

Association between varicella zoster virus infection and atopic dermatitis in early and late childhood: A case-control study

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Background: Wild-type varicella zoster virus infection (WTVZV) early in childhood has been shown to protect against the development of asthma and atopy.

Objective: To determine whether WTVZV in childhood protects against atopic dermatitis (AD).

Methods: This retrospective, practice-based, case-control study randomly sampled 256 children and adolescents (age 1-18 years) with AD and 422 age-matched healthy controls from 2005 to 2007. Observations were made before the *a priori* hypothesis.

Results: (1) A single episode of WTVZV in childhood is associated with decreased odds ratio (OR) of developing AD (conditional logistic regression; OR, 0.55; 95% CI, 0.34-0.89; $P = .01$). (2) When using intervals for age corresponding to bimodal distribution of age of WTVZV infection, the effects of WTVZV infection are significant when occurring at age 0 to 8 years (OR, 0.56; 95% CI, 0.35-0.90; $P = .02$), but not at 8 to 18 years (OR, 0.50; 95% CI, 0.19-1.31; $P = .16$). Considering 5-year intervals has similar findings. (3) WTVZV is associated with decreased odds of moderate AD (multinomial logistic regression; OR, 0.08, 95% CI, 0.04-0.15; $P < .0001$) or severe AD (OR, 0.04; 95% CI, 0.01-0.13; $P < .0001$). (4) WTVZV in children is associated with prolonged AD-free survival (Kaplan-Meier; median, 15.3 years; 95% CI, 10.9-18.0) compared with controls (median, 7.5 years; 95% CI, 4.8-11.9; log-rank test, $P < .0001$). (5) Children with WTVZV, compared with vaccine, who eventually develop AD require fewer pediatrician sick visits for management of AD (logistic regression; OR, 0.17; 95% CI, 0.06-0.51; $P = .001$).

Conclusion: WTVZV in childhood protects up to 10 years of age against AD, delays onset of AD symptoms, and decreases AD severity and office visits. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: Atopic dermatitis, varicella zoster virus, chickenpox, varicella vaccine, Varivax, eczema, atopy, asthma, allergic rhinitis, rhinoconjunctivitis, food allergy

Atopic dermatitis (AD) is a chronic, relapsing pruritic inflammatory disorder of skin that has reached epidemic proportions throughout the world. The prevalence of AD in schoolchildren in the United States is 17%,¹ up to 20% in children worldwide, and 1% to 3% in US adults.^{2,3} Prevalence rates of AD have rapidly increased over the past 30 years and continue to increase in many developing countries, although with significant variation between countries.⁴⁻¹⁰ Reasons for this increase are not known.

The etiology of AD is multifactorial. There exists a significant link between AD and genetic mutation of the filaggrin gene *FLG*, resulting in impaired skin-barrier function.¹¹⁻¹⁹ However, the rapid increase of AD prevalence suggests that there are likely additional factors that may either trigger or aggravate AD.

Improved hygiene in developed countries may account for the increase in AD (the hygiene hypothesis). Strachan²⁰ suggested that infections and unhygienic contact in childhood may confer protection against hay fever, allergic rhinoconjunctivitis (AR), and AD. Several studies have explained the hygiene hypothesis based on the observations that T_H1 responses induced by microbial infections can counterbalance allergen-induced T_H2 responses.²¹⁻²³ Certain childhood viral infections are associated with lower IgE levels,^{24,25} decreased IgE sensitization,²⁶ and asthma.²⁷ However, several studies have demonstrated no AD protective effects with some childhood infections, such as measles, actually increasing risk of AD.²⁸ It may be that only specific infections confer protection from AD, whereas others do not.

It is unknown whether wild-type varicella zoster virus infection (WTVZV) in early or late childhood is protective against development of AD. The identification of specific viral infections that protect against AD could help elucidate underlying mechanisms for suppression of AD, identify children at higher risk for AD, and potentially affect vaccination coverage for children.

