The Incidence and Clinical Characteristics of Herpes Zoster Among Children and Adolescents After Implementation of Varicella Vaccination

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Background: The varicella-zoster virus (VZV) vaccine strain may reactivate to cause herpes zoster. Limited data suggest that the risk of herpes zoster in vaccinated children could be lower than in children with naturally acquired varicella. We examine incidence trends, risk and epidemiologic and clinical features of herpes zoster disease among children and adolescents by vaccination status.

Methods: Population-based active surveillance was conducted among <20 years old residents in Antelope Valley, California, from 2000 through 2006. Structured telephone interviews collected demographic, varicella vaccination and disease histories, and clinical information.

Results: From 2000 to 2006, the incidence of herpes zoster among children <10 years of age declined by 55%, from 42 cases reported in 2000 (74.8/100,000 persons; 95% confidence interval [95% CI]: 55.3–101.2) to 18 reported in 2006 (33.3/100,000; 95% CI: 20.9–52.8; $P < 0.001$). During the same period, the incidence of herpes zoster among 10- to 19-year-olds increased by 63%, from 35 cases reported in 2000 (59.5/100,000 persons; 95% CI: 42.7–82.9) to 64 reported in 2006 (96.7/100,000; 95% CI: 75.7–123.6; $P < 0.02$). Among children aged <10 years, those with a history of varicella vaccination had a 4 to 12 times lower risk for developing herpes zoster compared with children with history of varicella disease.

Conclusions: Varicella vaccine substantially decreases the risk of herpes zoster among vaccinated children and its widespread use will likely reduce overall herpes zoster burden in the United States. The increase in herpes zoster incidence among 10- to 19-year-olds could not be confidently explained and needs to be confirmed from other data sources.

Key Words: herpes zoster, varicella vaccine, varicella-zoster virus, impact of varicella vaccination, herpes zoster incidence, active surveillance

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Varicella-zoster virus (VZV) causes varicella as a primary infection, and after remaining latent within sensory ganglia, the virus can reactivate and cause herpes zoster.[1] Herpes zoster is associated with a decline in cell-mediated immunity due to aging or to an immunosuppressive illness or treatment.[2] Herpes zoster is more common in older adults, but it can occur in healthy children and young adults, in whom disease is usually milder.[3–6]

In the United States, a 1-dose childhood varicella vaccination program was initiated in 1995,[7] and a 2-dose schedule was recommended in 2006.[8] By 2006, national varicella vaccine coverage among children 19 to 35 months of age reached 89%[9] and varicella disease morbidity and mortality declined by as much as 80% to 90%.[10–12] Some studies suggest that immunity of individuals who have had varicella disease may be boosted through repeated exposures to VZV, and this immununologic boost would prevent or delay development of herpes zoster.[13–15] Given this scenario, the vaccine-related reduction in varicella disease incidence in the United States would lead to fewer opportunities for VZV exposures and consequent immune boosting, which could increase the risk of herpes zoster among persons with prior varicella disease.[13,16]

Like wild-type VZV, vaccine strain virus also can result in latent infection and reactivation in vaccine recipients.[17–19] Studies in immunosuppressed and healthy children have indicated that the risk and severity of herpes zoster in vaccinated children are lower than in children with a history of wild-type VZV infection.[19–24] Data on the risk of vaccine strain VZV reactivation, however, are limited, and no studies have reported on clinical features and incidence of herpes zoster in children since implementation of the varicella vaccination program. We used data from a prospective community-based surveillance project (*a*) to compare the clinical presentation of herpes zoster in children and adolescents with a history of varicella vaccination or disease; (*b*) to examine changes in the incidence of herpes zoster in children and adolescents by age; and (*c*) to estimate the relative risk of herpes zoster among children <10 years with a history of varicella vaccination compared with those with a history of disease.

