

ORIGINAL ARTICLE

Loss of Vaccine-Induced Immunity to Varicella over Time

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ABSTRACT

BACKGROUND

The introduction of universal varicella vaccination in 1995 has substantially reduced varicella-related morbidity and mortality in the United States. However, it remains unclear whether vaccine-induced immunity wanes over time, a condition that may result in increased susceptibility later in life, when the risk of serious complications may be greater than in childhood.

METHODS

We examined 10 years (1995 to 2004) of active surveillance data from a sentinel population of 350,000 subjects to determine whether the severity and incidence of breakthrough varicella (with an onset of rash >42 days after vaccination) increased with the time since vaccination. We used multivariate logistic regression to adjust for the year of disease onset (calendar year) and the subject's age at both disease onset and vaccination.

RESULTS

A total of 11,356 subjects were reported to have varicella during the surveillance period, of whom 1080 (9.5%) had breakthrough disease. Children between the ages of 8 and 12 years who had been vaccinated at least 5 years previously were significantly more likely to have moderate or severe disease than were those who had been vaccinated less than 5 years previously (risk ratio, 2.6; 95% confidence interval [CI], 1.2 to 5.8). The annual rate of breakthrough varicella significantly increased with the time since vaccination, from 1.6 cases per 1000 person-years (95% CI, 1.2 to 2.0) within 1 year after vaccination to 9.0 per 1000 person-years (95% CI, 6.9 to 11.7) at 5 years and 58.2 per 1000 person-years (95% CI, 36.0 to 94.0) at 9 years.

CONCLUSIONS

A second dose of varicella vaccine, now recommended for all children, could improve protection from both primary vaccine failure and waning vaccine-induced immunity.

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THE IMPLEMENTATION OF A UNIVERSAL varicella vaccination program in the United States in 1995 has resulted in a substantial reduction in morbidity, mortality, and health care costs associated with the disease.¹⁻⁵ Despite this success, however, outbreaks of varicella continue to occur, mostly in highly vaccinated school communities.⁶⁻⁸ Several studies of these school outbreaks have suggested that the time since vaccination may be associated with the risk of breakthrough varicella.⁶⁻¹⁰ It has been hypothesized that exogenous reexposure to the virus may be needed to boost humoral and cellular immunity to varicella-zoster virus (VZV).¹¹ As the incidence of varicella has decreased, so have the opportunities for community exposure to varicella needed to boost vaccine-induced immunity. However, these investigations of small outbreaks were not sufficiently powerful to conclude that immunity to varicella wanes after vaccination.

Serologic studies have indicated that the result of an enzyme-linked immunosorbent assay for a specific level of immunity to varicella (VZV glycoprotein antigen of ≥ 5 units per milliliter) is an approximate correlate of protection against varicella. On the basis of the results of this assay, studies have shown that about 15% of children receiving one dose of varicella vaccine do not have levels of antibody that protect them from acquiring disease.¹² This finding is compatible with postlicensure studies indicating that one dose of varicella vaccine is about 80 to 85% effective against any disease presentation.^{6-8,13-15} Thus, 15 to 20% of vaccinated children are at risk for varicella if they are exposed to VZV, either because they had no immune response or because vaccination provided only partial protection.

Waning of immunity after varicella vaccination in terms of measurable antibodies has been demonstrated to occur in health care workers.¹⁶ To assess whether vaccine-induced immunity to varicella wanes, we used 10 years of data from a community-based active surveillance site to look at the independent effect of the time since vaccination on the severity and incidence of breakthrough varicella. Waning of immunity is of particular public health interest because it may result in increased susceptibility later in life, when the risk of severe complications may be greater than that in childhood.