In the current investigation, we use a retrospective case-control study of a pediatric cohort to determine the effect of WTVZV in early and late childhood on development of AD. The results of this study suggest that WTVZV infection up to 8 to 10 years of age protects against developing AD and is associated with decreased severity and delayed onset of AD symptoms and fewer AD office visits to the pediatrician.

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Abbreviations used

AAP: American Academy of Pediatrics
 AD: Atopic dermatitis
 AR: Allergic rhinoconjunctivitis
 IQR: Interquartile range
 OR: Odds ratio
 RSV: Respiratory syncytial virus
 Treg: Regulatory T
 VV: Varicella vaccine
 WTVZV: Wild-type varicella zoster virus infection

METHODS**Subjects and matching**

The study was approved by the institutional review board for human subjects of the SUNY Downstate Medical Center, Brooklyn, NY. Patients with AD (International Classification of Diseases, Ninth Revision diagnosis code: 691.8) and controls were randomly selected from the electronic medical record of outpatient pediatric practices in Brooklyn, NY, between January 2005 and December 2007. Selection for this retrospective case-control study was done using a computerized random-number generator list provided by a statistician who was not involved in the data collection. Inclusion criteria were children that received primary care at these practices, male or female, age 1 to 18 years. Exclusion criteria included diagnosis of AD before exposure to either WTVZV or first dose of varicella vaccine (VV), *in utero* WTVZV infection, history of autoimmune disorders or immunodeficiency, use of corticosteroids or immunotherapy, personal or family history of cigarette smoking, and incomplete follow-up. Controls were pairwise matched by age in years, with preferably 2 controls per case; however, cases in which only 1 age-matched control was found were also included. Cases and controls were linked by a blocking variable that was used for conditional logistic regression.

AD

Criteria for diagnosis of AD were based on guidelines from Hanifin and Rajka.^{29,30} Characteristics of AD lesions typically vary with age, although chronic and recurrent pruritis is found in all age groups. Distribution of eczematous lesions shifts with age, affecting cheeks and extensor surfaces of the extremities in infancy, and flexural areas and dorsal extremities in childhood and adolescence. At each well visit and sick visit for allergic disease, parents were routinely asked, as part of the review of systems, about symptoms of allergy affecting the skin, eyes, nose/oropharynx, lower airway, gastrointestinal tract, and any relationship to environmental and dietary triggers. The children were routinely examined by a pediatrician, and physical signs of AD, AR, and wheeze were documented. Date of diagnosis for these disorders was documented as the date of initial presentation of symptoms. Severity of AD was classified by a pediatrician as mild, moderate, or severe based on the extent and intensity of eczematous lesions, pruritus, and sleep disturbance without the use of an established scoring system.

WTVZV

History and date of onset of WTVZV were routinely screened by a physician to determine eligibility for VV by asking parents at well visits and physical examination at all visits. Date of WTVZV was documented as the date of initial presentation of symptoms.

Varicella vaccine

All patients who did not have a history of WTVZV were given the live attenuated VV (Varivax; Merck and Company, Inc, West Point, Pa) according to the recommended schedule of the American Academy of Pediatrics (AAP).³¹ From 1995 to 2006, patients received a single-dose vaccine; in 2006, the AAP's 2-dose vaccine schedule was initiated. The first dose was given at 12 to 15 months of age. The second dose was given at 4 to 6 years of age, but may have been given earlier provided that it was at least 3 months

after the first dose. Children 13 years or older received 2 doses at least 28 days apart according to the catch-up immunization schedule of the AAP.³¹

Sample size calculation

A priori power analysis was based on the Fisher exact test assuming 90% power, with the use of 2-sided tests, and an α level of .05.³² The nonexposure rate in the AD or referent group was predicted to be 85% on the basis of data from previous epidemiologic studies demonstrating 85% vaccine effectiveness at preventing WTVZV (see review³³). The odds ratio (OR) of developing AD after WTVZV was predicted to be 0.5 based on previous studies of asthma after ≥ 1 herpes-type virus infection, including WTVZV.²⁷ With 2:1 control matching, the number of patients needed was estimated to be 657, with 219 AD cases and 438 controls.

