Asthma and risk of breakthrough varicella infection in children

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ABSTRACT

Background: We recently reported a more rapid waning of vaccine-induced humoral immunity (measles vaccine) in children with asthma. It is unknown if asthma affects susceptibility to vaccine-preventable diseases.

Objective: To determine whether asthma is associated with an increased risk of vaccine-preventable disease, e.g., breakthrough varicella infection.

Methods: This was a retrospective population-based case-control study that examined cases of breakthrough varicella among children between 2005 and 2011. Children with a diagnosis of breakthrough varicella infection in Olmsted County, Minnesota (infection of >42 days after vaccination) between 2005 and 2011 and two age- and sex-matched controls were enrolled for each case. Asthma status was determined by using predetermined criteria. Conditional logistic regression models were used to calculate matched odds ratios (OR) and their corresponding 95% confidence intervals (CI).

Results: Of the 165 cases and their 330 matched controls, 48% were boys and the mean (standard deviation) age at the index date was 6.6 ± 3.5 years for both cases and controls. Of the 330 controls, 80 (24%) had two doses of the varicella vaccine compared with only 23 (14%) of the 165 cases (OR 0.29 [95% CI, 0.14–0.61]; $p = 0.001$). Children with a history of asthma ever had a higher risk of developing breakthrough varicella compared with those without a history of asthma (adjusted OR 1.63 [95% CI, 1.04–2.55]; $p = 0.032$) when adjusting for elapsed time since the first varicella vaccination and the number of varicella vaccine doses.

Conclusions: A history of asthma might be an unrecognized risk factor for breakthrough varicella infection. Children with asthma should follow the two-dose varicella vaccine policy.

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In addition to asthma-related morbidity (e.g., poorly controlled asthma), asthma has been associated with increased risks of serious (e.g., serious pneumococcal disease and pertussis), and common (e.g., otitis media) microbial infections among individuals with both severe and less-severe asthma.¹ The Advisory Committee on Immunization Practices now recommends that people with asthma ages 19–64 years receive a single dose of 23-valent pneumococcal polysaccharide vaccine.² As discussed in the recent review, it has been postulated that T-helper 2 predominant immune milieu observed in individuals with asthma or

other atopic conditions results in suboptimal innate and adaptive immunity and an increased propensity to microbial infections, including vaccine-preventable disease, e.g., pertussis.¹

On exploring the mechanisms that underlie the association between asthma and increased risk of vaccine-preventable infections, e.g., measles or pertussis,^{3,4} we recently examined a possibility of waning of vaccine-induced humoral immunity over time in children with asthma (i.e., secondary vaccine failure). We found that, compared with children without asthma, those with asthma who had received one dose of measles, mumps, rubella vaccine had a more rapid waning of measles vaccine virus-specific immunoglobulin G levels over time.⁴ This differential waning resulted in a lower seropositive rate in children with asthma than in children without asthma (73 versus 84%; $p = 0.038$). Importantly, children who developed asthma subsequently (i.e., no asthma at the time of antibody measurement) also had a more rapid waning of anti-measles antibody levels than children without asthma. Although analysis of these data indicated a more rapid waning of vaccine-induced adaptive immune function against the measles virus over time in children with asthma, it was difficult to address the question, whether this waning, indeed, increases the risk of clin-

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ical measles because there were no measles occurrences in our study population.

Instead, breakthrough varicella infection in children provides a more feasible disease model to test the hypothesis. Asthma may increase the risk of breakthrough varicella infection through a potentially more rapid waning of vaccine-induced adaptive immune function over time in children. Yet, little is known about the risk of breakthrough varicella in children with asthma,⁵⁻⁷ and the current literature has limitations in addressing the association because previous studies were based on a small sample size, did not account for steroid use, and relied solely on International Statistical Classification of Diseases, Ninth Revision (ICD-9) codes for identification of breakthrough varicella infection and asthma.^{8,9} To address the limitations of previous studies, we conducted a population-based case-control study in Olmsted County, Minnesota, which applied predetermined criteria for both breakthrough varicella infections and asthma instead of ICD codes or self-report.