METHODS

STUDY DESIGN

The Varicella Active Surveillance Project has been described previously.¹ Briefly, since January 1995, enhanced community-based surveillance for varicella has been conducted among a population of 350,000 persons in Antelope Valley, California, a well-defined area 40 miles northeast of Los Angeles. The population is predominantly white (80%); of these persons, about 30% describe themselves as Hispanic. The surveillance system comprises 300 reporting sites, which include child care centers, public and private schools, physicians in private practice, health maintenance organizations, and public health clinics. Sites report on varicella every 2 weeks, regardless of whether a subject with disease has been identified. Local personnel conduct a structured telephone interview with all subjects (or their parents or guardians) to collect demographic, clinical, and epidemiologic data. Vaccination status is determined by a parental report of the child's vaccination record. Since 1997, at least 80% of parental reports have been verified with health care providers or school records. The number of doses of varicella vaccine that are administered each month has also been collected since 1995. We estimated that from 1995 to 2004, on the basis of capture-recapture techniques, the annual reporting of varicella among children between the ages of 2 and 18 years was approximately 70% complete (range, 66 to 84). Our study was evaluated by officials at the Centers for Disease Control and Prevention (CDC) and the collaborating institutions. It was deemed that we did not need to obtain individual informed consent from the subjects.

DEFINITIONS OF DISEASE

We defined a case of varicella as an acute onset of a diffuse maculopapular-vesicular rash without another apparent cause. We defined breakthrough varicella as a rash that developed more than 42 days after the subject had been vaccinated with the live attenuated VZV vaccine Oka/Merck (Varivax, Merck). Since the vaccine itself may cause rash, we excluded subjects with varicella who had been vaccinated within the previous 42 days. We categorized the severity of disease as either mild (< 50 lesions) or moderate to severe (≥ 50 lesions).

STATISTICAL ANALYSIS

We examined any association between potential predictors of increased severity of disease separately for subjects who were vaccinated and those who were not vaccinated, using a two-sided chi-square test. We constructed two unconditional logistic-regression models — one for vaccinated subjects and one for unvaccinated subjects — to determine which variables remained independent predictors that subjects would have moderate-to-severe disease. Variables that had a significant association with disease severity in the univariate analysis were included in the multivariate regression models. Variables that were not significantly associated with disease severity but that changed the odds ratio for severity by 10% or more when removed from the analysis were also kept in the final model.¹⁷

To determine the effect of the time since vaccination on the incidence of breakthrough varicella of any severity, we constructed a Poisson regression model. We used the data on doses of varicella vaccine administered each month to children between the ages of 1 and 12 years from 1995 through 2004 to create a study cohort for calculating person-years at risk for each year after vaccination. We excluded children over the age of 12 years, who may have received two doses. Person-years at risk were defined as beginning at the time of vaccination and ending at disease onset. Within each calendar year, however, person-years were not calculated for individual subjects but were aggregated within groups as defined by age at vaccination and age at disease onset. The rate of varicella in each year after vaccination was then adjusted for the age at disease onset and the year at risk for disease. Both variables were considered predictors of the likelihood of exposure to VZV and therefore potential confounders for the association of the risk of breakthrough disease with the time since vaccination. All data were analyzed at the CDC with the use of SAS software, version 9.01 (SAS Institute).

