

A Retrospective Cohort Study of the Association of Varicella Vaccine Failure With Asthma, Steroid Use, Age at Vaccination, and Measles-Mumps-Rubella Vaccination

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ABSTRACT. *Objective.* Varicella breakthrough, the occurrence of varicella disease >42 days after vaccination, is indicative of vaccination failure. A sevenfold increased risk of breakthrough among vaccinated children with asthma was observed in a 1996 varicella outbreak in a child care center. More recent outbreak investigations have also identified age at vaccination as a potential risk factor for breakthrough. We assessed the association of varicella breakthrough with asthma, steroids, age at varicella vaccination, and timing of measles-mumps-rubella (MMR) vaccination.

Methods. We performed a retrospective cohort study among children born after 1993 and followed up through 1999 at 2 health maintenance organizations ([HMOs] A and B) in the United States. Information was obtained from automated vaccination, clinic, hospital discharge, and pharmacy records.

Results. We identified 268 and 97 breakthrough cases among 80 584 and 8181 children vaccinated against varicella at HMOs A and B, respectively. Varicella breakthrough was not associated with asthma, inhaled steroids prescribed at any time, and oral steroids prescribed before vaccination. An increased risk of varicella breakthrough was found in the 3 months immediately after prescription for oral steroids at HMO A (adjusted relative risk [aRR]: 2.4; 95% confidence interval [CI]: 1.3–4.4) and HMO B (aRR: 2.8; 95% CI: 1.0–7.8), when varicella vaccine was given before 15 months of age at HMO A (aRR: 1.4; 95% CI: 1.1–1.9), and when varicella vaccination followed MMR vaccine within 28 days at HMO A (aRR: 3.1; 95% CI: 1.5–6.4).

Conclusions. Varicella vaccine failure in children was not associated with asthma or the use of inhaled steroids, but with the use of oral steroids. Administration of varicella vaccine before the age of 15 months may be associated with a slightly increased risk of breakthrough disease. As currently recommended, varicella vaccination should not be administered for 28 days after MMR vaccination. *Pediatrics* 2003;112:e98–e103. URL: <http://www.pediatrics.org/cgi/content/full/112/2/e98>; *varicella*

vaccine, asthma, steroids, measles-mumps-rubella vaccine, chickenpox.

ABBREVIATIONS. Th2, T helper type 2; RR, relative risk; CI, confidence interval; VSD, Vaccine Safety Datalink; MMR, measles-mumps-rubella vaccine; HMO, health maintenance organization; ICD9, *International Classification of Diseases, Ninth Revision*; aRR, adjusted relative risk.

Varicella vaccine is recommended in the United States for universal use in children 1 to 12 years of age without a history of chickenpox.¹ Among children 19 to 35 months of age, vaccination coverage rates reached 76.3% in 2001.² The proportion of vaccinated children (or adults) developing varicella after vaccination is an epidemiologic measure of the postlicensure effectiveness of the vaccine, which has ranged from 44% to 86%.^{3,4}

An estimated 4.8 million or more children are affected by asthma in the United States.⁵ Asthma has been ascribed to a disturbed balance of the immune system in which T helper type 2 (Th2) responses prevail over type 1 responses.^{6–8} This Th2 predominance is natural in the fetus and neonate, but is normally replaced by T helper type 1 predominance in the first years of life.⁹ It is unclear why this Th2 predominance persists among children with asthma and how it interacts with vaccinations.^{10,11} In a study of the effectiveness of varicella vaccine during a varicella outbreak in a child care center, Izurieta and colleagues¹² noted an increased risk (relative risk [RR]: 7.1; 95% confidence intervals [CIs]: 2.4–21.3) of breakthrough disease in children with asthma. However, the number of children with asthma was quite small in this outbreak and steroid use for asthma was not studied. Steroids have been associated previously with severe varicella in unvaccinated persons.^{13–16} Several more recent varicella outbreak investigations have also noted an increasing risk of breakthrough with decreasing age at vaccination.^{17–19} In an Illinois outbreak,¹⁷ the increase was nearly fourfold for children vaccinated under 16 months, whereas in a Pennsylvania outbreak,¹⁸ this increase was threefold for children vaccinated under 14 months.

