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Two-dose Varicella Vaccine Effectiveness and Rash Severity in Outbreaks of Varicella Among Public School Students

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Abstract

Background—Universal 2-dose varicella vaccination was recommended in 2006 to further reduce varicella disease burden. This study examined 2-dose varicella vaccine effectiveness (VE) and rash severity in the setting of school-associated varicella outbreaks.

Methods—A case control study was conducted from January 2010 to May 2011 in all West Virginia public schools. Clinically diagnosed cases from varicella outbreaks were matched with classmate controls. Vaccination information was collected from school, health department and healthcare provider immunization information systems.

Results—Among the 133 cases and 365 controls enrolled, VE against all varicella was 83.2% [95% confidence interval (CI): 69.2%–90.8%] for 1-dose of varicella vaccine and 93.9% (95% CI: 86.9%–97.1%) for 2-dose; the incremental VE (2-dose vs. 1-dose) was 63.6% (95% CI: 32.6%–80.3%). In preventing moderate/severe varicella, 1-dose varicella vaccine was 88.2% (95% CI: 72.7%– 94.9%) effective, and 2-dose vaccination was 97.5% (95% CI: 91.6%–99.2%) effective, with the incremental VE of 78.6% (95% CI: 40.9%–92.3%). One-dose VE declined along with time since vaccination (VE = 93.0%, 88.0% and 81.8% in <5, 5–9 and ≥10 years after vaccination, $P = 0.001$ for trend). Both 1- and 2-dose breakthrough cases had milder rash than unvaccinated cases (<50 lesion: 24.6%, 49.1% and 70.0% in unvaccinated, 1-dose and 2-dose cases, $P < 0.001$), and no severe disease was found in 2-dose cases.

Conclusions—Two-dose varicella vaccination is highly effective and confers higher protection than a 1-dose regimen. High 2-dose varicella vaccination coverage should maximize the benefits of the varicella vaccination program and further reduce varicella disease burden in the United States.

Keywords

varicella; varicella vaccine; vaccine effectiveness; break-through varicella

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Varicella (chickenpox) is a highly contagious disease caused by the varicella zoster virus (VZV), which, in the absence of vaccination, is a universal infection acquired mainly in childhood. Prior to introduction of varicella vaccine in 1995, an estimated 4 million varicella cases, 11,000 hospitalizations and 100 deaths occurred each year in the United States.[1] Since introduction of 1-dose varicella vaccination in the United States, dramatic declines were documented in the number of varicella cases,[2] outbreaks,[3] varicella-related hospitalizations and deaths.[4,5] However, albeit smaller in size and shorter in duration, varicella outbreaks continued to occur in school and daycare settings with high 1-dose varicella vaccination coverage[6-9]; therefore, a routine 2-dose varicella vaccination was recommended in 2006 for school-aged children and a catch-up vaccination for children of all ages who lacked evidence of immunity.[10]

The 2-dose program appears to have been rapidly implemented in the United States in the first 5 years since it was recommended. For the 2012–2013 school-year, median 2-dose varicella vaccination coverage among the 36 states and District of Columbia requiring and reporting 2 doses was 93.8% (range: 84.6% in Colorado to ≥99.9% in Mississippi); 14 reported coverage ≥95%.[11,12] There are limited data on the effectiveness of the 2-dose varicella vaccine regimen and very limited numbers of 2-dose breakthrough cases reported, thus more data are needed to describe 2-dose vaccine effectiveness (VE) and rash presentations of 2-dose breakthrough varicella. Therefore, a case control study was conducted in West Virginia public schools during 2010 and 2011 to evaluate 1-dose, 2-dose and incremental varicella VE and characterize 2-dose breakthrough varicella.