RESULTS

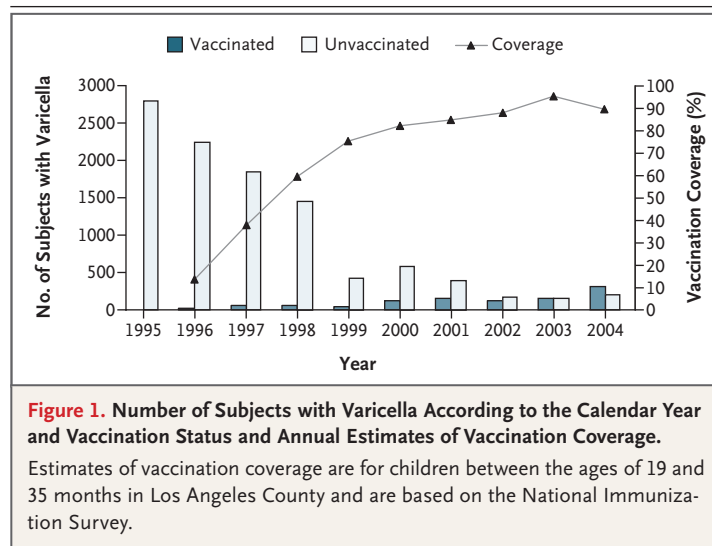
SUBJECTS WITH VARICELLA

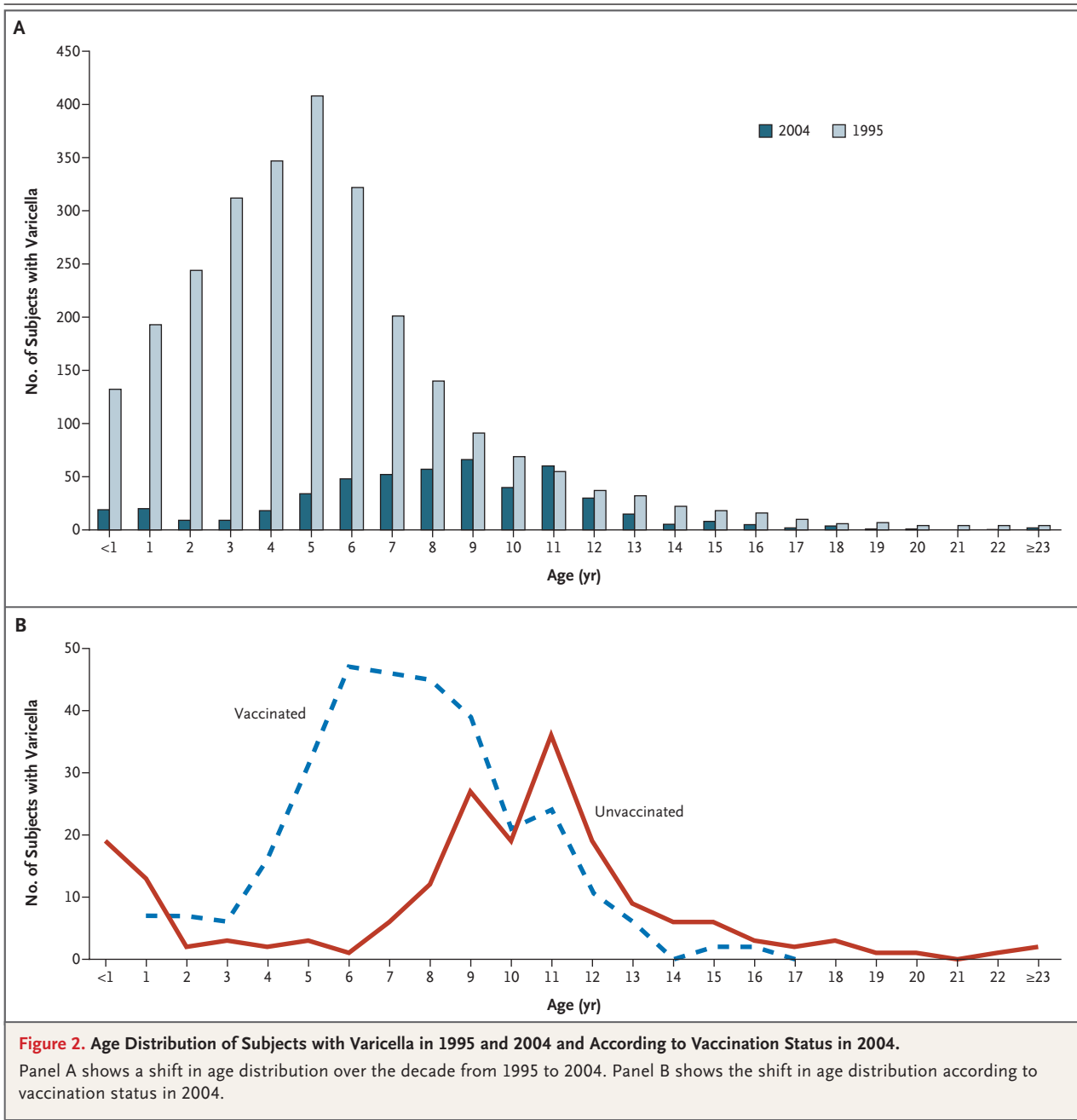
During the decade from January 1995 through December 2004, a total of 11,356 subjects with varicella were identified. Among them, 1080 sub-

