

# Long-term Effectiveness of Varicella Vaccine: A 14-Year, Prospective Cohort Study

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## KEY WORDS

chicken pox, children, effectiveness, vaccine, varicella, zoster

## ABBREVIATIONS

CI—confidence interval

HZ—herpes zoster

KPNC—Kaiser Permanente Northern California

PY—person-years

RR—relative risk

VZV—varicella virus zoster

Dr Baxter supervised data collection and analyses, drafted the initial manuscript, and approved the final manuscript as submitted; Ms Ray designed data collection instruments, coordinated interviews and data collection, performed analyses, reviewed the manuscript, and approved the final manuscript as submitted; Dr Tran assisted with analyses and the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted; Drs Black and Shinefield assisted with the original concept and design, supervised early data collection and analyses, and reviewed and approved the manuscript as submitted; Dr Coplan assisted with original design and statistical plan, and reviewed and approved the manuscript as submitted; Mr Lewis assisted with the design and statistical plan, assisted with analyses, critically reviewed the manuscript, and approved the final manuscript as submitted; Mr Fireman assisted with the original concept and design, worked on analyses, critically reviewed the manuscript, and approved the final manuscript as submitted; and Dr Saddier assisted with analyses and the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted.

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**WHAT'S KNOWN ON THIS SUBJECT:** Varicella vaccine is known to be highly effective, with added benefit from a second dose.



**WHAT THIS STUDY ADDS:** This study demonstrates the lasting effectiveness of varicella vaccine and the benefit of the second dose. Breakthrough varicella occurred soon after vaccination, varicella rates did not increase over 14 years, and there was no increase in zoster in the cohort.

## abstract

**BACKGROUND:** Varicella vaccine was licensed in the United States in 1995 for individuals  $\geq 12$  months of age. A second dose was recommended in the United States in June 2006. Varicella incidence and vaccine effectiveness were assessed in a 14-year prospective study conducted at Kaiser Permanente Northern California.

**METHODS:** A total of 7585 children vaccinated with varicella vaccine in their second year of life in 1995 were followed up prospectively for breakthrough varicella and herpes zoster (HZ) through 2009. A total of 2826 of these children received a second dose in 2006–2009. Incidences of varicella and HZ were estimated and compared with prevaccine era rates.

**RESULTS:** In this cohort of vaccinated children, the average incidence of varicella was 15.9 per 1000 person-years, nine- to tenfold lower than in the prevaccine era. Vaccine effectiveness at the end of the study period was 90%, with no indication of waning over time. Most cases of varicella were mild and occurred early after vaccination. No child developed varicella after a second dose. HZ cases were mild, and rates were lower in the cohort of vaccinated children than in unvaccinated children during the prevaccine era (relative risk: 0.61 [95% confidence interval: 0.43–0.89]).

**CONCLUSIONS:** This study confirmed that varicella vaccine is effective at preventing chicken pox, with no waning noted over a 14-year period. One dose provided excellent protection against moderate to severe disease, and most cases occurred shortly after the cohort was vaccinated. The study data also suggest that varicella vaccination may reduce the risks of HZ in vaccinated children. *Pediatrics* 2013;131:e1389–e1396

Varivax (Oka/Merck varicella vaccine live [Merck Sharp & Dohme Corp, Whitehouse Station, NJ]), based on the Oka strain developed by Takahashi et al in the 1970s,<sup>1</sup> was licensed in the United States in 1995 and recommended soon after by the Advisory Committee on Immunization Practices for routine administration to all immunocompetent children.<sup>2</sup> Before that time, varicella virus zoster (VZV) infection was ubiquitous, with >90% of people experiencing infection by the age of 20 years, and resulting in thousands of hospitalizations with ~100 deaths annually in the United States.<sup>3–6</sup> After introduction of the vaccine in the United States, disease incidence fell markedly.<sup>7,8</sup>

Efficacy of 1 dose of vaccine was high in clinical trials,<sup>9</sup> and the vaccine's effectiveness was confirmed in post-licensure studies to be 80% to 94%<sup>10,11</sup> in preventing chicken pox and highly effective in preventing moderate to severe disease. However, breakthrough disease was noted and outbreaks still occurred,<sup>12–14</sup> leading to a recommendation by the Advisory Committee on Immunization Practices in 2006 for a second dose of the vaccine at 4 to 6 years of age.<sup>15</sup> Since implementation of the second dose, studies have reported that varicella incidence has declined further.<sup>11,16</sup> Effectiveness of the 2-dose series was calculated to be 98% in 2 separate studies, a randomized, prospective study<sup>11</sup> and a case-control study.<sup>17</sup>