METHODS

This study was approved by the institutional review boards of both the Mayo Clinic and the Olmsted Medical Center. P.J. Umaretiya participated in the study design, collected data, interpreted the results, and drafted and approved the manuscript; J.B. Swanson participated in the study design, interpreted the results, and reviewed and approved the final manuscript; H.J. Kwon collected data, interpreted the results, and reviewed and approved the manuscript; C. Grose participated in the study design, interpreted the results, and reviewed and approved the final manuscript; C. Lohse performed data analysis, interpreted the results, and reviewed and approved the final manuscript; and Y.J. Juhn, applied for the funding, participated in the study design, interpreted the results, and helped to draft the manuscript. All the authors reviewed and approved the manuscript.

Study Design

This study was designed as a population-based case-control study. We identified population-based patients with breakthrough varicella infection between January 1, 2005, and December 31, 2011, who met the criteria for breakthrough varicella infection as described in the Identification of Cases section.¹⁰ We enrolled two birthdate (within 6 months) matched and sex-matched control subjects who had been vaccinated with at least one dose of the varicella vaccine and had not developed varicella infection before the index date of their corresponding matched cases.

Study Subjects: Identification of Cases

Breakthrough varicella infection was defined as an illness with acute onset of generalized papulovesicular rash without other apparent cause that occurred >42 days after varicella vaccination.¹⁰ All varicella cases were initially identified by using the ICD-9 code 052.xx (varicella zoster infection) from January 1, 2005, to December 31, 2011, in children <18 years of age at the index date of infection. Subsequently, we reviewed medical records to ascertain case status. A case was defined as “definite” if documentation indicated characteristic varicella skin rash (generalized papulovesicular or multistage rash or papular rash with vesicle, pustule, or scabbed over lesions but no history of varicella infection in the past) and the presence of a confirmed epidemiologic link or confirmatory laboratory testing. A case was defined as “probable” if documentation indicated characteristic varicella rash with a physician diagnosis or only a confirmed epidemiologic link with a physician diagnosis. A case was defined as “possible” if only physician diagnosis of varicella zoster infection was present. The exclusion criteria included the following: (1) a history of chicken pox and/or varicella zoster per medical record review; (2) no research authorization; (3) not an Olmsted County, Minnesota, resident at the index date; (4) unable to locate a medical record or insufficient information; (5) other viral or microbial disease at the index date (*e.g.*, herpes simplex infection); (6) did not receive varicella vaccine before the index date; (7) did not meet criteria for breakthrough varicella (varicella infection within 42 days of varicella vaccination for cases); (8) chronic health conditions that make ascertainment of asthma difficult, such as chronic lung diseases (cystic fibrosis, pulmonary fibrosis, α 1-antitrypsin deficiency, major chest deformity that compromises lung function, and bronchiectasis), tracheobronchial foreign body at or about the incidence date of asthma, hypogammaglobulinemia (immunoglobulin G < 2.0 mg/mL), primary immunodeficiency, or other immunosuppression; (9) wheezing that occurs only in response to anesthesia or medications; and (10) physician diagnosis of herpes simplex or zoster.

Selection of Control Subjects

The matching criteria for controls included the original clinic registration date within 1 year, closest clinic visit date to the index date of the corresponding matched cases within 1 year, birthdate within 6 months, and sex. We randomly selected two controls who met the matching criteria from a list of Olmsted County pediatric residents during the study period by using the resources of the Rochester Epidemiology Project. Because we matched the registration year and index date between patients and their controls, the