Statistical analysis

The baseline characteristics of those patients with and without AD were examined. Comparisons for categorical variables were done by χ^2 tests. All continuous variables of patient characteristics, including ages of WTVZV, VV, and first AD episode, were not normally distributed as judged by analysis of normality using Shapiro-Wilk and Kolmogorov-Smirnov tests ($P < .01$).^{34,35} Therefore, comparisons for continuous variables were done by nonparametric Mann-Whitney *U* tests. Data are presented as medians, interquartile ranges (IQRs), and ranges.

Regression analysis

Conditional logistic regression for matched analysis was used to determine whether WTVZV was associated with AD. Models were stratified by a blocking variable that represented age-matched pairs and included age as a covariate. WTVZV infection was encoded as a binary variable. The OR for AD was calculated with the 95% CI. To determine the association between WTVZV and other atopic diseases, logistic regression was used with asthma, AR, and food allergies, in particular, as the dependent variables. Because subjects were age-matched, current age was included as a covariate in all models.

Logistic regression was used to determine whether WTVZV was associated with more sick visits specifically for AD evaluation and/or management. The dependent variable was encoded as binary and represented as 0 or 1 versus >1 visits for AD.

Multinomial logistic regression was used to determine whether WTVZV was associated with decreased severity of AD. The dependent variable was encoded as a categorical variable from 1 to 3 representing mild, moderate, and severe, respectively. This approach was used because the model did not satisfy the proportional odds assumption.

Correction for multiple dependent tests ($k = 10$) with the approaches of Bonferroni, Benjamini and Hochberg,³⁶ and Benjamini and Yekutieli³⁷ yielded critical *P* values of .005, .03, and .017, respectively.

Survival analysis

Survival analyses with the Kaplan-Meier method³⁸ were used to determine whether WTVZV delayed the onset of AD. The time-to-event variable in all models was the time from either WTVZV or VV to diagnosis of AD or censoring, with the censoring variable based on AD status. Models were stratified by history of WTVZV. Log-rank statistics were calculated for testing homogeneity of survival functions across strata.³⁹ Median, mean, and SEM AD-free survival time were estimated. In some instances, the median value could not be calculated because the Kaplan-Meier and Lifetable estimators for these data never reached a failure probability greater than 0.50.

RESULTS**Population characteristics**

Two hundred ninety patients with AD were randomly selected for the study; 10 were excluded because of incomplete follow-up, and 24 were excluded on the basis of exclusion criteria. Four

TABLE I. Characteristics of the patients

Variable	AD (n = 256)	Control (n = 422)	P value†
Male sex, no. (%)	129 (50.4)	219 (52.4)	.61
Season of birth, no. (%)‡			
Winter	68 (26.6)	92 (22.0)	.34
Spring	78 (30.4)	120 (28.7)	
Summer	49 (19.1)	100 (23.9)	
Autumn	61 (23.8)	106 (25.4)	
Age (y)*	6.2 (6.6, 18.7)	6.6 (6.8, 18.8)	.44
Age at first AD episode (y)*	2.4 (4.6, 17.4)	—	—
Season of first AD episode, no. (%)‡			
Winter	72 (28.1)	—	.61
Spring	59 (23.1)	—	
Summer	66 (25.8)	—	
Autumn	59 (23.1)	—	
Age at WTVZV infection (y)*	3.2 (3.8, 13.5)	3.0 (4.9, 16.9)	.98
Age at first varicella vaccine (y)*	1.4 (1.3, 14.4)	1.4 (1.2, 15.0)	.64
Two doses of vaccine, no (%)	65 (25.4)	132 (31.3)	.10
Caucasian race, no. (%)	251 (98.1)	414 (99.0)	.27
IUTD§	252 (98.4)	416 (98.5)	.88

*Values are median (IQR, range).