The effect of varicella vaccination programs on the incidence of herpes zoster (HZ) in the general population is not well known. HZ risk was found to be lower in vaccinated children aged <10 years than in unvaccinated children of the same age with a history of varicella.<sup>18,19</sup> However, concerns arose that widespread vaccination of children could decrease VZV immune-boosting opportunities and lead to an increase in HZ in adults.<sup>20–23</sup>

In the current study, we prospectively followed up a cohort of children for 14 years who received varicella vaccine in their second year of life (in 1995) to assess the long-term effectiveness of the vaccine and the impact on the epidemiology of varicella and HZ. We also observed the impact of the second dose of varicella vaccine introduced in 2006. This study was conducted as a post-licensure commitment to health authorities, initially in the United States and then worldwide.

## METHODS

### Study Population

The study was conducted at multiple sites in Kaiser Permanente Northern California (KPNC), an integrated health care delivery system serving 3.2 million members. The membership reflects the racial and economic diversity of the general population in the northern California region, although it underrepresents the low end of the economic spectrum.<sup>24–26</sup> Members obtain almost all their medical care at KPNC facilities. KPNC databases store detailed information on all health care encounters, which are linked by using the patient's unique medical record number.

Parents or guardians of children 12 to 23 months of age, who received varicella vaccine between June and November 1995 as a part of routine care, were contacted by telephone interviewers 6 months after receipt of the vaccine and asked to participate in a long-term follow-up study of varicella. Parents of 7585 vaccinated children consented to participate.

### Data Collection

Telephone interviews were scheduled every 6 months for 14 years, from vaccination through 2009. At each contact, parents were asked about the occurrence of varicella and zoster since

the last interview. Parents were provided a toll-free telephone number to report new varicella in their child between interviews or to ask questions. During each interview, parents were reminded about the clinical features of varicella and zoster, and instructed to call immediately if signs or symptoms of either of these arose.

### Outcomes Definitions

Breakthrough varicella cases were based on parental report; no medical confirmation of the diagnosis was required. Parents were asked whether there were ≤50 lesions (mild); 51 to 300 lesions (moderate); or >300 lesions (severe). Cases occurring within 6 weeks of vaccination were excluded to avoid including vaccine-related rash/varicella or wild-type disease that may have been contracted before vaccination. For the description of rates of varicella after the second dose, only children with continuous KPNC membership from June 2006 (when the second dose was recommended) to November 2009 (the end of the study) were included to ensure reliable vaccine information. Cases of HZ required a diagnosis by a medical provider, confirmed by chart review, but did not require any laboratory confirmation. No testing was done to determine whether HZ cases were due to wild-type or vaccine-derived virus.

### Analyses

#### Varicella

We measured the incidence of breakthrough varicella in vaccinees every 6 months and estimated annual rates. The person-time denominator was the total follow-up time contributed since the last interview by subjects who completed the interview for that phase.

The primary analysis was based on the first occurrence of varicella, and person-time was censored at the time of the first episode, ignoring subsequent

episodes. We also measured total varicella incidence including recurrent cases after the first occurrence of varicella and all of the available person-time of follow-up.

Because the entire cohort was vaccinated, we used historical varicella incidence rates as the comparator to estimate varicella vaccine effectiveness, based on published studies conducted before vaccine licensure.<sup>5,6,27–30</sup> Two of the published studies were population based, used parent-reported varicella, and provided age-specific incidence rates of varicella in children.<sup>5,6</sup> We used susceptibility-adjusted rates, based on only susceptible individuals, from these published studies.<sup>6,30,31</sup> To obtain the average historical varicella incidence rate over the duration of the study for comparison, we calculated a weighted average historical incidence rate, assuming all children were vaccinated at 18 months of age (the midpoint of the second year) and using the contribution of each age group to the total follow-up of the study cohort as the weight (Table 1).

## HZ

To compare rates of HZ in the study cohort with rates of HZ in unvaccinated children, we reviewed the literature on the incidence of HZ before vaccine licensure. We identified only 2 population-based epidemiologic studies providing incidence rates of physician-diagnosed HZ in children.<sup>6,32</sup> We chose HZ reference

rates from the only study that restricted the analysis to children who had experienced varicella<sup>6</sup> (Table 2).