MATERIALS AND METHODS

Study Population and Data Collection

West Virginia Department of Health and Human Resources was one of 6 sites to receive American Recovery and Reinvestment Act funding through the Centers for Disease Control and Prevention to conduct school-based varicella outbreak surveillance from January 2010 to December 2011. In West Virginia, 2-dose varicella vaccination became school entry requirement in 2008, and the vaccination coverage reached 88.9% among children enrolled in kindergartens in 2011–12 school year.[13] From January to May 2010 and September 2010 to May 2011, the 220 school nurses serving all 688 public elementary, middle/junior and high schools in West Virginia reported via monthly electronic surveys whether any varicella outbreak had occurred in the school during the previous month and, if any had been detected, the number of outbreak-associated cases. A case of varicella was defined as an acute maculopapulovesicular rash without other apparent cause[14] in a West Virginia public school student 5 through 18 years of age. Breakthrough varicella was defined as a case that developed >42 days after vaccination. A school outbreak was defined as 3 or more cases of varicella, with each case having rash onset within 1 incubation period (21 days) of the previous case within the same school. Whenever possible, lesion or scab samples from outbreak-associated cases were collected and sent to Centers for Disease Control and Prevention for VZV testing using a polymerase chain reaction assay to detect the presence of wild-type VZV DNA; an inadequate specimen was defined as one in which neither VZV DNA nor β-Actin (the control) was detected.

For each case, an alphabetic list of classmates was provided by school nurses regardless of age and immunization status. The first 5 classmates on the list were contacted initially, and the remainders were contacted only if <3 eligible controls out of the first 5 classmates contacted were enrolled. The enrollment ended when 3 controls were enrolled or all eligible classmates were contacted. A control was only enrolled in the study once. School nurses and/or West Virginia Department of Health and Human Resources staff used a standard form to collect demographic, clinical and epidemiologic data from cases and controls after obtaining consent from parents/guardians. A study nurse trained school nurses on recognizing varicella, including mild breakthrough varicella, and categorizing rash severity. Case and control candidates with prior varicella history based on physician diagnosis or parental report were excluded from VE analyses. In addition, children who were receiving immunosuppressive therapy, had an acquired or congenital immune deficiency, had contraindication to varicella vaccine or had received varicella vaccine within 42 days of rash onset (for cases) or date of rash onset of the matched case (for controls) were not eligible for participation. School nurses categorized rash severity based on the number of skin lesions observed (<50, 50–249, 250–500 and >500) as mild (<50 lesions), moderate (50–500), severe (>500) or moderate/severe (≥50). Any hospitalization or serious complication such as secondary bacterial infection or neurologic complications would be recorded; sequelae such as scarring were not collected. Vaccination dates were verified using the West Virginia Statewide Immunization Information System, West Virginia Education Information System or participants' physician offices. Valid doses of varicella vaccine were defined as dose 1 administered not earlier than 4 days before age 12 months, and dose 2 administered at least 28 days after dose 1. The type of varicella vaccine received was not recorded, and only 2 varicella vaccines (Varivax and ProQuad) from Merck & Co., Inc. (Whitehouse Station, NJ) were available in the United States.

Statistical Analyses

The date of rash onset in the case was used to assess vaccination status of the matched controls. Varicella VE was defined as [1 − odds ratio] ×100%; odds ratios were calculated using conditional logistic regression. The unvaccinated subjects served as the reference group for 1-dose and 2-dose VE calculation. The 1-dose recipients were the reference group for calculating incremental VE, defined as the additional protection conferred by 2-dose vaccination compared with 1-dose vaccination. Changes in VE by time since vaccination were calculated using previously described methods.[15] Time since vaccination was defined as the time interval between the date of the most recently administered valid dose of varicella vaccine and the rash onset date. The trend of VE changes along time since vaccination was assessed with modification on the cited method[15] by assigning ordered values to the categories of time since vaccination by length of time since vaccination and the unvaccinated were the reference group. The distribution of categorical or continuous variables between cases and controls were examined with Mantel–Haenszel χ^2 or Student *t* test, respectively. All analyses were performed with SAS version 9.3 (SAS Inc., Cary, NC).