METHODS

Study

Antelope Valley (Los Angeles County), California, population ~350,000, is 1 of 2 US surveillance project sites (the other being West Philadelphia, PA) that have collected community-based active surveillance data for varicella in residents of all ages since 1995[25] and for herpes zoster in residents <20 years of age since

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2000. Details of the populations and methods for this surveillance have been described.[25] Every 2 weeks, preschools, schools, hospitals, and public and private healthcare providers report on cases of varicella and herpes zoster, even when no cases are identified. Additional herpes zoster cases are also found through querying all verified varicella case-patients as to possible herpes zoster case exposures within or outside of their household. Since 1995, all providers in the surveillance area have also reported the number of varicella vaccine doses administered by age of recipient on a monthly basis. Using a standardized questionnaire, research staff interview all cases or their caretakers to collect demographic and epidemiologic data, including information on varicella vaccination and clinical herpes zoster presentation (eg, presence and severity of pain, rash size, and location). Pain severity was estimated using a categorized schedule of increased intensity from mild, moderate, severe, to excruciating. This project was evaluated by officials at the Centers for Disease Control and Prevention and the collaborating institutions, and it was deemed that individual informed consent from subjects was not needed.

Case Definition

We defined a case of herpes zoster as a unilateral maculopapular or vesicular rash involving at least one dermatome, diagnosed by a physician in an Antelope Valley resident. Cases were verified by medical record review. Information on vaccination status was obtained from medical provider or school immunization records. History of and age at varicella disease were self-reported and were validated through medical chart review when possible.

Population at Risk

We determined the population at risk for herpes zoster from 2000 to 2006 among children aged <10 years with a history of varicella vaccination and among children aged <10 years with a history of varicella disease.

To create a denominator for at-risk children <10 years of age with a history of vaccination, we used data on varicella vaccine doses administered by age. Children cumulatively contributed to the cohort at risk for herpes zoster for each year of life after vaccination until their 10th birthday.

To create a denominator for at-risk children <10 years of age with a history of varicella disease, we used 2 different methods. The first of these 2 methods was based on the number of unvaccinated varicella disease cases reported to the active surveillance project. During the study period (2000–2006), the cohort of children aged <10 years comprised those born between 1991 and 2006. To account for children who may have acquired varicella disease before the beginning of the varicella surveillance system in 1995, we extrapolated age-specific varicella incidence rates obtained from 1995 to census data from 1991 to1994. Using this method, we accounted for children who, since as early as 1991, cumulatively contributed to the cohort at risk for herpes zoster for each year of life after having varicella. To account for under reported varicella cases, we used capture-recapture methodology,[26] which compares 2 surveillance sources, childcare/preschools/schools, and medical providers. We estimated that between 1995 and 2006, the completeness of annual reporting for varicella cases among 2- to 18-year-old children ranged from 65.7% to 75.8%. Thus, we increased the denominator of children aged <10 years with varicella disease for each surveillance year (1995–2006) by the number estimated to be under-reported (1-completeness for each year; range: 24.2%–34.3%).

The second method for creating an at-risk denominator for children <10 years with a history of varicella disease was based on the annual Antelope Valley census data. In this method, we used the estimated population of children <10 years with varicella vaccination described earlier, to subtracted the vaccinated cohorts from the annual Antelope Valley census, and then discounted that number by another 10%.[27] This percentage is considered to approximate the number of varicella-susceptible children (ie, those who were not vaccinated and escaped infection).

Statistical Analysis

SAS version 9.1 software (SAS Institute, Cary, NC) was used to analyze data. Categorical variables were compared by use of a 2-sided χ^2 test, and continuous variables were compared by use of the nonparametric Wilcoxon rank sum test. We used 2000 to 2006 population estimates from the United States Census Bureau to calculate the age-specific annual incidence of herpes zoster, disregarding specific exposure history. Trends in overall and specific incidence rates by age group were evaluated using Poisson regression. Statistical significance was set at 0.05. Age was categorized by 10-year age groups.

We estimated the population at risk for herpes zoster by vaccination and disease history status to calculate the annual risk ratio (RR) of herpes zoster among children aged <10 years from 2000 to 2006 by comparing the incidence of herpes zoster among those who were vaccinated with the incidence among those with a history of varicella disease (described in Population at Risk section). For the estimation of RR, herpes zoster case-patients were considered to have a history of varicella disease if they had no documented history of vaccination or an unknown history of vaccination. Herpes zoster case-patients were considered to have a history of varicella vaccination if they had (1) a history of vaccination but not of varicella disease, (2) a history of vaccination and an unknown history of varicella, or (3) a history of both vaccination and varicella. Wald χ^2 test was used to estimate the probability of the RR being statistically significantly different from 1.0, and 95% Wald confidence intervals (CI) were estimated.