Table 1 Definition of asthma

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 months when symptoms were absent
3. Two or more of the following:
 - Sleep disturbance caused by nocturnal cough and wheeze
 - Nonsmoking status (>14 years old)
 - Nasal polyps
 - Blood eosinophil count > 300/ μ L
 - Positive wheal-and-flare skin test results or increased serum IgE levels;
 - History of hay fever or infantile eczema or cough, dyspnea, and wheezing regularly on exposure to an antigen
 - Pulmonary function tests that show one FEV₁ or forced vital capacity measurement of >70% of predicted value and another with at least 20% improvement to an FEV₁ or >70% of predicted value or a methacholine challenge test that shows a $\geq$ 20% decrease in FEV₁
 - A favorable clinical response to bronchodilator (>12%)

IgE = immunoglobulin E; FEV₁ = forced expiratory volume in 1 second.
Subjects classified as having either definite or probable asthma were included as subjects with asthma in analyses because previous studies showed that most subjects with probable asthma subsequently become subjects with definite asthma.
Definite asthma: If all three criteria listed were present or physician diagnosis plus any of two criteria listed.
Probable asthma: Only the first two criteria were present or documentation of physician-diagnosed asthma.

follow-up duration for the patients and the controls was similar. Exclusion criteria for the controls were the same as the cases.

Exposure Ascertainment (asthma status)

The predetermined criteria used to determine asthma status in all case and control subjects is depicted in Table 1. The predetermined criteria used in this study have been found to have high reliability (80–94% agreement rate) by previous studies in asthma epidemiology, and these criteria have been extensively used in previous epidemiologic investigations for asthma.^{1,11} Subjects classified as having either definite or probable asthma were included as subjects with asthma in analyses because previous studies showed that most subjects with probable asthma subsequently become subjects with definite asthma.^{12,13} Asthma control status was defined by asthma symptoms, asthma-related health care utilizations, or therapy (medication use) for asthma within 6 months before the index date of breakthrough varicella infection.¹⁴

Data Analysis

The primary aim of the analysis was to determine the association between a history of asthma and the risk of breakthrough varicella infection when adjusting for the number of varicella vaccinations and the elapsed time since varicella vaccinations. Data were fit to conditional logistic regression models to calculate odds ratios (OR) and their corresponding 95% confidence in-

tervals (CI). As a secondary analysis, the effectiveness of two-dose varicella vaccine in preventing breakthrough varicella infection was calculated by the following $(1 - [\text{the matched OR for two-dose varicella vaccine}]) \times 100$.¹⁵ Statistical analyses were performed by using the SAS software package (SAS Institute, Cary, NC). All the tests were two-sided, and *p*-values of <0.05 were considered statistically significant.

RESULTS

Study Subjects with Breakthrough Varicella

The characteristics of the study subjects are summarized in Table 2. We identified 207 potential varicella cases by using ICD-9 codes during the study period. Of these 207 cases, 42 were excluded: 21 subjects did not receive varicella vaccine before the index date, 12 subjects did not meet the criteria for breakthrough varicella infection, 5 subjects developed other viral or bacterial infections (*e.g.*, herpes simplex infection), 1 subject did not have research authorization, 1 subject had insufficient information in the medical record to determine asthma status, and 2 subjects had immunosuppression (*n* = 1) and major chest deformity that compromised lung function (*n* = 1). A total of 330 birthday- and sex-matched controls were enrolled from an eligible pool of controls who met the matching and enrollment criteria by using the resources of the Rochester Epidemiology Project. Among the 165 cases, 48% were boys and 85% were white. The mean (SD)

Table 2 Sociodemographic and clinical characteristics of study subjects in relation to the risk of breakthrough varicella infection