We conducted a retrospective cohort study in the Vaccine Safety Datalink (VSD) project to explore the association between varicella breakthrough, asthma,

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the use of inhaled and oral steroids, and vaccine administration before 15 months of age. We also took advantage of this study to examine the risk of breakthrough disease if the current recommendation for administering varicella vaccine at least 28 days after receipt of measles-mumps-rubella vaccine (MMR) were not followed.²⁰

METHODS

Study Population

The VSD project was initiated in 1991 by the Centers for Disease Control and Prevention for postlicensure vaccine safety studies. It links computerized vaccination records to clinic and hospital discharge records of children from large health maintenance organizations (HMOs) in the United States and covers an estimated 2.5% of the US population. Its data collection methods and quality have been previously described.^{21,22} We selected a cohort of children who had received varicella vaccine from the 2 HMOs (HMOs A and B) with the earliest available clinic data and the highest uptake of varicella vaccine. Both HMOs are located on the West coast.

Varicella vaccine was introduced in 1995 in both HMOs. Clinic data were available from 1995 through 1999 at HMO A and from 1996 through 1999 at HMO B. To ensure capture of breakthrough varicella diagnoses in the clinic data, we selected a cohort of children that would be at most 1 year old when these data became available, ie, children born from January 1, 1994, onwards at HMO A and from January 1, 1995, onwards at HMO B. To ensure capture of any asthma diagnosis, children had to be continuously enrolled in the HMO from birth until varicella vaccination. We excluded children whose automated vaccination records indicated the receipt of varicella vaccine before the age of 12 months because the vaccine is recommended for those 12 months of age and older. We also excluded children in whom varicella occurred before vaccination and children with varicella within 42 days after vaccination, to rule out vaccine-related rashes.

Case Ascertainment

Breakthrough varicella was defined as a clinician-diagnosed case of varicella at an office visit, at the hospital, or by telephone consultation, in a child vaccinated >42 days before diagnosis of varicella. To identify such cases, we screened automated clinic, hospital discharge records, and telephone contact records for the *International Classification of Diseases, Ninth Revision (ICD9)* code 052. Telephone records were available only for HMO B.

Exposure Assessment

To identify children with asthma, we used criteria applied in earlier VSD studies of children with asthma.^{23,24} Children were classified as having asthma if they fulfilled any of the following 3 criteria: 1) at least 1 ICD9 code 493 for asthma plus 1 prescription for asthma medication; 2) at least 1 prescription for a β -agonist and 1 for cromolyn; or 3) 5 or more prescriptions for any asthma medication. Additionally, at least 2 of the conditions within each criterion had to occur within 2 years of each other and at least 1 condition had to have occurred after the age of 1.

We evaluated steroid use by checking for prescriptions of steroids in the automated pharmacy files, and differentiated between oral and inhaled steroids. To evaluate the direct effect of steroids on vaccination, we examined the association between breakthrough disease and prescriptions of steroids in the 3 months preceding vaccination. To examine the more immediate effects of steroids on breakthrough disease, we also evaluated the risk of breakthrough in the first 3 months after a prescription, irrespective of its timing compared with vaccination. We selected a period of 3 months as an estimated average of the combined time of obtaining the steroid, its use, and its potential residual effect. The timing of MMR vaccination relative to varicella vaccine was calculated from the automated vaccination records.

Statistical Analyses

We used Cox proportional hazards models to assess the association of breakthrough disease with the risk factors of interest. The time variable in the models starts at the time of vaccination

and ends at whichever of the following occurs first: breakthrough disease, disenrollment from the HMO, or the last date of data collection (December 31, 1999). We stratified all the analyses on year of birth and calendar year and month of varicella vaccination to ensure comparing children of similar age and age at vaccination (to within a year) as well as to account for varicella seasonality. We obtained crude RR estimates from univariate models and adjusted relative risk (aRR) estimates from multivariate models that included all covariates, irrespective of their statistical significance. Interaction between asthma and the use of steroids and between asthma and the frequency of health care use was also evaluated, but retained only in the multivariate model if significant at a 0.1 significance level.

As the VSD database only collects information on events that come to medical attention, there is a potential health care utilization bias. Parents of children with asthma may be more likely to seek medical care when their children have chickenpox, which would lead to overestimating the association between asthma and breakthrough varicella. To account for this, we included a time-varying count of all health care visits not related to respiratory or dermatologic illnesses in the preceding 3 months before breakthrough disease as a measure of frequency of health care use in our adjusted models. We used SAS version 8 (SAS Institute, Cary, NC) for all analyses.