jects (9.5%) had an onset of rash more than 42 days after vaccination (breakthrough varicella). Of these subjects, 770 (71.3%) either were evaluated by a physician or received a laboratory diagnosis. Among all vaccinated and unvaccinated subjects, the proportion of children between the ages of 8 and 12 years was higher in the vaccinated group than in the unvaccinated group (26% vs. 19%, $P < 0.001$). Vaccination status was similar in boys and girls, and racial and ethnic characteristics in both the vaccinated and unvaccinated groups reflected the population profile in the surveillance area.

In 2003 and 2004, the average number of reported cases of varicella was 420, representing an 85% decline from the total number of 2794 cases reported in 1995. In the last 3 years of the decade under study, however, no substantial reduction in disease was observed, despite a steady increase in estimates of vaccination coverage among children 19 to 35 months of age (Fig. 1). The proportion of cases that occurred in vaccinated children increased from 1% (23 of 2269 subjects) in 1996 to 18% (126 of 704) in 2000 to 60% (312 of 521) in 2004.

In 1995, before the full implementation of the varicella vaccination program, approximately 73% of cases of varicella occurred in children 6 years of age or younger, with peak disease frequency between the ages of 3 and 6 years (Fig. 2A). This pattern of disease distribution has changed in recent years. In 2004, children who were 6 years





of age or younger accounted for only 30% of all cases of varicella in the surveillance area. Among vaccinated children, disease frequency peaked between the ages of 6 and 9 years, whereas among unvaccinated children, the peak occurred between the ages of 9 and 12 years (Fig. 2B).

SEVERITY OF DISEASE

In univariate analysis, we assessed various factors associated with the severity of varicella according

to vaccination status. The frequency of moderate-to-severe disease increased with increasing age regardless of vaccination status. Moderate-to-severe disease among vaccinated subjects increased in frequency from 22% among children between the ages of 1 and 7 years to 44% among those 13 years of age or older ($P < 0.001$ by the chi-square test for trend) (Table 1). Among vaccinees, the frequency of moderate-to-severe disease increased from 18% in the period from 1995 to 1998 to

Table 1. Factors Associated with the Severity of Varicella According to Vaccination Status.*

Variable	Moderate-to-Severe Varicella			
	Vaccinated Subjects no./total no. (%)	P Value†	Unvaccinated Subjects no./total no. (%)	P Value†
Age at disease onset				
<1 yr	0	<0.001	334/567 (59)	<0.001
1–7 yr	166/771 (22)		4204/6753 (62)	
8–12 yr	104/281 (37)		1335/1946 (69)	
≥13 yr	12/27 (44)		764/1004 (76)	
Period at risk				
1995–1998	28/156 (18)	<0.001	5379/8336 (65)	0.008
1999–2000	71/327 (22)		881/1399 (63)	
2001–2004	183/596 (31)		377/535 (70)	
Reporting source				
Parents	101/467 (22)	0.01	4694/7310 (64)	0.03
Schools	5/17 (29)		126/215 (59)	
Health care providers	176/595 (30)		1815/2742 (66)	
Age at vaccination				
1–2 yr	154/667 (23)	0.004	NA	
3–5 yr	88/304 (29)			
≥6 yr	40/108 (37)			
Time since vaccination				
<5 yr	172/744 (23)	<0.001	NA	
≥5 yr	110/335 (33)			

* NA denotes not applicable.

† All P values are for comparisons with the last category in each variable and were calculated by the chi-square test for trend.