†Season of birth: winter, December through February; spring, March through May; summer, June through August; autumn, September through November.

‡P values for the comparison between the atopic dermatitis and control group were calculated by Mann-Whitney U test, or χ^2 test, as appropriate.

§IUTD: all other immunizations up to date, including hepatitis A virus, hepatitis B virus, influenza, inactivated polio vaccine, and measles-mumps-rubella, according to the recommended vaccination schedule of the AAP.

hundred ninety-eight age-matched patients without history of AD were randomly selected as controls; 52 were excluded because of incomplete follow-up, and 24 were excluded on the basis of exclusion criteria. Patients with AD were similar to control patients with respect to sex (50.4% vs 52.4%; $P = .61$), race/ethnicity (98.1% vs 99.0%; $P = .27$), season of birth ($P = .34$), current age (median $\pm$ IQR, 6.2 ± 6.6 vs 6.6 ± 6.8 years; $P = .44$), age at WTVZV (median $\pm$ IQR, 3.2 ± 3.8 vs 3.0 ± 4.9 ; $P = .98$), and VV (median $\pm$ IQR, 1.4 ± 1.3 vs 1.4 ± 1.2 ; $P = .64$), number of doses of VV (25.4% vs 31.3% 2-dose vaccine; $P = .10$), and being up-to-date with other vaccinations (98.4% vs 98.5%; $P = .88$; Table I). Patients with AD were diagnosed at a median age of 6.2 years (IQR, 4.6), evenly throughout all 4 seasons ($P = .61$).

WTVZV protects against AD

Conditional logistic regression models were constructed by using the blocking variable based on current-age matching. Therefore, current age was included as a covariate in all final models, and increasing age was associated with decreased odds of AD (OR, 0.52; 95% CI, 0.31-0.87; $P = .02$).

Wild-type varicella zoster virus infection was associated with decreased odds of AD (conditional logistic regression; OR, 0.55; 95% CI, 0.34-0.89; $P = .01$; Table II). The association between WTVZV and AD remained significant in confounding models that included sex, ethnicity, season of birth, being up-to-date with other immunizations, and number of vaccine doses ($P = .001$ -.01).

The effect of age of WTVZV on the OR of AD was determined by constructing conditional logistic regression models using dummy variable coding of various intervals for age of WTVZV.

TABLE II. Conditional logistic regression analysis of effects of WTVZV and atopic disease on developing AD

Variables	No. of patients (%)		AD	
	AD	Control	OR (95% CI)†	P value
Age	—	—	0.52 (0.31-0.87)	.02
WTVZV	52 (20.31)	119 (28.20)	0.55 (0.34-0.89)	.01

†All conditional logistic regression models were stratified by blocking (matching) variable. There were no significant effects of controlling for sex, ethnicity, season of birth, other immunization up-to-date status, and number of VV doses in the model. Therefore, data are presented as ORs from parsimonious models with age included as a fixed covariate.

TABLE III. Multinomial logistic regression analysis of effects of WTVZV on severity of AD

Severity of AD	No. of patients (%)		AD	
	AD	Control	OR (95% CI)*	P value
Mild	125 (73.1)	35 (17.3)	1.00	—
Moderate	37 (21.6)	152 (75.3)	0.08 (0.04-0.15)	<.0001
Severe	9 (5.3)	15 (7.4)	0.04 (0.01-0.13)	<.0001

*All multinomial logistic regression models were stratified by blocking (matching) variable. There were no significant effects of controlling for sex, ethnicity, season of birth, other immunization up-to-date status, and number of VV doses in the model. Therefore, data are presented as ORs from parsimonious models with age included as a fixed covariate.