RESULTS

Data were available on 212 389 children born from January 1, 1994, onwards at HMO A and 22 990 children born from January 1, 1995, onwards at HMO B. A total of 80 584 from HMO A, and 8181 from HMO B were retained in the final cohort that we analyzed. The main characteristics of the 2 cohorts are summarized in Table 1. As expected, the average follow-up time of children in HMO B were lower than those in HMO A. A total of 15 208 children (18.9%) at HMO A and 1062 (13.4%) at HMO B were diagnosed with asthma. Whereas oral steroids were prescribed to similar proportions of children in the 2 HMOs, inhaled steroids were rarely prescribed at HMO B. Around half of the children received their vaccine before 15 months of age: 35 826 (44.5%) at HMO A and 4728 (58.5%) at HMO B. Very few children received varicella vaccine within 28 days after MMR in both HMOs: 519 (0.6%) at HMO A and 42 (0.5%) at HMO B. More children in HMO B (46.6%) than in HMO A (29.8%) had at least 1 health care visit not related to respiratory or dermatologic problems.

There were 268 children with breakthrough varicella at HMO A and 97 at HMO B. The crude RRs and aRRs of breakthrough associated with each covariate of interest and their respective 95% CIs are summarized by HMO in Tables 2 and 3. No elevated risk of breakthrough was associated with asthma or with prescription of inhaled steroids. Whereas prescription of oral steroids within 3 months before varicella vaccination was not associated with an increased risk of breakthrough in either HMO, there was an increased risk of breakthrough in the 3 months immediately after an oral steroid prescription at both HMOs: aRR = 2.4 (95% CI: 1.3–4.4) in HMO A and 2.8 (95% CI: 1.0–7.8) in HMO B. Having been vaccinated before 15 months of age was associated with an increased risk at HMO A: aRR = 1.4 (95% CI: 1.1–1.9). Receipt of varicella vaccine within 28 days after MMR was also associated with an increased risk of breakthrough at HMO A: aRR = 3.1 (95% CI: 1.5–6.2). There was only 1 child who devel-

TABLE 1. Characteristics of the Children Selected Into Study Cohort, HMOs A and B, 1995–1999

Characteristic	HMO A (N = 80 584)	HMO B (N = 8181)
Continuous variables		
Range of age of cohort	12 mo–6 y	12 mo–5 y
Mean and range of follow-up time	21.3 mo, 1 d–4.6 y	14.7 mo, 1 d–3.9 y
Total follow-up time	142 673.85 person-y	10 026.3 person-y
Mean and range of age at varicella vaccination	16.8 mo, 12–71 mo	15.7 mo, 12–58 mo
Categorical variables		
	N (%)	N (%)
Females	39 154 (48.6)	4068 (49.7)
Number of children with asthma	15 208 (18.9)	1062 (13.0)
Number of breakthrough cases	268 (0.3)	97 (1.2)
Inhaled steroid prescription 3 mo before varicella vaccination	758 (0.9)	0
Breakthrough in 3 mo after inhaled steroid prescription*	1843 (2.3)	13 (0.2)
Oral steroid prescription 3 mo before varicella vaccination	1827 (2.3)	157 (1.9)
Breakthrough in 3 mo after oral steroid prescription*	1770 (2.2)	144 (1.8)
Varicella vaccination before 15 mo of age	35 826 (44.5)	4789 (58.5)
Received MMR	80 038 (99.3)	8139 (99.5)
Varicella vaccination within 28 d after MMR	546 (0.7)	42 (0.5)

* For noncases, the exposure is calculated relative to the time equivalent to the occurrence of breakthrough in the matched case.

TABLE 2. RR and 95% CIs Associated With Various Covariates, HMO A, 1995–1999

Covariate	Number of Breakthrough Cases (%)	Number of Noncases (%)	Crude RR (95% CI)	aRR (95% CI)
Asthma	79 (29.5)	15 129 (18.8)	1.3 (1.0–1.7)	1.2 (0.9–1.6)
Inhaled steroids in 3 mo before varicella vaccination	2 (0.8)	756 (0.9)	1.1 (0.3–4.3)	1.5 (0.7–3.6)
Breakthrough in 3 mo after inhaled steroids*	3 (1.1)	1840 (2.3)	0.7 (0.2–2.1)	0.3 (0.1–1.1)
Oral steroids in 3 mo before varicella vaccination	7 (2.6)	1820 (2.3)	1.2 (0.5–2.4)	0.8 (0.4–1.6)
Breakthrough in 3 mo after oral steroids*	13 (4.9)	1757 (2.2)	2.7 (1.6–4.8)**	2.4 (1.3–4.4)**
Varicella vaccination before 15 mo of age	122 (45.5)	35 704 (44.5)	1.5 (1.2–1.9)**	1.4 (1.1–1.9)**
Varicella vaccination within 28 d after MMR	8 (3.0)	538 (0.7)	3.1 (1.5–6.3)**	3.1 (1.5–6.4)**

* For noncases the exposure is calculated relative to the time equivalent to the occurrence of breakthrough in the matched case.