RESULTS

Study Population

From January 2010 through May 2011, 30 varicella outbreaks with a total of 266 cases were reported from 30 schools in 17 counties. Classmate contact information, used for identifying controls, was not available for 13 outbreaks (103 cases). The remaining 163 cases from 17 outbreaks were contacted for the case control study; they did not differ significantly from the non-participating cases by age (11.1 vs. 11.1 years, $P = 0.78$), sex (male: 52.1% vs. 56.3%, $P = 0.51$) or rash severity (mild rash: 41% vs. 40%, $P = 0.92$). The characteristics of the outbreaks from which the participating cases were identified did not differ significantly from those of the non-participating cases in average number of cases per outbreak (9.6 vs. 7.9, $P = 0.49$), or proportion of breakthrough cases in the outbreak (61.4% vs. 53.3%, $P = 0.22$).

Of the 163 cases, 133 (86.9%) were enrolled in the study. Of the 30 cases excluded, 10 cases had prior disease history, 8 cases lacked immunization records and the parents of 12 cases refused participation. Of 12 cases with specimens collected, 11 were confirmed as varicella, and 1 had an inadequate specimen. Over half the cases (70, 53.0%) had moderate rash, 7 (5.3%) had severe rash (none of them were 2-dose recipients) and 55 (41.7%) had mild rash. None of the cases developed complications or were hospitalized due to varicella. No vaccinated cases had rash onset within 42 days after receipt of varicella vaccine.

Among 816 students contacted for enrollment as controls, parents/guardians of 346 students (42.4%) did not respond, 105 were ineligible for participation due to prior varicella history (n = 83), missing vaccination status (n = 18), or receipt of varicella vaccine within 42 days of the first case of the outbreak (n = 4). The remaining 365 eligible students were enrolled as controls producing a total of 498 participants, with an average of 3 matched controls per case (range: 1–5 controls/case). The majority of participants were elementary school students (305, 61.2%), with half of the participants (246, 49.4%) being female with an average age of 11 years (range 5.3–18.7 years). There was no difference between cases and controls in age and sex ($P = 0.27$ and 0.58, respectively), but proportionally more cases were unvaccinated and more controls had received 2 doses of varicella vaccine ($P < 0.001$). Cases had longer time intervals since last vaccination than controls (7.5 vs. 5.7 years, $P < 0.001$), were younger at the time of 2-dose vaccination (6.2 vs. 8.2 years, $P = 0.007$) and proportionally more received the second dose of vaccine at <6 years of age (60.0% vs. 33.1%, $P = 0.03$). There were no differences between cases and controls in age at the time of receipt of the first dose of varicella vaccine or interval between 1-dose and 2-dose varicella vaccine ($P = 0.31$ and 0.09, respectively) (Table 1).

Varicella Vaccine Effectiveness

The effectiveness against all varicella was 83.2% [95% confidence interval (CI): 69.2%–90.8%] for 1-dose of varicella vaccine and 93.9% (95% CI: 86.9%–97.1%) for 2-dose; the incremental VE (2-dose vs. 1-dose) was 63.6% (95% CI: 32.6%–80.3%) (Table 2). In preventing moderate/severe varicella, 1-dose varicella vaccine was 88.2% (95% CI: 72.7%–94.9%) effective, and 2-dose vaccination was 97.5% (95% CI: 91.6%–99.2%) effective,

with an incremental VE of 78.6% (95% CI: 40.9%–92.3%). One-dose VE decreased by time since vaccination: VE was 93.0% within 5 years after vaccination, 88.0% from 5 to 9 years after vaccination, and 81.8% with ≥10 years after vaccination ($P = 0.001$ for trend) (Table 3). No change in 2-dose VE was observed along with time since vaccination (92.8%, 87.8% and 50.7% for those who received vaccine at ≤2 years, 3–5 years and >5 years before, $P = 0.73$ for trend) (Table 3). There was no difference in 1-dose VE by age at first dose (<15 months vs. ≥15 months, $P = 0.11$), and 2-dose VE by age at second dose (<6 years vs. ≥6 years, $P = 0.88$) or by length of time interval between 1-dose and 2-dose vaccination (≤5 years vs. >5 years, $P = 0.94$).