	Controls (N = 330)	Cases (N = 165)	OR (95% CI)
Sociodemographic and clinical characteristics			
Age at index date of breakthrough varicella, y*			
Mean (SD)	6.6 ± 3.5	6.6 ± 3.5	—
Median (IQR)	6 (4–9)	7 (4–9)	—
Male sex, no. (%)	158 (48)	79 (48)	—
Age at the first varicella vaccination, mo			
Mean (SD)	20 ± 18.5	17.5 ± 14.4	0.98 (0.97–1.0)
Median (IQR)	12 (12–15)	12 (12–15)	
Race (N = 475), no. (%)			
White, non-Hispanic	265 (83)	133 (85)	1.23 (0.72–2.12)
Other	53 (17)	24 (15)	1.0 (reference)
Maternal educational status (n = 131), no. (%)			0.22 (0–0.82)#
No high school or high school graduates	5 (5)	7 (19)	
Some college or more	10 (11)	5 (14)	
College	53 (56)	22 (61)	
Graduate education	27 (28)	2 (6)	
Unknown	235	129	
Household tobacco exposure, no. (%)			
No	263 (90)	122 (84)	1.0 (reference)
Yes	30 (10)	24 (16)	1.80 (0.96–3.38)
Unknown	37	19	
Influenza vaccination before index date, no. (%)			
No	163 (50)	89 (54)	1.0 (reference)
Yes	165 (50)	75 (46)	0.81 (0.54–1.22)
Unknown	2	1	
Asthma before index control status, no. (%)			
No asthma	266 (81)	124 (75)	1.0 (reference)
Asthma well controlled	61 (18)	39 (24)	1.39 (0.87–2.21)
Asthma not well controlled	3 (1)	2 (1)	1.48 (0.25–8.95)
ICS use 12 mo before the index date, no. (%)			
No asthma	266 (81)	124 (75)	1.0 (reference)
Asthma without ICS use	55 (17)	35 (21)	1.39 (0.85–2.27)
Asthma with ICS use	9 (3)	6 (4)	1.41 (0.50–3.99)
ICS 3 mo before varicella vaccination, no. (%)			
No	307 (99)	147 (97)	1.0 (reference)
Yes	4 (1)	4 (3)	1.50 (0.34–6.70)
Systemic corticosteroids use 3 mo before varicella vaccination, no. (%)			
No	309 (99)	148 (97)	1.0 (reference)
Yes	3 (1)	4 (3)	2.67 (0.60–11.92)
Comorbid condition, no. (%)§			
No	324 (98)	164 (99)	1.0 (reference)
Yes	6 (2)	1 (1)	0.33 (0.04–2.77)
Vaccine associated variables			
Varicella vaccination status at index date, no. (%)			
1 dose	250 (76)	142 (86)	1.0 (reference)
2 doses	80 (24)	23 (14)	0.29 (0.14–0.61)

Continued

Table 2 Continued

	Controls (N = 330)	Cases (N = 165)	OR (95% CI)
Time from first varicella vaccination to index date, no. (%)			
<4 y	125 (38)	53 (32)	1.0 (reference)
≥4 y but <7 y	94 (28)	51 (31)	4.68 (1.33–16.55)
≥7 y	111 (34)	61 (37)	7.30 (1.71–31.22)
Time since varicella vaccine dose 1, y			
Mean (SD)	5.3 ± 3.1	5.6 ± 3.1	1.29 (1.05–1.59)
Median (IQR)	5.3 (2.7–7.8)	5.6 (2.8–8.1)	
Time since varicella vaccine dose 2, y			
Mean (SD)	1.4 ± 1.6	2.5 ± 1.9	1.63 (0.97–2.75)
Median (IQR)	1.0 (0.2–2.0)	2.1 (1.2–3.6)	
Atopic conditions			
History of asthma ever, no. (%)			
No	245 (74)	108 (65)	1.0 (reference)
Yes	85 (26)	57 (35)	1.60 (1.03–2.47)
History of atopic dermatitis ever (N = 494), no. (%)			
No	249 (75)	118 (72)	1.0 (reference)
Yes	81 (25)	46 (28)	1.21 (0.79–1.85)
History of allergic rhinitis ever, no. (%)			
No	231 (70)	108 (65)	1.0 (reference)
Yes	99 (30)	57 (35)	1.24 (0.83–1.84)
History of food allergy ever, no. (%)			
No	317 (96)	155 (94)	1.0 (reference)
Yes	13 (4)	10 (6)	1.57 (0.67–3.67)

OR = odds ratio; CI = confidence interval; SD = standard deviation; IQR = interquartile range; ICS = inhaled corticosteroid.