RESULTS

Herpes Zoster Case Reports and Demographics

From 2000 through 2006, 579 cases of herpes zoster among persons aged <20 years were reported. Of these, 120 were excluded from the study: 36 (30%) lived outside the surveillance area, 10 (8%) were reporting errors, 7 (6%) did not meet the case definition because they were not physician diagnosed, and 67 (56%) had alternative diagnoses (24 cases of herpes simplex virus infection, 13 cases of allergic dermatitis or other skin rashes, 4 cases of localized bacterial infection, 2 cases of ringworm, 1 case of scabies, 9 cases with laboratory results negative for infectious etiologies, and 14 cases with unspecific diagnoses). The remaining 459 cases of herpes zoster, had case investigations and medical records review completed.

Of the 459 herpes zoster cases, 154 (34%) were <10 years old and 305 (66%) were between 10 to 19 years. The median age was 12 years (range: 11 months–19 years), 215 (47%) were male, 220 (48%) were white non-Hispanics, 156 (34%) were Hispanics, 51 (11%) were African Americans, and 16 (3.5%) were Asian/American Indians.

Vaccination Status of Herpes Zoster Cases

Among the 154 cases <10 years old, 40 (26%) reported a history of varicella vaccination only, 81 (53%) reported a history of varicella disease only, 24 (15.5%) reported either an unknown history of varicella disease and/or vaccine, 8 (5%) reported a history of both varicella disease and vaccine, and 1 (0.5%) denied a history of both.

Among the 305 cases from 10 to 19 years of age, 6 (2%) reported a history of varicella vaccination alone, 245 (80%) re-

ported a history of varicella disease only, 45 (15%) reported either an unknown history of varicella disease and/or vaccine, 5 (2%) reported a history of both varicella disease and vaccine, and 4 (1%) denied a history of both.

Clinical Characteristics of Herpes Zoster Cases

Of the 459 herpes zoster cases, 372 (81%) had complete clinical and vaccination information (Table, Supplemental Digital Content 1, http://links.lww.com/A1165). The majority (82%) of those were healthy children and adolescents. Nine (2%) herpes zoster cases had underlying immunocompromised conditions; all had a history of varicella disease and none were vaccinated. The clinical characteristics of herpes zoster among those with a history of varicella did not differ significantly by age group (<10 vs. 10–19 years old), except that those aged 10 to 19 years were more likely to report presence of pain (87% vs. 77%; $P = 0.02$) and use of acyclovir (67% vs. 42%; $P < 0.0001$) than <10-year-olds.

Comparisons of clinical presentation by vaccination status were limited to children <10 years. Compared with children with a history of varicella, vaccinated children with herpes zoster were younger (median age: 5 vs. 8 years, respectively), more likely to have herpes zoster rash located in the area of the lumbar/sacral dermatomes (28% vs. 11%, respectively; $P = 0.02$), less likely to report pain (45% vs. 77%; $P < 0.001$) and, when pain was reported, they reported less intense pain ($P = 0.03$). They were also less likely to have rash lesions described as vesicles (53% vs. 63%, respectively), and have a somewhat smaller rash area however, these 2 characteristics were not statistically significantly different by vaccination status.

Hospitalization

Four herpes zoster cases were hospitalized, with lengths of stay ranging from 3 to 8 days, and all received intravenous acyclovir. Three of these patients, ranging from 14 to 18 years old, had a history of varicella and underlying medical conditions: leukemia and bone marrow transplant (4 months before herpes zoster onset); Crohn disease requiring chronic immunosuppressive therapy; and systemic lupus erythematosus requiring chronic use of oral steroids. The fourth patient was a healthy 7-year-old boy who was vaccinated 6 years previously and had no history of varicella. He was admitted with fever and severe herpes zoster pain with facial rash. Overall, the rate of herpes zoster-related hospitalization per 100,000 population aged <20 years was 0.6 (95% CI: 0.25–146), and the rate of hospitalization per 1000 herpes zoster cases was 10.9 (95% CI: 4.5–26.2).