** $P < .01$.

oped breakthrough varicella among those who had received MMR within 28 days after receiving MMR in HMO B. We observed no interaction between asthma and the use of steroids at any time or between asthma and the frequency of health care use on the risk of breakthrough.

DISCUSSION

The findings of this study did not confirm the association between asthma and breakthrough varicella found by Izurieta and colleagues.¹² Our study also did not find an association between breakthrough disease and prescription of inhaled steroids at any time or oral steroids within 3 months before varicella vaccination. However, we found an increased risk of breakthrough disease in the 3 months immediately after prescription of oral steroids, when varicella vaccine was administered before 15 months

of age and when it was administered within 28 days after MMR.

Circulation of wild-type varicella-zoster virus will decrease to low levels as varicella vaccine coverage increases. Until then, a period of persistent circulation of wild-type varicella-zoster virus coincides with rapidly increasing numbers of vaccinees, offering a unique opportunity to study varicella vaccine effectiveness. We took advantage of the VSD's detailed computerized information on vaccinations, medication, and clinic visits for a large number of children in this period to conduct a retrospective cohort study of possible risk factors for varicella vaccination failure.

The study by Izurieta and colleagues, which observed a seven-fold increased risk of varicella breakthrough among children with asthma, relied on a small sample of 65 children, 5 of whom had asthma.

TABLE 3. RRs and 95% CIs Associated With Various Covariates, HMO B, 1995–1999

Covariate	Number of Breakthrough Cases (%)	Number of Noncases (%)	Crude RR (95% CI)	aRR (95% CI)
Asthma	16 (16.5)	1046 (12.9)	1.1 (0.6–1.9)	0.9 (0.5–1.6)
Inhaled steroids in 3 mo before varicella vaccination	0	0	Not estimable	
Breakthrough in 3 mo after inhaled steroids*	0	13 (0.2)	Not estimable	
Oral steroids in 3 mo before varicella vaccination	3 (3.1)	154 (1.9)	1.9 (0.6–6.1)	1.7 (0.8–3.6)
Breakthrough in 3 mo after oral steroids*	5 (5.2)	139 (1.7)	3.1 (1.2–7.7)**	2.8 (1.0–7.8)**
Varicella vaccination before 15 mo of age	61 (62.9)	4728 (58.5)	1.2 (0.8–1.9)	1.2 (0.8–1.9)
Varicella vaccination within 28 d after MMR	1 (1.0)	41 (0.5)	2.0 (0.3–14.3)	2.1 (0.3–16.3)

* For noncases the exposure is calculated relative to the time equivalent to the occurrence of breakthrough in the matched case.

** $P < .05$.

Its results may differ from ours because the study was done during an outbreak in a child care center and all varicella cases, regardless of contact with a health care provider, were included. Also, the effect of the use of steroids by 2 of the 3 children with asthma in which the vaccine failed was not examined. Our results are in line, however, with previous immunogenicity studies that found no decreased immune response among children with asthma for influenza, pneumococcal, diphtheria, and tetanus vaccines.^{25–28}

Our study also showed no association between inhaled steroids at any time and varicella breakthrough. This is reassuring given the increased emphasis on the use of inhaled steroids in the management of asthma.²⁹ Our finding in 1 HMO of an increased risk of breakthrough after oral steroids before vaccination did not persist after adjusting for health care utilization. This may be an indication that the group of children with asthma using steroids at such young age is particularly prone to a health care utilization bias. Previous studies also found no association of inhaled steroid use among asthmatics before or around the time of vaccination with the immunogenicity of (killed) influenza and (polysaccharide) pneumococcal vaccines.^{27–32}

The association with oral steroids in the preceding 3 months was observed in both HMOs. An association of steroids with severe varicella in unvaccinated persons has been repeatedly described.^{13–16} If steroids also increase the severity of breakthrough varicella, it is possible that the observed association with steroids was attributable to a higher likelihood of these more severe cases coming to medical attention, rather than a real increase in the number of breakthrough cases. As we lacked information on the severity of our cases, we could not distinguish between these 2 possibilities. The association between steroids and breakthrough did not differ between children with asthma or children without asthma. This, as well as the lack of interaction between asthma and steroids on the risk of breakthrough, suggests that the effect of steroids is independent of asthma. In children without asthma, the 3 most common diag-

noses assigned on the same day as a steroid prescription were croup syndrome, respiratory distress, and otitis media in decreasing order of frequency at both HMOs.