## Statistical Methods

Person-time was calculated according to interview cycle. For varicella, the relative risk (RR) was calculated as the ratio of the observed versus the prevaccine incidence rates. Vaccine effectiveness was calculated as 1 minus the RR. For HZ, the RR was the ratio of the total number of observed HZ cases in the study cohort and the total number of expected cases in unvaccinated children of the same age with a history of naturally acquired varicella during the same period of time.

This study was approved by the KPNC institutional review board.

## RESULTS

### Follow-up

The parents/guardians of 9316 children 12 through 23 months of age, vaccinated between June and November 1995, were invited to participate in this study. Overall, 9.9% could not be reached by telephone, 6.2% refused to participate, and 2.5% were ineligible because of age or language barriers, yielding an initial cohort of 7585 (81.4%) patients enrolled by December 1995. Fourteen years later, at the end of November 2009, a total of 7386 enrollees (97.4% of the original cohort) were still being contacted and interviewed by study staff. A total

of 103 098 person-years (PY) of follow-up data were collected.

Given the high retention rate of the study cohort, the racial/ethnic distribution remained essentially the same after 14 years of follow-up. In our final round of interviews, 51% of participants were male; 6.5% were black or African American, 12% were Asian, 15% were Hispanic, 43% were white, 23% were multiracial, and 0.4% were categorized as other.

### Breakthrough Varicella (>6 Weeks After Vaccination)

A total of 1505 breakthrough cases of varicella were reported in the 14 years after varicella vaccination. All cases were reported after the first dose of vaccine; no cases were reported after dose 2. Of all breakthrough cases, including repeat episodes, 356 (24% of 1505) reported 51 to 300 lesions (moderate cases) and 30 (2%) reported >300 lesions (severe cases). Of the 1505 reports, 80 cases (5.3%) were reported as repeat cases of varicella. The incidence rates of first episode of breakthrough varicella are presented in Table 3.

The average incidence rate of breakthrough varicella over the 14 years of follow-up was 15.9 per 1000 PY (95% confidence interval [CI]: 15.1–16.7) for varicella episodes with any number of lesions. Considering all episodes (including recurrences), the average incidence rate of breakthrough varicella was 14.6 per 1000 PY (95% CI: 13.9–15.4) for any symptoms, 3.7 per 1000 PY (95% CI: 3.4–4.1) for >50 lesions, and 0.3 per 1000 PY (95% CI: 0.2–0.5) for >300 lesions (data not shown).

Annual breakthrough rates of varicella were stable at ~26 per 1000 PY in the first 4 years after vaccination. They decreased to <20 per 1000 PY after the fourth year, to ~9 per 1000 PY at the end of 11 years of follow-up, then to 2 per 1000 in 2009, the last year of follow-up. A total of 28 first-incident

**TABLE 1** Average Historical Incidence Rates of Varicella From Published Population-based Studies of Unvaccinated Children (Prevaccine Era) per 1000 PY

Age Group	NHIS <sup>1</sup>		Kentucky <sup>2</sup>	
	Unadjusted Rate	Susceptibility-adjusted Rate <sup>a</sup>	Unadjusted Rate	Susceptibility-adjusted Rate <sup>a</sup>
1–4 y	82.1	97	99.4	120
5–9 y	90.3	197	80.7	231
10–15 y	17.5	116	13.5	117
Weighted average historical rate <sup>b</sup>		140.1		158.9

NHIS, National Health Interview Survey.

<sup>a</sup> From Vessey et al, 2001.<sup>30</sup>

<sup>b</sup> Historical incidence rate of varicella expected to be observed in the study cohort at the end of the 14-year follow-up.

**TABLE 2** Incidence of HZ According to Age Group and Compared With Historical Rates

Age Group <sup>a</sup>	PY <sup>b</sup>	Expected		Observed			RR Observed/Expected	
		Historical Rate <sup>c,d</sup>	No. of Expected Cases <sup>c</sup>	Observed Cases	Observed Rate <sup>d</sup>	95% CI	RR	95% CI
<5 y	25 313	1.10	27.8	4	0.16	0.04–0.40	0.14	0.05–0.35
5–9 y	37 176	0.51	19.0	17	0.46	0.27–0.73	0.89	0.54–1.40
10–15 y	40 609	0.69	28.0	25	0.62	0.40–0.91	0.89	0.52–1.53
All ages (1–15 y)	103 098	0.73	74.8	46	0.45	0.33–0.60	0.61	0.43–0.89

<sup>a</sup> Age was estimated on interview cycle since vaccination, assuming that all children were vaccinated at 18 months of age.

<sup>b</sup> Person-time denominators were based on the total follow-up time since the last interview by subjects with completed interviews for that phase.