Herpes Zoster Incidence

The estimated annual incidence of herpes zoster by age group fluctuated between 2000 and 2006 in the study area (Table 1). Among children <10 years of age, herpes zoster incidence had an overall decreasing trend ($P < 0.001$), and declined by 56%, from 74.8 cases/100,000 children in 2000 to 33.3 cases/100,000 children in 2006 (95% CI: 55.30–101.2 and 20.9–52.8, respectively; $P < 0.001$). Among those 10 to 19 years of age, herpes zoster incidence had an overall increasing trend ($P < 0.002$), and increased by 63%, from 59.5 cases/100,000 children in 2000 to 96.7 cases/100,000 children in 2006 (95% CI: 42.7–82.9 and 75.7–123.6, respectively; $P = 0.002$). Overall, herpes zoster incidence rates were higher among women than men (60.84 vs. 51.17 cases per 100,000 persons, respectively), although this difference was not statistically significant.

TABLE 1. Annual Incidence of Herpes Zoster by Age Group, N = 459

Age (Yr)	Incidence by Yr*																	
	2000		2001		2002		2003		2004		2005		2006		2000–2006	
	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)
0–9†	42	74.8 (55.3–101.2)	27	49.4 (33.8–71.9)	19	35.6 (22.7–55.8)	23	43.9 (29.2–66.1)	12	22.8 (12.9–40.2)	13	24.5 (14.24–42.24)	18	33.3 (20.9–52.8)	154	40.9 (34.9–47.9)
10–19‡	35	59.5 (42.7–82.9)	34	55.5 (39.7–77.7)	39	61.8 (45.1–84.6)	31	48.3 (34.0–68.7)	54	82.45 (63.1–107.6)	48	72.4 (54.6–96.13)	64	96.7 (75.7–123.6)	305	68.5 (61.2–76.6)
Total	77	67.0 (53.6–83.7)	61	52.6 (40.9–67.6)	58	49.8 (38.5–64.4)	54	46.3 (35.5–60.5)	66	55.9 (43.9–71.1)	61	51.1 (39.9–65.7)	82	68.2 (54.9–84.7)	459	55.9 (51.0–61.2)

*Incidence rate based on US census data per 100,000 population.
†Incidence rate significantly decreased from 2000 to 2006 ($P < 0.001$).
‡Incidence rate significantly increased from 2000 to 2006 ($P < 0.002$).

Estimation of Risk of Herpes Zoster by Vaccination and Disease History Among Children <10 Years of Age

From 2000 through 2006, there were 376,154 children aged <10 years living in Antelope Valley. For the same time period, we estimated that 265,916 children aged 1 to 9 years were vaccinated against varicella. The rate of herpes zoster among vaccinated children was 19.2 (95% CI: 14.6–25.2) per 100,000 for the combined years 2000 to 2006. From 2000 to 2006, the incidence of herpes zoster among vaccinated children did not vary significantly: 95% CIs were wide and overlapping for each year's risk estimate. Using method 1, we estimated that 35,213 unvaccinated children <10 years of age had natural varicella disease during the study period. The rate of herpes zoster in children with a history of natural varicella disease was 238.5 (95% CI, 192.6–295.4) per 100,000 for the combined years 2000 to 2006, and there were considerable fluctuations in annual risk estimates, likely due to small numbers of cases and the declining denominator. The RR of herpes zoster in the vaccinated group compared with those with a history of varicella disease did not vary significantly by year ($P = 0.35$); and the overall 7-year RR was 0.08 (95% CI: 0.06–0.11; $P < 0.005$) (Table 2). Using method 2 the overall 7-year RR was 0.23 (95% CI: 0.16–0.32; $P < 0.0001$)–(data not presented).