Age of WTVZV infection had a bimodal distribution (0-8 and 8-18 years; data not shown). When using these intervals, the effects of WTVZV infection were significant only when occurring at age 0 to 8 years (OR, 0.56; 95% CI, 0.35-0.90; $P = .02$), but not at 8 to 18 years (OR, 0.50; 95% CI, 0.19-1.31; $P = .16$). Similarly, when dividing age of WTVZV infection into 5-year intervals, the effects of WTVZV infection were significant when occurring at age 0 to 5 years (OR, 0.58; 95% CI, 0.36-0.94; $P = .03$) and 5 to 10 years (OR, 0.36; 95% CI, 0.13-0.99; $P = .047$), but not at 10 to 18 years (OR, 0.46; 95% CI, 0.16-1.30; $P = .14$). These data suggest that WTVZV even in late childhood is protective against AD.

Wild-type varicella zoster virus infection was associated with decreased odds of moderate AD (multinomial logistic regression; OR, 0.08; 95% CI, 0.04-0.15; $P < .0001$) or severe AD (OR, 0.04; 95% CI, 0.01-0.13; $P < .0001$; Table III). The association between WTVZV and severity of AD remained significant in confounding models that included sex, ethnicity, season of birth, being up-to-date with other immunizations, and number of vaccine doses ($P < .0001$).

WTVZV delays onset of AD

Kaplan-Meier analysis was used to assess whether WTVZV delayed onset of AD. WTVZV was found to prolong AD-free survival significantly compared with VV controls (median [95% CI], 15.3 [10.9-18.0] and 7.5 [4.8-11.9], respectively; log-rank test, $P < .0001$; Fig 1).

WTVZV results in fewer office visits for AD

The majority of patients with AD, with or without WTVZV, had only 1 office visit devoted to AD care (73.1% and 60.3%, respectively). However, patients with WTVZV had a lower maximum number of AD office visits than without WTVZV (4

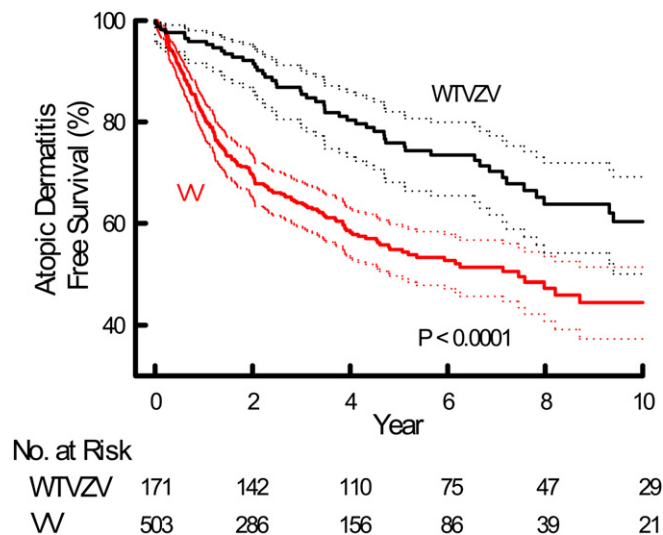


FIG 1. Kaplan-Meier survival analysis. Atopic dermatitis-free survival for pediatric patients with exposure to either WTVZV (black) or VV controls (red); survival plots (solid), 95% CIs (dotted). Log rank test *P* value presented.

vs 12). WTVZV was associated with decreased odds of multiple AD office visits (>1 ; logistic regression; OR, 0.08; 95% CI, 0.03-0.23; $P < .0001$; age-adjusted OR, 0.17; 95% CI, 0.06-0.51; $P = .001$).

WTVZV protects against asthma

The effects of WTVZV on asthma, allergic rhinoconjunctivitis, and food allergies were performed by logistic regression using the aforementioned variables as the dependent variable, and included current age as a covariate. WTVZV was associated with decreased odds of asthma (OR, 0.69; 95% CI, 0.65-0.73; $P = .002$), but not allergic rhinoconjunctivitis (OR, 0.70; 95% CI, 0.35-1.41) or food allergies (OR, 0.68; 95% CI, 0.21-2.20).