31% in the period from 2001 to 2004 ($P < 0.001$). Among unvaccinated subjects, the increased percentage of subjects with moderate-to-severe disease was noticeable only during the period from 2001 to 2004. Vaccinated children with 50 or more lesions were twice as likely to have complications such as pneumonia, ataxia, and skin superinfection as were those with fewer than 50 lesions ($P = 0.03$ by Fisher's exact test) (data not shown).

When assessed according to the time since vaccination, the frequency of moderate-to-severe disease among vaccinated children increased 1.4 times among those who had been vaccinated 5 or more years previously, as compared with those who had been vaccinated less than 5 years previously (33% vs. 23%, $P < 0.001$) (Table 1). Vaccination at the age of 6 years or older was also associated with moderate-to-severe disease, as compared with vaccination during the first or second year ($P = 0.004$). The frequency of moderate-to-severe

disease among both vaccinated and unvaccinated children was associated with the reporting source. Health care providers were somewhat more likely to report cases of moderate-to-severe disease than were parents (Table 1).

The final logistic-regression model for the unvaccinated group included the subject's age at the onset of disease, the year of disease onset (calendar year), and the reporting source. Among unvaccinated subjects, the age at disease onset was the only independent predictor of disease severity (Table 2). As compared with infants, subjects who were 13 years of age or older were 2.2 times as likely to have moderate-to-severe disease ($P < 0.001$).

In the vaccinated group, the time since vaccination, the age at vaccination, and the age at disease onset were identified as collinear predictors for severity and could not be simultaneously included in the logistic-regression model. There-

Table 2. Multivariate Analysis of Factors Associated with the Severity of Varicella among Unvaccinated Children.*

Variable	Adjusted Odds Ratio	95% CI	P Value
Period of disease onset			
2001–2004	1.00		
1999–2000	0.81	0.65–1.01	0.06
1995–1998	0.91	0.74–1.11	0.36
Age at onset			
<1 yr	1.00		
1–7 yr	1.16	0.97–1.38	0.09
8–12 yr	1.53	1.26–1.85	<0.001
≥13 yr	2.20	1.76–2.74	<0.001
Reporting source			
Health care providers	1.00		
School	0.96	0.87–1.06	0.45
Parents	0.78	0.56–1.04	0.09

* Odds ratios are for moderate-to-severe disease; the odds ratio for each variable has been adjusted for the other variables. P values and 95% confidence intervals (CIs) were calculated with the use of the Wald chi-square test.

fore, in order to control for the effect of age at the onset of disease on the severity of disease among vaccinated children, we included only vaccinees within the narrow age band of 8 to 12 years. This age group had the greatest variability in the age at vaccination, which allowed for the examination of the independent effect of the time since vaccination. Moreover, among subjects between the ages of 8 and 12 years, no significant difference in the percentage of subjects with moderate-to-severe disease according to the year of age was found ($P=0.40$).

The logistic-regression model for vaccinated children between the ages of 8 and 12 years retained the effects of the time since vaccination, the age at vaccination, and the calendar year as predictors of disease severity. The calendar year was used as a continuous variable and represented the variation of background rates of varicella since the introduction of the vaccination program. Among vaccinated children between the ages of 8 and 12 years at disease onset, after adjustment for the age at vaccination and the calendar year, subjects who had been vaccinated 5 or more years previously were 2.6 times as likely to have moderate-to-severe disease as were those who had been vaccinated less than 5 years previously ($P=0.01$) (Table 3).

Overall, 71% of breakthrough cases were confirmed by laboratory analysis or diagnosed by a physician, although this factor varied according to the age group. When we restricted our analysis of the severity of breakthrough varicella to the time from vaccination to laboratory confirmation or a physician's diagnosis, the findings were similar. However, these findings were no longer statistically significant owing to smaller numbers. Among 209 vaccinated children between the ages of 8 and 12 years, subjects who had been vaccinated 5 years or more years previously were 2.0 times as likely to have moderate-to-severe breakthrough disease (after adjustment for the age at vaccination and the calendar year) as were children who had been vaccinated less than 5 years previously (95% confidence interval [CI], 0.9 to 4.7; $P=0.09$).