DISCUSSION

This study among residents in Antelope Valley (Los Angeles County), California, is the largest population-based study to assess the risk and clinical presentation of herpes zoster among children vaccinated with varicella vaccine in a community where varicella disease burden has declined significantly (74%, 1995–2001 and 90%, 1995–2005).[11,25] From 2000 through 2006, the incidence of herpes zoster among children aged <10 years also declined (55%), while the incidence among unvaccinated residents aged 10 to 19 years with history of varicella disease increased by 63%. The estimated risk of herpes zoster among vaccinated children <10 years of age was 4 to 12 times lower than that among children of similar age with a history of varicella.

Similar to previous findings in children with leukemia,[20] our study documented that varicella vaccination modified the clinical presentation of herpes zoster. Among children <10 years of age, those with a history of vaccination reported less pain compared with those with a history of varicella, although, this difference could be related to child's age, as those with a history of varicella disease were slightly older than those with vaccination (median age: 8 years vs. 5 years, respectively). However, among vaccinated children, besides pain, there were other clinical features of herpes zoster that were modified. Herpes zoster rash in vaccinated children more often affected areas of the lumbar/sacral dermatomes and tended to be smaller in size and to have fewer vesicular lesions. The greater proportion of vaccinated children presenting with rash located in the lumbosacral region could be explained by the practice of administering vaccines in a child's thigh when vaccinated at 12 to 15 months of age; thus, corroborating other studies' finding an association of injection site and location of rash.[28,29] In contrast, herpes zoster in children <10 years with wild-type VZV most often involves thoracic dermatomes,[6] which might be related to the intensity of the centrally distributed rash in varicella.

Our results confirm and extend previously reported data of a decline in herpes zoster incidence among varicella vaccinated <10-year-olds.[2] In contrast, for children and adolescents 10 to 19 years, we observed a trend of increasing zoster incidence. Some studies have suggested that widespread varicella vaccination may increase the incidence of herpes zoster among those who have had varicella; these studies reported a protective effect against herpes zoster in adults who were exposed to varicella cases or to children.[13,21,30] Two studies utilizing mathematical models that assume immunologic boosts from exposure to varicella cases predict an increased incidence of herpes zoster relative to the prevaccine incidence.[13,31] One model predicts that persons aged 10 to 44 years will be most affected 10 years after the start of a universal vaccination program, assuming an immediate impact (elimination) on varicella disease.[13] Both models predict an eventual decrease in the incidence of herpes zoster to levels below the prevaricella vaccine incidence.[13,31] Universal varicella vaccination in the United States started in 1995, and national vaccine coverage among children 19 to 35 months of age increased from 26% in 1997 to 90% in 2006, while in Los Angeles County vaccination

TABLE 2. Estimated RR of Herpes Zoster in Residents Aged <10 Years With a History of Varicella Vaccination Versus Those With a History of Varicella Disease

Yr	Vaccination History			Disease History			RR#*** (95% CI)
	No. Cases*	Population	IR (95% CI)†‡	No. Cases§	Population‖	IR (95% CI)¶	
2000	4	23,752	16.8 (6.3–44.8)	35	11,065	316.3 (227.1–440.5)	0.05 (0.02–0.15)
2001	5	30,512	16.3 (6.8–39.3)	20	8563	233.5 (150.6–362.0)	0.07 (0.02–0.19)
2002	7	35,722	19.6 (9.3–41.1)	8	5939	134.7 (67.3–269.3)	0.15 (0.05–0.40)
2003	9	39,924	22.5 (11.7–43.3)	10	4399	227.3 (122.3–422.5)	0.09 (0.04–0.24)
2004	8	43,046	18.5 (9.3–37.1)	2	2649	75.5 (18.88–301.8)	0.25 (0.05–1.16)
2005	8	45,694	17.5 (8.7–35.0)	4	1522	262.8 (98.6–700.2)	0.07 (0.02–0.22)
2006	10	47,266	21.1 (11.4–39.3)	5	1076	464.6 (193.4–1116.4)	0.046 (0.01–0.13)
2000–2006	51	265,916	19.2 (14.6–25.2)	84	35,213	238.5 (192.6–295.4)	0.080 (0.06–0.11)

*Herpes zoster cases with a varicella vaccination include those with vaccine history only (n = 40), vaccine and unknown disease history (n = 3), and vaccine and disease history (n = 8).