<sup>c</sup> Age-specific population-based rates in individuals with a history of varicella were obtained from Guess et al, 1986.<sup>6</sup>

<sup>d</sup> Rate per 1000 PYs.

breakthrough varicella cases with >300 lesions were reported over the 14 years of follow-up, including 13 in the first 4 years after vaccination. Overall, there did not seem to be an increase in the severity of breakthrough varicella cases over time in vaccinated children (Fig 1).

### Comparison With Historical Incidence Rates of Varicella

Based on susceptibility-adjusted historical rates of varicella for children 1 to 15 years old in the 2 reference studies, the expected average varicella incidence rates in the cohort children, had they remained unvaccinated, were 140.1 and 158.9 per 1000 PY (Table 1). The observed incidence rate of 15.9 per 1000 PY in the 1- to 15-year-old vac-

inated children in the study was therefore 9 to 10 times lower than the historical rates in children of the same age in the prevaccine era. The overall vaccine effectiveness at the end of the study was 89% to 90% depending on the reference study used. Annual vaccine effectiveness ranged from 73% to 80% in 1996–1997 (the first 2 years of the study) to 80% to 90% in 2000–2009 (the last 10 years of the study).

### Racial Differences in Breakthrough Varicella Rates

The average incidence rate of reported breakthrough varicella was slightly lower in Asian (12.4 per 1000 PY [95% CI: 10.6–14.5]) and African-American (11.5 per 1000 PY [95% CI: 9.2–14.4]) children

than in white children (16.0 per 1000 PY [95% CI: 14.8–17.2]). For Hispanic children, the rate was 13.0 per 1000 PY (95% CI: 11.3–15.0), and for multiracial participants, it was 15.1 per 1000 PY (95% CI: 13.6–16.8).

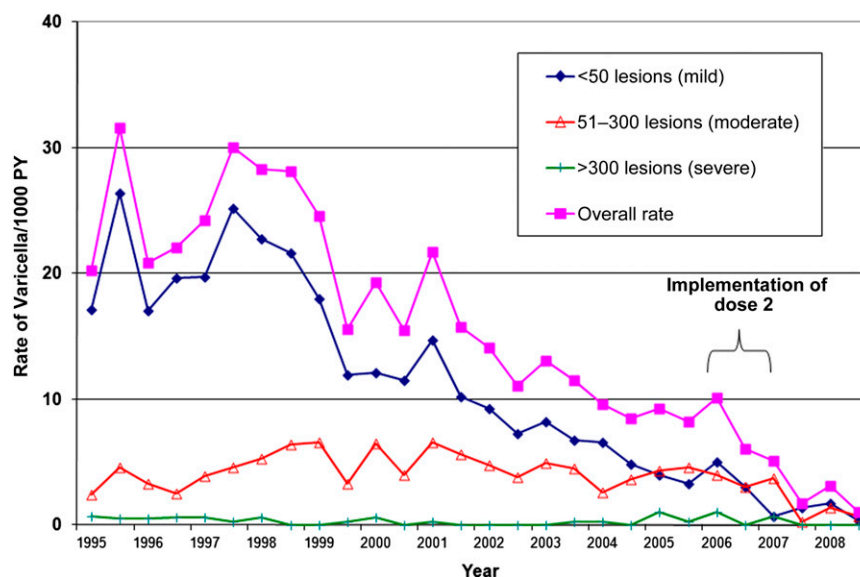
### Breakthrough Varicella in Study Participants Who Received a Second Dose

Among the study participants who were still active in the last survey year, 4546 (62%) were continuous KPNC health plan members from June 2006 to November 2009. Of these, 2829 children (62% [or 38.3% of the study cohort]) received a second dose of varicella vaccine. No breakthrough varicella cases were reported after receipt of a second dose.

**TABLE 3** Incidence Rate of Breakthrough Varicella (First Episode Only) According to Year Since Vaccination (Rate per 1000 PYs): KPNC, 1996–2009