*Matched variables for analysis.

#OR per a 1-unit increase of educational level as a continuous variable.

§The comorbid conditions included neurosurgical trauma or procedure (n = 3), inflammatory bowel disease (n = 2), type I diabetes (n = 1), and cardiac disease (n = 1).

age at the index date was 6.6 ± 3.5 years for both subjects and controls. The number of definite, probable, and possible breakthrough varicella cases were 19 (12%), 131 (79%), and 15 (9%), respectively. The majority of the patients (83%) had mild cases (defined as having <50 skin lesions).

Varicella Vaccination Schedules and Risk of Breakthrough Varicella Infection

Of the 330 controls, 80 (24%) had two doses of vaccination compared with only 23 (14%) of the 165 cases (OR 0.29 [95% CI, 0.14–0.61]; $p = 0.001$). The elapsed time in years since the first varicella vaccination was significantly associated with an increased risk of breakthrough varicella infection. Compared with the subjects with an elapsed time of <4 years since varicella vaccination, those with an elapsed time of 4–7 years (OR 4.68 years [95% CI, 1.33–16.55 years]; $p = 0.017$) and those with an elapsed time of >7 years (OR 7.30

[95% CI, 1.71–31.22]; $p = 0.007$) had significantly higher risks of breakthrough varicella infections.

Asthma and the Risk of Breakthrough Varicella Infection

The results on the association between asthma and the risk of breakthrough varicella infection are summarized in Tables 2 and 3 (multivariate models adjusted for the number of varicella vaccinations and elapsed time since the first varicella vaccination). Of the 165 cases, 57 (35%) had asthma ever, whereas 85 (26%) of the 330 controls had asthma ever (OR 1.60 [95% CI, 1.04–2.47]; $p = 0.033$). The association between asthma ever and breakthrough varicella remained significant (OR 1.63 [95% CI, 1.04–2.55]) after adjusting for the number of varicella vaccinations before the index date and for the elapsed time in years since the first varicella vaccination. When we limited the analysis to definite asthma ($n = 50$ of all 142 the subjects with asthma),

Table 3 Multivariate analyses for the association between a history of asthma ever and the risk of breakthrough varicella infection

	Odds ratio (95% confidence interval)
Model 1	
Asthma ever	
No	1.0 (reference)
Yes	1.60 (1.03–2.49)
Varicella vaccinations	
1 dose	1.0 (reference)
2 doses	0.29 (0.14–0.61)
Model 2	
Asthma ever	
No	1.0 (reference)
Yes	1.61 (1.04–2.49)
Time from varicella vaccination to index date	
<4 y	1.0 (reference)
≥4 y but <7 y	4.76 (1.35–16.78)
≥7 y	7.21 (1.69–30.74)
Model 3	
Asthma ever	
No	1.0 (reference)
Yes	1.63 (1.04–2.55)
Time from varicella vaccination to index date	
<4 y	1.0 (reference)
≥4 y but <7 y	7.08 (1.83–27.37)
≥7 y	11.26 (2.36–53.82)
Varicella vaccinations	
1 dose	1.0 (reference)
2 doses	0.24 (0.11–0.52)

definite asthma was significantly associated with the risk of breakthrough varicella infection when controlling for the vaccine doses and elapsed time (adjusted OR 1.91 [95% CI, 1.14–3.19]).