†IR = herpes zoster cases/100,000 persons.

‡Trend test of IR among those with a history of varicella vaccination (2000–2006), $\chi^2 = 0.10$, $P = 0.76$.

§Herpes zoster cases with a varicella disease history include those with disease history only (n = 81) and those with disease history and unknown vaccine history (n = 3).

‖Population with a history of varicella disease corrected by annual completeness of case reporting.

¶Trend test of IR among those with a history of varicella disease (2000–2006), $\chi^2 = 1.04$, $P = 0.31$.

#RR = vaccinated IR/disease history IR.

**Trend test for RR (2000–2006), $\chi^2 = 0.84$, $P = 0.35$.

IR indicate incidence rate.

coverage increased from 37% to 89%. Our data show an increase in herpes zoster in 2004, 3 years after the first evidence of varicella vaccine impact was described (2000) and an increase of 63% by 2006. This increase is higher and in a younger age group than predicted; thus, unlikely that it can be explained by varicella vaccination alone. Additionally, some studies have reported an increase in zoster incidence in adults even before varicella vaccine was available. Ragozzino et al[3] reported a 28% increase in zoster among women and a 41% increase among men between the 1940s and 1950s in Minnesota; and Brisson et al[32] reported a 31% increase between 1979 and 1997 in Canada. A more recent study in Minnesota reported a 22% increase among adults between 1996 and 2001, a time when there was minimal, if any, evidence of vaccine impact.[33]

Another explanation to consider for the observed increase in herpes zoster among persons 10 to 19 years of age includes improvement in the herpes zoster surveillance system. Improved reporting of herpes zoster during the surveillance period, as has occurred for varicella reporting, could have had a role in this increase, although we were not able to evaluate this hypothesis.

The incidence of herpes zoster among children and adolescents varies markedly in published studies, likely reflecting differences in case ascertainment and populations from which samples were drawn. Our population-based annual herpes zoster incidence rates of 23 to 75/100,000 population in persons aged <10 years and of 59 to 97/100,000 population for persons aged 10 to 19 years fall within the range of the incidence rates reported in previous studies conducted during the prevaccine era.[1,3–6] In addition, despite recent studies showing that women have a higher incidence of herpes zoster than men,[34,35] we did not find a statistically significant difference in herpes zoster incidence by sex.

Our results also confirm data from studies conducted among children with leukemia that reported a 3-fold lower risk of herpes zoster among children with a history of vaccination compared with those with a history of varicella.[19–21] The lower risk of VZV reactivation in vaccine recipients may be related to the lower risk of vaccine strain VZV to cause varicella-like rash after vaccination (ie, <5% of vaccinated healthy children will develop vaccine-related varicella rash, compared with the almost universal occurrence of rash, with 200–400 lesions, in varicella caused by wild-type VZV). It is hypothesized that skin lesions that occur with primary VZV infection acquired naturally or through vaccination, are important in the pathogenesis of herpes zoster because infection in the dermis involves cutaneous sensory nerves with retrograde spread of VZV to sensory ganglia, where latency is established.[19] However, it should be noted that herpes zoster has also been reported in vaccine recipients in whom no previous vaccine-related varicella-like rash was identified.[17,19] If this lower risk among vaccinated children is maintained throughout life-assuming high vaccine coverage levels in future cohorts and less exposure to wild VZV, the varicella vaccination program would reduce the number of zoster cases in the long term as vaccinated children cohort move into older age groups, complementing the expected impact of the herpes zoster vaccination program in the older population.[36]

There are several limitations to consider when interpreting our results. First, we did not have pre-2000 herpes zoster data; thus, we could not assess baseline trends in herpes zoster disease incidence before implementation of or in the early years of the varicella vaccine program. Second, because herpes zoster is a rare disease in children and adolescents, small fluctuations in the annual number of cases reported can result in marked changes in disease incidence rates. However, we found that from 2000 to 2006, the herpes zoster incidence trend declined significantly among children aged <10 years. Third, our case definition did not rely on a laboratory based diagnosis which could have led to a higher number of mild cases of herpes zoster being missed. If a higher proportion of mild cases were disproportionately missed among vaccine recipients, this could overestimate the protective effect of varicella vaccination on herpes zoster.