DISCUSSION

The current study demonstrates a strong association between WTVZV and protection against AD. We found that (1) a single episode of WTVZV in children is associated with decreased OR of developing AD, (2) these AD protective effects are found when WTVZV occurs up to 8 to 10 years of age, (3) WTVZV is associated with decreased OR of moderate or severe AD, (4) WTVZV delays onset of AD in children/adolescents that develop AD, (5) children with WTVZV who eventually develop AD require fewer pediatrician sick visits devoted to management of AD, and (6) WTVZV was also associated with decreased OR of developing asthma.

These findings in AD and asthma are consistent with studies of Illi et al²⁷ showing that children with WTVZV by age 3 years were less likely to develop asthma by age 7 years. Further, recent studies from our group demonstrated asthma-protective effects of WTVZV, with prolonged age of asthma onset and decreased symptoms and flare-ups.⁴⁰ However, Nilsson et al²⁶ found no association between past WTVZV and IgE sensitization. Prolonged protection by WTVZV could play an important role in risk

stratification and medical treatment of patients who are high risk for AD and atopy.

VV (Varivax) has been US Food and Drug Administration–approved since 1995 and has a well established safety profile.^{41,42} Numerous studies have demonstrated a significant decline of morbidity and mortality related to WTVZV in the United States after the introduction of widespread vaccination.^{43,44} We conclude that VV, despite its proven safety and benefit, by its very purpose is unable to confer the immunologic advantages that result from WTVZV. The introduction of widespread varicella vaccination and resultant decline of WTVZV in the United States may be a contributing factor in the increased prevalence of AD over the past few decades.^{1,45}

The results of this study suggest decreased health care utilization in patients who had WTVZV infection: (1) patients with WTVZV infection are less likely to develop AD and asthma; (2) patients with WTVZV infection who do progress to AD have a significantly prolonged AD-free survival before development of symptoms; and (3) it is therefore not surprising that patients with AD who had preceding WTVZV infection had fewer pediatric office visits devoted to their AD. Moreover, previous studies demonstrated decreased atopic disease after WTVZV infection.^{24-27,40} AD and the aforementioned atopic disorders constitute major public health and economic burdens. Previous studies using cost-effectiveness models have suggested that widespread varicella vaccination programs in childhood are cost-effective compared with the financial burden of WTVZV infection and its complications.^{44,46,47} However, such studies have not factored the secondary decrease in risk of AD and asthma. Because the AD-protective effects of WTVZV infection occur until 8 to 10 years of age, it is possible that delaying vaccination until such time would increase cost-effectiveness of widespread vaccination, improve long-term health outcomes with decreased atopic disease, and still effectively result in herd immunity.

Our finding that WTVZV occurring until 8 to 10 years of age protects against AD opposes the hypothesis that the protective effects of viral illnesses against atopic disease in children are solely attributable to the immature immune system found in the first year of life.^{27,48,49} Previous studies reported that WTVZV early in childhood was asthma-protective⁴⁰ and resulted in decreased serum IgE levels.²⁵ It is unknown whether the protective effects from atopy are specific to WTVZV. WTVZV directly infects immune cells, including peripheral T cells and monocytes (see review⁵⁰), suggesting that infection may directly influence these cells, resulting in long-term, or even permanent, changes of T-cell subsets or function. Verhagen et al⁵¹ found reduced numbers of CD4⁺CD25⁺ regulatory T (Treg) cells in skin of patients with AD. It is possible that WTVZV directly, or indirectly via other skin cells involved in Treg cell recruitment, restores local Treg cell function in skin. Alternatively, Fujimura et al⁵² suggested that improvement of AD after WTVZV could occur by WTVZV stimulation of IL-12 production in skin, resulting in local infiltration of Th1-dominant cells and/or suppression of IgE production. As yet, the mechanism behind the association of WTVZV and AD remains unknown. However, VV does not elicit similar protection from asthma and allergy, despite being a live attenuated vaccine and inducing robust innate and memory immune responses,⁵³ suggesting that WTVZV, but not VZV *per se*, is necessary.