When we limited analysis to definite, probable, and possible breakthrough varicella cases separately, we found similar trends of positive associations between asthma status and increased risks of breakthrough varicella infection, but individual comparisons did not reach statistical significance due to smaller sample sizes: OR 3.17 (95% CI, 0.80–12.64) for definite cases, OR 1.26 (95% CI, 0.77–2.05) for probable cases, and OR 5.62 (95% CI, 1.14–27.79) for possible cases. There was no significant difference in the mean (SD) age at the first varicella vaccination between subjects with asthma and those without asthma (18.7 ± 12.7 versus 19.3 ± 18.2 months; $p = 0.21$). There was no statistically

significant difference between the proportion of cases (25%) and controls (19%) who had asthma before the index date ($p = 0.16$). Asthma control status (well controlled versus uncontrolled) did not affect the risk of breakthrough varicella infection. A history of atopic dermatitis, allergic rhinitis, or food allergy was associated with slightly increased risks of breakthrough varicella infection, but the associations were not statistically significant, as shown in Table 2.

Corticosteroid Use and the Risk of Breakthrough Varicella

Inhaled corticosteroid or systemic corticosteroid use in the 3 months before varicella vaccination was not significantly associated with an increased risk of breakthrough varicella infection. Similarly, inhaled corticosteroid use before the index date of breakthrough varicella was not associated with the risk of breakthrough varicella.

DISCUSSION

Given our previous observation of a more rapid waning of vaccine-induced humoral immunity, analysis of our study results supported the hypothesis that asthma increases the risk of breakthrough varicella infection. This association persisted despite adjusting for doses of vaccination and elapsed time since the first vaccination. Our study confirmed the effectiveness of two-dose varicella vaccine in preventing breakthrough varicella infection.^{15,16} The effectiveness of two-dose varicella vaccine in preventing breakthrough varicella infection in our study was 71% (1–0.29) whereas previous studies showed 64% (estimated from the provided data)¹⁶ to 95%.¹⁵ Although one-dose varicella vaccine efficacy significantly wanes over time, as reported previously, two-dose varicella vaccine efficacy seems less likely to wane over time, which supported previous observations.^{15,17}

Although a concurrent history of asthma before the index date was not associated with the risk of breakthrough varicella infection, a history of asthma ever was associated with an increased risk of breakthrough varicella infection independent of age, sex, number of varicella vaccinations, and elapsed time since the first varicella vaccination. These results indicated that children with an immunogenetic predisposition to asthma may still have a potential risk for breakthrough varicella infection because they already have airway, clinical, and immunologic features of asthma before the development of clinical asthma.^{4,18,19} There is evidence that the effect of atopic conditions on the risk of microbial infections or immune dysfunction might begin before the onset of clinical asthma.^{19–21} These findings may be consistent with the notion that some phenotypic features of asthma (e.g., poor lung function)

begin before the development of clinical asthma in children (even during newborn period) (*i.e.*, the “hypothesis of early programming of asthma”).¹⁸

Previous studies have been conflicting in their evidence for the association between asthma or other atopic conditions and the risk of breakthrough varicella infection due to a small number of cases (*i.e.*, number of the study subjects were between 14–81) at specific settings (*e.g.*, day care),^{8,22,23} and case definitions based solely on ICD-9 codes with an unclear definition of asthma status and overadjustment.⁹ In our population-based study, we used predetermined criteria for breakthrough varicella and asthma status. Inhaled or systemic corticosteroid use before varicella vaccination and the index date, which was not assessed in previous studies, did not account for the association between asthma status and the risk of breakthrough varicella infection, but the sample size was too small to address this association. Influenza vaccination rates were similar between cases and controls (slightly higher in controls than in cases), which ensures similar health care access to immunization practice and supports discriminant validity because influenza vaccination is not supposed to be associated with the risk of breakthrough varicella infection.