Dworkin and Galil^{17,18} observed four- and three-fold increased risks of breakthrough in outbreaks among daycare center children vaccinated before 16 months in Illinois and before 14 months in Pennsylvania, respectively. Galil¹⁹ also observed an association between younger median age at vaccination and breakthrough in an outbreak in New Hampshire. A limitation of outbreak investigations is the relatively small number of cases which limit the ability of researchers to conduct multivariate analyses and thus examine the independent effect of risk factors for vaccine failure. We used 15 months as a cutoff point, as this is the age to which measles vaccination was deferred to in 1976.³³ Our finding of an increased risk at HMO A, after controlling for the effects of other risk factors, provides further evidence to the existence of a true association between age at vaccination and risk of breakthrough. As the risk appears to be relatively small, however, we probably lacked sufficient power to observe this at HMO B. Further analyses of postmarketing surveillance data may be needed to better define the age above which the risk of breakthrough is no longer elevated.

Current varicella vaccine recommendations warn against the administration of varicella vaccine within 28 days after MMR.¹⁷ This recommendation is based on the observed reduction in responsiveness to smallpox vaccine after measles vaccine.³⁴ Our finding of an increased risk of vaccine failure in children who received varicella vaccine within 28 days after MMR at HMO A, was also previously reported in a recent review of the effect of the timing of varicella vaccination relative to other vaccinations.³⁵ Cell-mediated immune depression, similar to that observed after natural measles infection,^{36,37} might explain this finding. The absence of an association at HMO B between MMR and increased risk of breakthrough disease is probably attributable to the limited sample size in this HMO with only 1 exposed case. The current recommendations also warn against

the use of varicella vaccine within 28 days *before* MMR vaccine. Although we assumed this to be biologically less plausible, we also checked this and did not find any decreased effectiveness of varicella vaccination when administered within 28 days before MMR vaccination (data not shown).

Our study has some limitations. In relying solely on automated medical encounter data, we have underestimated the incidence of varicella breakthrough disease, especially at HMO A, where telephone consultation records were not available. This is not surprising, as varicella breakthrough disease is usually mild and may not be brought to medical attention.³⁸ This underascertainment may be differential as parents of children with asthma may be more likely to report such a mild breakthrough illness. In fact, the median number of visits not related to respiratory or dermatologic problems was higher among children with asthma compared with children without asthma (4 vs 3 at HMO A, 8 vs 6 at HMO B). Such differential underascertainment would lead to finding a falsely increased risk of breakthrough among children with asthma. However, our finding of no increased risk associated with asthma suggests that this did not occur. At HMO B, 72 of the 97 breakthrough cases were identified from the telephone records only. Restricting the analyses to these presumably mild cases did not affect any of the results for this HMO.

Some misclassification of varicella breakthrough cases by relying on ICD9 codes for clinical diagnoses or parental reports from telephone records is to be expected. In HMO B, the positive predictive value of the assigned codes for breakthrough varicella was estimated at 67% through medical record reviews. Such diagnostic misclassification, assuming it is not differential, would result in underestimating any existing association. We could also have missed a true association between asthma and varicella breakthrough if cases occurring among children with asthma would be relatively less severe and thus more likely to be missed by the automated system.

We have probably overestimated the incidence of asthma. We observed annual asthma incidence rates of up to 11.3% in the second year of life at HMO A. This rate is almost as high as the self-reported lifetime prevalence of asthma (11.5%) for this region in 2000⁵ and more than double the annual asthma attack rate in children as estimated in a national survey in 1998 (5.3%).³⁹ Overestimating asthma incidence would also bias our findings toward underestimating an association between asthma and varicella breakthrough. As for the steroid use, we had no information on the dosages and we had to assume that prescribed steroids were effectively used. Finally, our power to detect any small effect was reduced by 2 factors: the limited follow-up time and lack of information on exposure to varicella.

CONCLUSIONS

We found no increased risk of varicella vaccine failure among children with asthma. We also observed no association between varicella vaccine failure and the use of inhaled steroids. Our finding of an

increased risk of varicella breakthrough in the 3 months after an oral steroid prescription for any condition requires confirmation in future studies. The previous finding of asthma as a risk factor for vaccine failure may be attributable to the confounding effect of steroid treatment for asthma which was not examined. We confirmed previous observations of an increased risk of breakthrough in children vaccinated before 15 months of age in 1 HMO, and that MMR should not precede varicella vaccine by <28 days.

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