ANNUAL RATES OF BREAKTHROUGH DISEASE

The Poisson regression model showed that among children who had been vaccinated between 12 months and 12 years of age, the annual rates of breakthrough varicella increased with the time since vaccination, even after adjustment for the age at disease onset and the calendar year as potential confounders for changes in the likelihood of exposure. The rate of breakthrough varicella increased significantly with each year after vaccination, from 1.6 cases per 1000 person-years (95% CI, 1.2 to 2.0) within the first year to 9.0 per 1000 person-years (95% CI, 6.9 to 11.7) at 5 years and 20.4 per 1000 person-years (95% CI, 14.1 to 29.6) at 8 years. The rate of breakthrough varicella 9 years after vaccination was 58.2 per 1000 person-years (95% CI, 36.0 to 94.0), but owing to a small number of subjects, the 95% CI was very wide, even though it did not overlap with the CI estimated for previous years (Fig. 3).

DISCUSSION

Our analysis provides evidence that the protection afforded by one dose of varicella vaccine in children may wane with time. We found that both the severity and incidence of breakthrough disease among vaccinees increased with the time since vaccination. Children between the ages of 8 and 12 years who had been vaccinated 5 years or more previously were two times as likely to have moderate-to-severe breakthrough disease as were those who had been vaccinated less than 5 years previ-

ously, regardless of the age at disease onset, the age at vaccination, and the calendar year when the disease developed. Furthermore, incidence rates of breakthrough varicella increased more than 12 times from the first year of vaccination to year 8 after vaccination, after adjustment for age and calendar year, factors that were considered to be surrogates for changes in exposure. This increase in breakthrough disease was observed in the context of a substantial decline in varicella.

The effect of the varicella vaccination program in the Antelope Valley surveillance area has been documented previously.¹ From 1995 to 2000, there was an overall decrease in disease incidence of 71%, with a documented reduction in disease burden among all age groups — findings that are consistent with herd immunity. Our data show a decline of 85% in varicella from 1995 to 2003–2004. The reduction in exposure to VZV increases the risk that the remaining unvaccinated children and adolescents may be susceptible to varicella and its complications when they reach adulthood.^{11,18} Implementation of a vaccination policy that requires documentation of varicella vaccination or other evidence of immunity for entry to middle school, high school, and college is critical for the protection of this susceptible cohort.^{8,19}

The reduced circulation of VZV in the study area or an inadequate initial response to vaccination may have contributed to the waning of vaccine-induced immunity to varicella.^{11,18,20} An assessment of the duration of protection afforded by one dose of the varicella vaccine administered to children under the age of 13 years between December 1991 and January 1993 showed an increase in the geometric mean titer of varicella IgG antibody during a 10-year follow-up period.²¹ The most likely explanation for this increase was an anamnestic immune response due to exposure to wild-type VZV, since varicella was still common during that period.

These data suggest a steady decline over a period of years in disease protection afforded by a single dose of the varicella vaccine in the context of diminished circulation of wild-type virus. In contrast, a case-control study showed a 13% decline in vaccine effectiveness during the first year of vaccination, followed by stable levels of protection from 2 to 8 years after vaccination.²² Numerous studies of postlicensure effectiveness that were performed during the vaccine era showed

Table 3. Multivariate Analysis of Factors Associated with the Severity of Varicella among Vaccinated Children between the Ages of 8 and 12 Years.*

Variable	Adjusted Odds Ratio	95% CI	P Value
Time since vaccination			
≥5 yr	2.60	1.20–5.80	0.01
<5 yr	1.00		
Age at vaccination			
1–2 yr	0.42	0.15–1.15	0.13
3–5 yr	0.56	0.25–1.24	0.56
≥6 yr	1.00		
Calendar year	0.96	0.81–1.31	0.61