Previous studies by others found EBV early in life is associated with lower prevalence of elevated IgE.²⁴ Moreover, both runny

nose and herpes-type viral infections, including varicella, herpes (zoster, febrilis, labialis), exanthema subitum, and stomatitis, are associated with decreased risk of asthma at school age.²⁷ This is in contrast to the proallergy and asthma effects seen with other respiratory viral infections such as respiratory syncytial virus (RSV), which can induce a virus-specific IgE response.⁵⁴⁻⁵⁸ One explanation for these differences is that proallergic epitopes exist in RSV that are not present in VZV. RSV-soluble G glycoprotein contains a T-cell superantigen that binds to the high-affinity IgE receptor on hematopoietic cells, basophils, mast cells, and monocytes, resulting in mast cell degranulation and release of T_H2 cytokines into the blood (see review⁵⁹). Moreover, although both VZV and RSV are respiratory viruses, VZV also results in cutaneous infection that has been suggested to promote ongoing local IFN production, T_H1-dominant skin infiltrates, and/or suppression of cutaneous IgE production.⁵² However, it is unknown whether the protective effects from atopy found in this study are secondary to VZV infection, specifically, severity and duration of any viral illness, or a combination thereof.

The results of this study found no association between gender and either AD or other atopic disorders. This is consistent with previous studies that found no predilection of either sex for AD.⁶⁰⁻⁶² However, other studies have found increased risk of AD in females.^{1,63-67}

This study has several strengths, including well powered sample sizes of cases and controls, and multiple statistical methodologies, all with consistent and significant results. The data used in this study are less likely to be affected by subjective parental interpretation and recall bias because diagnoses and other clinical information were obtained by a physician during clinical encounter and were not parent-based or questionnaire-based. Moreover, the incidence of WTVZV has decreased in some parts of the United States up to 84% between 1990 and 2001 after the introduction of VV.⁶⁸ Thus, a retrospective study was useful for recruiting adequate numbers of WTVZV cases.

This study has potential limitations. A retrospective/observational study may be more prone to selection bias. This was addressed by using a computerized random-number generator list for patient selection. A potential source of recall bias is that there can be an imprecision, on the order of days to weeks, for the reporting of ages of onset of WTVZV and AD. These potential recall biases were addressed by using the dates when respective symptoms first began rather than office visit dates. Despite having an adequate number of WTVZV cases and vaccine controls, there were no patients who were naive to VZV antigens—that is, neither WTVZV nor VV; we were unable to determine whether exposure to VZV antigen from VV may in and of itself decrease AD, compared with patients who were naive to VZV antigen. Because this study was retrospective, several important clinical factors were not collected, including stress and irritant exposures, and food and/or environmental histories. Moreover, AD scoring systems, such as the Scoring Atopic Dermatitis or the Eczema Area and Severity Index,^{69,70} were not recorded by the pediatrician during evaluation. Finally, this study is a limited-site study and should be confirmed in larger-scale studies.

In conclusion, the findings of this study help to elucidate further the protective role of WTVZV against AD. These studies suggest that children with WTVZV are less likely to develop AD, which may affect varicella vaccination in childhood and play a role in risk stratification and medical treatment of patients who are at high risk for AD and atopic disease. Moreover, the AD-protective

effects of WTVZV are found even when infection occurs in late childhood. Further studies are required to confirm, and to determine the mechanism of, WTVZV suppression of AD.

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Clinical implications: This study may affect varicella vaccination in childhood and play a role in risk stratification and medical treatment of patients who are at high risk for AD and atopic disease.

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