Years Since Vaccination	Follow-up in PY	Any Lesions			Mild (1–50 Lesions)			Moderate (51–299 Lesions)			Severe (>300 Lesions)		
		N	Rate	95% CI	n	Rate	95% CI	n	Rate	95% CI	n	Rate	95% CI
1	6531	174	26.6	22.9–31.0	150	23.0	19.5–27.0	20	3.1	1.9–4.8	4	0.6	0.2–1.7
2	7311	157	21.5	18.3–25.1	136	18.6	15.7–22.0	17	2.3	1.4–3.8	4	0.5	0.2–1.5
3	7044	191	27.1	23.5–31.3	161	22.9	19.6–26.7	27	3.8	2.6–5.7	3	0.4	0.1–1.4
4	6841	193	28.2	24.5–32.5	153	22.4	19.1–26.2	38	5.6	4.0–7.7	2	0.3	0.1–1.2
5	6671	134	20.1	16.9–23.8	101	15.1	12.4–18.4	32	4.8	3.3–6.9	1	0.1	0.0–1.0
6	6505	113	17.4	14.3–20.9	79	12.1	9.7–15.2	32	4.9	3.4–7.0	2	0.3	0.1–1.2
7	6425	120	12.6	15.6–22.4	81	12.6	10.1–15.7	38	5.9	4.2–8.2	1	0.2	0.0–1.0
8	6273	79	18.7	10.1–15.8	52	8.3	6.3–10.9	27	4.3	2.9–6.3	0	0.0	0.0–0.8
9	6172	76	12.3	9.8–15.5	47	7.6	5.7–10.2	28	4.5	3.1–6.6	1	0.2	0.0–1.1
10	6096	55	9.0	6.9–11.8	36	5.9	4.2–8.3	18	3.0	1.8–4.8	1	0.2	0.0–1.1
11	6058	53	8.7	6.6–11.5	26	4.3	2.9–6.4	23	3.8	2.5–5.8	4	0.7	0.2–1.8
12	5937	48	8.1	6.0–10.8	27	4.5	3.1–6.7	18	3.0	1.9–4.9	3	0.5	0.1–1.6
13	5945	20	3.4	2.1–5.3	8	1.3	0.6–2.8	10	1.7	0.9–3.2	2	0.3	0.1–1.4
14	5886	12	2.0	1.1–3.7	6	1.0	0.4–2.3	6	1.0	0.4–2.3	0	0.0	0.0–0.8
All years (0–14)	89 695	1425	15.9	15.1–16.7	1063	11.9	11.2–12.6	334	3.7	3.3–4.2	28	0.3	0.2–0.5

Breakthrough episodes were defined as any reported varicella with onset of symptoms occurring >6 weeks after vaccination.



**FIGURE 1**

Incidence rates of breakthrough varicella per 1000 PY (first episode only), according to calendar year, since vaccination in 1995.

### Incidence and Characteristics of HZ Cases Confirmed by Physician Diagnosis

There were 113 cases of HZ reported over the 14 years of follow-up, 99 of which were seen at KPNC and records were available. Ninety of these reviewable cases occurred after vaccination and were seen by a physician. Forty-six (51%) of the 90 cases had HZ confirmed by the physician. The 46 cases occurred over 103 098 PY of follow-up, resulting in an incidence rate of 0.45 per 1000 PY (95% CI: 0.33–0.60). The incidence of HZ increased slightly over time, as expected with increasing age (Table 2).

Of the 46 confirmed HZ cases, 18 (39%) were male subjects, and the mean age at HZ diagnosis was ~10 years (range: 2.0–15.0 years). Among the 46 HZ cases, 27 (59%) had HZ-related pain identified in their medical charts, 20 with documentation regarding pain severity. Of these 20 cases, 6 were recorded as mild and 14 as moderate. No post-herpetic neuralgia was reported. Of the 46 HZ cases, 40 resolved without sequelae, 5 had unknown outcome, and 1 was unresolved. The average time between varicella vaccination and HZ diagnosis was 8.4 years. Twenty of the

confirmed HZ cases had a previous report of breakthrough varicella. The average time interval between the reported breakthrough varicella and HZ was 6.1 years (range: 0.9–11.5 years). No cases of HZ were reported after a second dose.

### Comparison With Historical Incidence Rates of HZ in Children

Based on the historical rates of HZ after naturally acquired varicella,<sup>6</sup> ~75 cases of HZ were expected in the study cohort over the 14 years of follow-up, corresponding to an average incidence of 0.73 per 1000 PY. At the end of the study, the calculated RR was 0.61 (95% CI: 0.43–0.89), suggesting an ~40% decreased HZ incidence in vaccinated children over the first 14 years after vaccination compared with that in unvaccinated children of the same age who experienced naturally acquired varicella. The incidence of HZ was not increased in any age category compared with historical rates.

### DISCUSSION

To our knowledge, this is the largest and longest follow-up study of varicella

vaccine, with 14 years of active surveillance of both patient-reported varicella and physician-diagnosed HZ. Retention was excellent, with >97% of the 7585 children initially enrolled in the cohort completing the study.

