.5, 11.1)	9.7 (7.4, 11.4)	9.0 (7.8, 10.7)
Caucasian, n (%)	514 (92.3%)	147 (93.6%)	117 (94.4%)
Maternal education, n (%)			
Less than high school	3 (0.9%)	1 (1.0%)	1 (1.3%)
High school	42 (13.2%)	13 (13.3%)	8 (10.5%)
Some college	138 (43.4%)	48 (49.0%)	34 (44.7%)
College degree	135 (42.5%)	36 (36.7%)	33 (43.4%)
Not recorded	239	59	48
Family history of asthma, n (%)			
No	322 (70.2%)	66 (44.0%)	63 (54.3%)
Yes	137 (29.8%)	84 (56.0%)	53 (45.7%)
Not recorded	98	7	8
Family history of atopy, n (%)			
No	298 (66.2%)	65 (44.8%)	50 (43.1%)
Yes	152 (33.8%)	80 (55.2%)	66 (56.9%)
Not recorded	107	12	8
Elapsed time since vaccination (years)*			
Mean (SD)	7.8 (2.2)	7.9 (2.2)	7.6 (2.1)
Median (IQR)	7.8 (5.9, 9.7)	8.0 (5.8, 9.9)	7.3 (6.1, 9.2)
Range	(0.4-12.5)**	(2.9-11.9)	(1.8-11.7)
Follow-up duration (years)†			
Mean (SD)	14.2 (4.9)	15.8 (3.4)	15.7 (3.2)
Median (IQR)	16.6 (11.7, 18.0)	17.3 (14.8, 18.0)	17.3 (14.0, 18.0)
Range	(0-18.0)	(0.2-18.0)	(1.6-18.0)

SD, standard deviation; IQR, interquartile range.

* Elapsed time between measles vaccination and measurement of antibody.

** Although a majority of subjects had received the first MMR vaccine around 15 months, some subjects had received it at later age close to the time of study enrollment.

† Duration of follow-up was calculated from first clinic registration to the last follow-up date or 18th birthday, whichever came first.

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Table 2

Comparisons of 1) measles vaccine virus-specific antibody levels and 2) seropositivity of measles antibody between children with asthma and those without asthma before significant waning of measles antibody levels (1-7th deciles) and after significant waning of measles antibody (8-10th deciles)

The elapsed time since vaccination in *1-7th deciles* (*before* significant waning of measles antibody)					
Asthma status defined using two categories	**Measles antibody (mean ±SD)**	**p-value two-sample t-test**	**Asthma status defined using three categories**	**Measles antibody (mean ±SD)**	**Overall p-value by F-test from one-way ANOVA**
Non-asthmatics (N=385)	1.88 (0.80)	0.15	Non-asthmatics (N=385)	1.88 (0.80)	0.34
Asthmatics (N=201)	1.99 (0.84)		Asthmatics at enrollment (N=106)	1.98 (0.86)	
			Asthmatics after enrollment (N=95)	2.00 (0.82)	
Asthma status defined using two categories	**Seropositivity (%)**	p-value Chi-square test	Asthma status defined using three categories	**Seropositivity (%)**	p-value Chi-square test
Non-asthmatics (n=385)	339 (88.0%)	0.99	Non-asthmatics (N=385)	339 (88.0%)	p=0.99
Asthmatics (n=201)	177 (88.1%)		Asthmatics at enrollment (N= 106)	93 (87.7%)	
			Asthmatics after enrollment (N=95)	84 (88.4%)	
The elapsed time since vaccination in ***8-10th deciles*** (*after* significant waning of measles antibody)					
Asthma status defined using two categories	**Measles antibody (mean ±SD)**	p-value two-sample t-test	Asthma status defined using three categories	**Measles antibody (mean ±SD)**	Overall p-value by F-test from one-way ANOVA
Non-asthmatics (N=172)	1.67 (0.69)	0.008	Non-asthmatics (N=172)	1.67 (0.69)	0.024†
Asthmatics (N=80)	1.42 (0.67)		Asthmatics at enrollment (N=51)	1.38 (0.60)	
			Asthmatics after enrollment (N=29)	1.49 (0.77)	
Asthma status defined using two categories	**Seropositivity (%)**	p-value Chi-square test	Asthma status defined using three categories	**Seropositivity (%)**	p-value Chi-square test
Non-asthmatics (n=172)	144 (83.7%)	0.038	Non-asthmatics (N=172)	144(83.7%)	P=0.057
Asthmatics (n=80)	58 (72.5%)		Asthmatics at enrollment (N=51)	39(76.5%)	
			Asthmatics after enrollment (N=29)	19 (65.5%)	

†p=0.008 for the comparison of measles antibody levels between asthmatics at enrollment and non-asthmatics and p=0.21 for the comparison of measles antibody between asthmatics after enrollment and non-asthmatics