Finally, both an over- or underestimation of the denominators used could affect our herpes zoster risk estimates among children <10 years of age by history of varicella disease or vaccination. We attempted to correct the annual number of cases with a history of varicella to account for underreporting. However, the actual reporting completeness by year may still underestimate the total population at risk. This would bias our results toward overestimating the protection offered by the vaccine. In contrast, using the census data and subtracting the number of vaccinated and possible susceptible residents to determine the denominator may overestimate the population at risk because it assumes that the remaining children <10 years of age have had varicella disease. (between 1995 and 2005, the median age of unvaccinated persons infected with varicella increased 5–13 years in Antelope Valley).[11] This would lead to underestimating the protection offered by the vaccine. In our analysis, the first denominator (ie, that based on reported cases of varicella disease) was about one-third the second denominator (ie, that based on Antelope Valley census data) (35,213 vs. 99, 214, respectively), impacting the RR by the same magnitude (RR range: 0.08–0.23). This suggests that the risk of herpes zoster among persons with a vaccine history is lower than that among persons with a disease history and that the true RR may fall between the 2 estimates.

Among the vaccinated cohort, vaccine doses reported by providers compared well with doses distributed in the surveillance area by the vaccine manufacturer, varying only by 3% to 5% in any given year, which could represent wastage. We did not exam severe outcomes of herpes zoster by vaccination status due to small number of cases; although we noted that one hospitalized herpes zoster case was an otherwise healthy vaccinated child.

In summary, our study provides evidence, at least over a 7- to 10-year period, that children aged <10 years who are vaccinated for varicella have a much lower risk of developing herpes zoster than those with history of varicella disease. The widespread use of varicella vaccine could reduce herpes zoster incidence rates among the US vaccinated population; however, in our study, children and adolescents between 10 and 19 years of age experienced a significant increase in herpes zoster incidence. The possible reasons for this increased incidence cannot be confidently explained. A long-term follow-up study of this cohort is needed to assess the risk of herpes zoster as they age into adulthood.

Physicians should be aware of the potential of varicella vaccine virus reactivation and use appropriate laboratory tests to confirm a diagnosis of herpes zoster in vaccine recipients. Further monitoring of herpes zoster incidence is warranted in children and adolescents to detect changes in disease trends and to better describe the clinical presentation of the disease in the vaccinated population, especially in light of the new 2 dose varicella vaccine policy for children.[8]