Over the entire follow-up period, the incidence rate of varicella (any disease, regardless of severity) in this cohort of vaccinated children was 9 to 10 times lower than corresponding rates in unvaccinated children of the same age in the prevaccine era. This rate resulted in an overall vaccine effectiveness of ~90% (ranging from ~75% to 90%), consistent with previous studies in the United States<sup>9–11,33,34</sup> and Europe.<sup>35</sup>

The incidence rate of breakthrough varicella steadily decreased over time, and no increase was observed during the 14 years of follow-up. Few breakthrough cases were severe (only 28 of 7585 children over 14 years had >300 lesions), whereas in the prevaccine era, most children presented with >300 lesions.<sup>36</sup> Prevention of moderate to severe disease was achieved with 1 dose of varicella vaccine, which is consistent with previous studies.<sup>11,29,34,37</sup> Most breakthrough cases of varicella occurred in the early years of the study,

reflecting the likelihood of early vaccine failure at a time when VZV was still circulating. Our results seem to conflict with those in an earlier study,<sup>13</sup> in which breakthrough varicella seemed to be increasing in the years after vaccination. Because our population is based on nearly 100% capture of data, it is possible that this difference may be due to increased reporting and awareness of varicella over time in the earlier study.

The apparent increase in vaccine effectiveness over time may seem counterintuitive. It is likely the result of vaccine failure occurring early while breakthrough episodes became rare over time due to high vaccine effectiveness both directly and through herd immunity, with little sign of any waning of vaccine effectiveness. Because our cohort was all of the same age, and all vaccinated at the same time, we are unable to disentangle these effects with our analyses.

In this study, no breakthrough varicella was reported after the receipt of a second dose of varicella vaccine. Of note, due to a catch-up program at KPNC, 38% of the study cohort received a second dose. Few previous studies have examined the effectiveness of the second dose. One prospective study<sup>11</sup> and 2 observational studies<sup>16,17</sup> showed that the second dose was highly effective, and our findings are consistent with the results of those studies. The further decrease in breakthrough rates, observed in 2008 and 2009, may have been the result of the implementation of the second dose in 2006. Prevention of residual cases of varicella increases protection for infants too young to receive the vaccine and immunocompromised children who cannot receive a live vaccine, and decreases days lost to school or work.<sup>17,38</sup> In the United States, the second dose of var-

icella is typically given at ages 4 to 6 years, but it could potentially be of more benefit, if varicella is circulating, if given early after the first dose.

Overall, this study suggests that the incidence rate of HZ among vaccinated children may be lower than after naturally acquired varicella in unvaccinated children of the same age.<sup>19</sup> HZ rates have tended to increase over the last several decades in the United States, beginning before the introduction of varicella vaccination, as well as in other countries not routinely using varicella vaccine.<sup>39,40</sup> Thus, the historical rates of HZ we used from the 1960s to 1970s may underestimate current unvaccinated HZ rates. In addition, although the historical cases of HZ were all from wild-type virus, our study HZ cases were likely a mixture of wild-type and vaccine strain virus. In areas of high vaccine coverage, wild-type VZV may be much lower than during the early phase of our study. If these assumptions are correct, the protective effect of varicella vaccination on HZ in children could be of a greater magnitude than suggested from the study data.

Our study has some limitations. Although parental reports of varicella have been shown to be reliable for young children,<sup>5,6,9</sup> reporting of varicella in adolescents may be less reliable. In the vaccine era, even physician diagnosis of varicella may be less accurate. Thus, varicella may have been underreported or overreported in this study. Because most cases were reported only at the time of the 6-month interview, parents may not recall the severity of the rash, which could have resulted in misclassification of rash severity. Finally, comparisons of current rates of varicella and zoster versus published historical

rates may be somewhat problematic for several reasons, including possible changes over time in disease incidence and case ascertainment, and potential differences in underlying populations.

## CONCLUSIONS

This study demonstrated that varicella vaccine was effective at preventing chicken pox, and no evidence of waning protection was noted over a 14-year period. One dose of vaccine resulted in excellent protection against moderate to severe disease, and no cases of varicella occurred after a second dose. Most varicella cases occurred shortly after the cohort was vaccinated, during a time when VZV was still widely circulating. The risk of HZ was not increased in vaccinated children, and the risk seemed to be lower in vaccinated children than in the prevaccine era.

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## Long-term Effectiveness of Varicella Vaccine: A 14-Year, Prospective Cohort Study

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