Despite the different case definitions (*i.e.*, definite, probable, and possible), we found similar trends of positive associations between asthma status and an increased risk of breakthrough varicella infection, which indicated a consistent direction of the association between asthma status and the risk of breakthrough varicella infection. We analyzed the results after stratifying subjects by varicella vaccine doses (one versus two doses). Although the results approached statistical significance in each stratified result due to a smaller sample size, the association was consistent (positive association) (data not shown). Along these lines, recently, we reported that asthma status was associated with the increased risk of herpes zoster, which indicated the potential impact of asthma on reactivation of latent infection by varicella zoster virus.^{24,25}

The mechanisms that underlie the association between asthma and the risk of breakthrough varicella infection are unknown. Asthma is associated with impairment in innate and adaptive immunity and a T-helper 2 predominant immune response has been reported to be related to such immune dysfunctions.¹ Recently, we reported that children with clinical asthma and those with an immunogenetic predisposition to asthma (develop asthma later) have a more rapid waning of measles vaccine virus-specific immunoglobulin G levels over time than those without asthma (a decrement of -0.114 unit per year in children with asthma versus -0.046 unit per year in children without asthma; p value for trend = 0.01).⁴

Because a history of asthma ever is associated with the risk of breakthrough varicella infection, our study results might be consistent with these study findings. We postulated that asthma may affect the kinetics of vaccine-induced memory B cells or long-lived plasma cells. A previous longitudinal study assessed durability of varicella antibody through 9 years of follow-up and found that nearly 100% of subjects had maintained protective antibody titers (≥ 5 glycoprotein enzyme-linked immunosorbent assay units/mL), which indicated persistence or durability of varicella vaccine-induced antibody levels.¹⁶ However, the titers significantly increased over time (*e.g.*, the mean titer at 10 years postvaccination was 57.8 versus 12.5 at 6 weeks after vaccination), which indicated boosting immunity through exogenous exposure and/or endogenous reactivation.¹⁶ A direct comparison between well-characterized asthma status and different vaccine doses in relation to the risk of a breakthrough varicella infection should be made with clinical and/or epidemiologic and immunogenicity evaluation in a prospective study.

Although the literature and the current guidelines do not support suppressive effects of inhaled corticosteroids and a burst dose of oral steroids on humoral or cell-mediated responses to vaccines, including varicella vaccine,^{26–32} it is worth identifying a subgroup of patients with asthma who are treated with corticosteroids and who might have suboptimal immune responses to vaccines and develop severe varicella infection are needed.^{33,34} Along these lines, prospective studies are needed to determine whether patients with severe asthma, particularly steroid-dependent asthma, or with other severe atopic conditions are at an increased risk of breakthrough varicella infection or other vaccine-preventable diseases.

Strengths of our study included a population-based study design and epidemiologic advantages, including a self-contained health care environment and availability of a medical record linkage system for medical episodes, patients, and health care providers, which allowed us to capture all medical episodes to ascertain exposure and outcome status. Also, we relied on predetermined criteria for asthma and breakthrough varicella infection, not ICD-9 codes or self-report. Our study had inherent limitations as a retrospective study. We did not verify varicella infection in case ascertainment by using laboratory measures (*e.g.*, polymerase chain reaction) but used the definition for breakthrough varicella infection used in a previous study¹⁰ and is similar to that used for previous investigations for varicella, including the Council of State and Territorial Epidemiologists.^{16,35,36}

This case ascertainment is unlikely to result in differential misclassification bias given the consistent trends of positive associations between asthma status

and increased risks of breakthrough varicella infection among definite, probable, and possible cases. Certain variables were not available (*e.g.*, atopic sensitization status) and had significant missing data points. In our study, although the prevalence rates of allergic rhinitis (30%) and food allergy (4%) were similar to those at the national level (26–33% for allergic rhinitis^{37–39} and 3.8–4.3% for food allergy⁴⁰), the patients with asthma seemed to be overrepresented in our control group (26%) compared with that at the national level (range, 4–17%).^{41,42} Although we did not include varicella serology in our study, when considering the reported inconsistency of cutoff for protective titers, limited sensitivity, and variability of varicella-zoster virus assay methods, serology data may have been of little additional value in our study.^{43,44}

CONCLUSION

This first population-based case-control study, to our knowledge, indicated that children with a history of asthma might be at an increased risk of breakthrough varicella infection. Asthma might be a potentially unrecognized risk factor for breakthrough varicella infection.

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