* Odds ratios are for moderate-to-severe disease; the odds ratio for each variable has been adjusted for the other variables. P values and 95% confidence intervals (CIs) were calculated with the use of the Wald chi-square test.

an efficacy of varicella vaccine in the range of 44 to 100%.^{6–10,13–15,23} These studies suggested that an increased risk of breakthrough varicella may be associated with a history of asthma¹⁴ or eczema,¹⁰ vaccination with varicella vaccine within 28 days after the administration of live attenuated measles–mumps–rubella vaccine,²⁴ prescription of oral corticosteroids 3 months before the onset of varicella,²⁴ and an early age at vaccination (variously defined).^{9,10,13,24} However, these associations were not consistently reproduced in all studies. Furthermore, such factors are unlikely to have been confounders in our study, since they should not bear an association with the time since vaccination. As compared with previous studies,^{6,9,10,15,22} our study examined the independent effect of the time since vaccination on the risk of breakthrough varicella. Our data contained a sufficient number of subjects who had been vaccinated at different ages and for whom the interval between vaccination and the onset of disease varied, which allowed us to control for these factors.

Several limitations of our study should be considered when interpreting the results. Owing to constraints with respect to the number of subjects in our study, our definition of disease severity was limited to fewer than 50 lesions or 50 or more lesions and did not include complications or hospitalization. Nonetheless, complications were more likely to develop in vaccinated children with 50 or more lesions than in children with fewer than 50 lesions. Since breakthrough disease with few lesions may be mild, such cases may have

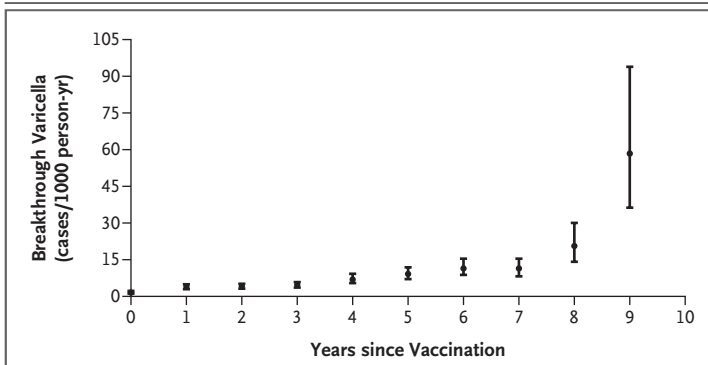


Figure 3. Adjusted Rates of Breakthrough Varicella among Children Vaccinated between the Ages of 12 Months and 12 Years, According to the Year after Vaccination.

Rates of disease were adjusted for the age at disease onset and the calendar year with the use of a Poisson regression model. All 95% confidence intervals, which are indicated by I bars, were calculated with the use of the Wald chi-square test.

been underreported, which could have led to an underestimation of the rates of breakthrough disease. A possible increase in rates of ascertainment of breakthrough varicella in recent years due to increased awareness would be unlikely to bias our results for either rates or severity of disease, since our analysis is based on the time since vaccination and not on the calendar year.

In summary, our study provides clinical evidence of the waning of vaccine-acquired immu-

nity to varicella. Clinical studies have suggested that a second dose of varicella vaccine could provide increased protection against disease by increasing the proportion of children with protective antibody titers and an improved cellular immune response.^{21,25-27} The findings from our study and other scientific evidence were taken into account when, in June 2006, the Advisory Committee on Immunization Practices adopted a recommendation that children between the ages of 4 and 6 years receive a second dose of varicella vaccine. The panel also recommended that a second catch-up dose of varicella vaccine be given to children, adolescents, and adults who previously had received one dose.¹⁹ No long-term data are available on the duration of immunity afforded by the second dose of vaccine.

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After completion of this study, Dr. Guris became an employee of Merck. Dr. Mascola reports receiving lecture fees from Merck and serving on the company's paid advisory board. No other potential conflict of interest relevant to this article was reported.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

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