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REFERENCES

1. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. *Proc R Soc Med*. 1965;58:9–20.
2. Cohen JI, Brunell PA, Straus SE, et al. Recent advances in varicella-zoster virus infection. *Ann Intern Med*. 1999;130:922–932.
3. Ragozzino MW, Melton LJ III, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. *Medicine*. 1982;61:310–316.
4. Guess HA, Broughton DD, Melton LJ III, et al. Epidemiology of herpes zoster in children and adolescents: a population-based study. *Pediatrics*. 1985;76:512–517.
5. Chidiac C, Bruxelle H, Daures JP, et al. Characteristics of patients with herpes zoster on presentation to practitioners in France. *Clin Infect Dis*. 2001;33:62–69.
6. Petursson G, Helgason S, Gudmundsson S, et al. Herpes zoster in children and adolescents. *Pediatr Infect Dis J*. 1998;17:905–908.
7. Marin M, Guris D, Chaves SS, et al. Prevention of Varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 1996; 45(RR11):1–25.
8. Marin M, Guris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1–40.
9. Immunization coverage in the United States–National Immunization Survey (NIS). Available at: http://www.cdc.gov/vaccines/stats-surv/imz-coverage.htm#nis. Accessed June 20, 2008.
10. Nguyen HQ, Jumaan AO, Seward JF. Decline in mortality due to varicella after implementation of varicella vaccination in the United States. *N Engl J Med*. 2005;352:450–458.
11. Guris D, Jumaan AO, Mascola L, et al. Changing varicella epidemiology in active surveillance sites-United States, 1995–2005. *J Infect Dis*. 2008; 197(suppl 2):S71–S75.
12. Zhou F, Harpaz R, Jumaan AO, et al. Impact of varicella vaccination on health care utilization. *JAMA*. 2005;294:797–802.
13. Brisson M, Gay NJ, Edmunds WJ, et al. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. *Vaccine*. 2002;20:2500–2507.
14. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? *Lancet Infect Dis*. 2004;4:26–33.
15. Terada K, Kawano S, Yoshihiro K, et al. Varicella-zoster virus (VZV)reactivation is related to the low response of VZV-specific immunity after chickenpox in infancy. *J Infect Dis*. 1994;169:650–652.
16. Ferguson NM, Anderson RM, Garnett GP. Mass vaccination to control chickenpox: the influence of zoster. *Proc Natl Acad Sci USA*. 1996;93: 7231–7235.
17. Uebe B, Sauerbrei A, Burdach S, et al. Herpes zoster by reactivated vaccine varicella zoster virus in a healthy child. *Eur J Pediatr*. 2002;161:442–444.
18. LaRussa P, Steinberg SP, Shapiro E, et al. Viral strain identification in varicella vaccinees with disseminated rashes. [Erratum in: *Pediatr Infect Dis J*. 2001;20:33]. *Pediatr Infect Dis J*. 2000;19:1037–1039.
19. Hardy I, Gershon AA, Steinberg SP, et al; the Varicella Vaccine Collaborative Study Group. The incidence of zoster after immunization with live attenuated varicella vaccine. *N Engl J Med*. 1991;325:1545–1550.
20. Brunell PA, Taylor-Wiedeman J, Geiser CF, et al. Risk of herpes zoster in children with leukemia: varicella vaccine compared with history of chickenpox. *Pediatrics*. 1986;77:53–56.
21. Gershon AA, LaRussa P, Steinberg S, et al. The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox. *J Infect Dis*. 1996;173:450–453.
22. Black S, Shinefield H, Ray P, et al. Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr Infect Dis J*. 1999;18:1041–1046.
23. White CJ, Kuter BJ, Hildebrand CS, et al. Varicella vaccine (VARIVAX) in healthy children and adolescents: results from clinical trials, 1987 to 1989. *Pediatrics*. 1991;87:604–610.
24. Jumaan AO, Yu O, Jackson LA, et al. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992–2002. *J Infect Dis*. 2005;191:2002–2007.
25. Seward JF, Watson BM, Peterson CL, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. *JAMA*. 2002;287:606–611.
26. Stephen C. Capture-recapture methods in epidemiological studies. *Infect Control Hosp Epidemiol*. 1996;17:262–266.
27. Kilgore PE, Kruszon-Moran D, Seward JF, et al. Varicella in Americans from NHANES III: implications for control through routine immunization. *J Med Virol*. 2003;70(suppl 1):S111–S118.
28. Sharrar RG, LaRussa P, Galea SA, et al. The postmarketing safety profile of varicella vaccine. *Vaccine*. 2000;19:916–923.
29. Galea AS, Sweet A, Beninger P, et al. The safety profile of varicella vaccine: a ten year review. *J Infect Dis*. 2008;197(suppl 2):S165–S169.
30. Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. *Lancet*. 2002;360:678–682.
31. Garnett GP, Grenfell BT. The epidemiology of varicella-zoster virus infection: the influence of varicella on the prevalence of herpes zoster. *Epidemiol Infect*. 1992;108:513–528.
32. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect*. 2001;127:305–314.
33. Yawn BP, Saddier P, Wollan PC, et al. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc*. 2007;82:1341–1349.
34. Fleming DM, Cross KW, Cobb WA, et al. Gender difference in the incidence of shingles. *Epidemiol Infect*. 2004;132:1–5.
35. Opstelten W, Van Essen GA, Schellevis F, et al. Gender as an independent risk factor for herpes zoster: a population-based prospective study. *Ann Epidemiol*. 2006;16:692–695.
36. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352: 2271–2284.