Rash Presentation

Among the 132 cases with available data, the rash severity decreased along with doses of vaccination received. The proportion of mild rash decreased from 70% in 2-dose cases, 49.1% in 1-dose cases, to 24.6% in unvaccinated cases, while the proportion of severe rash increased from 0% in 2-dose cases, 3.6% in 1-dose cases, to 8.8% in unvaccinated cases ($P < 0.001$) However, there was no overall difference in rash severity between 1-dose and 2-dose vaccinated cases ($P = 0.38$), even though no severe rash was observed in 2-dose cases in contrast to 3.6% in 1-dose cases (Table 4).

DISCUSSION

In varicella school outbreaks reported during 2010–2011, 2 doses of varicella vaccine conferred greater protection against all varicella and moderate/severe varicella than a single dose. Moreover, though 2-dose breakthrough varicella occurred, the majority of those cases were mild with no cases of severe rash observed among 2-dose vaccine recipients. These data, in addition to declines in varicella incidence and the reduced number and size of varicella outbreaks observed since the initiation of the 2-dose varicella vaccination regimen, provide evidence of the greater effectiveness of 2-dose varicella vaccination compared to the single dose regimen.[16-18]

This study adds to data on 2-dose varicella vaccine effectiveness. A pre-licensure, randomized clinical trial comparing 1-dose versus 2-dose varicella vaccine regimens using a historical varicella attack rate demonstrated a 2-dose VE of 98%.[19] Three subsequent case control studies of laboratory-confirmed cases reported similarly high 2-dose VE estimates of 98% in a study conducted in Connecticut during 2006–2010, 97% from a study conducted in Spain during 2010–2012, and 94% in a study conducted in Germany during 2008–2010.[20-22] Our 2-dose VE estimate of 94% is similar to these estimates. Use of laboratory-confirmed case definitions in vaccine effectiveness studies results in increases in case specificity and higher VE estimates.[23] The single published 2-dose varicella VE of <90% was reported from an investigation of a varicella outbreak in a school complex in Arkansas in which 2 doses of varicella vaccine did not appear to confer additional protection compared to 1-dose.[24] The reasons for the lower 2-dose VE reported from the Arkansas outbreak are unclear; however, it is likely that circulation of the virus has declined since that study was conducted and routine 2-dose varicella vaccination has been widely implemented.[11] The rapid take-up of 2-dose varicella vaccine in West Virginia, evidenced in the high vaccination

coverage in the controls of our study as well as high coverage in children in West Virginia kindergartens,[12] likely resulted in lower circulation of the virus and contributed to the observed higher VE. The incremental VE in the current study of 64% is similar to the 69.9% calculated from the clinical trial, within in the range of the reported 74% from case control study in Spain,[19,21] but lower than the 94.7% calculated from the case control study in Connecticut.[20] The higher incremental VE estimate from the Connecticut study may be explained in part by the lack of 2-dose cases available for the analysis.[20] To the best of our knowledge, this is the first since the clinical trial to report on 2-dose varicella VE against moderate/severe rash,[25] and the greater effectiveness of 2-dose vaccination in preventing moderate/severe varicella than against any varicella. The finding of greater effectiveness against moderate/severe varicella than against all varicella was also observed with the 1-dose varicella vaccination effectiveness.[26] In addition, the estimate of 1-dose VE of 83% in this study is consistent with the 1-dose varicella VE of 85% reported in the literature.[26] All these consistencies add to the credibility of the current findings.

In contrast to some studies,[27-29] our study and others[30-32] have found a trend of decreasing VE over time. These findings may reflect true waning of vaccine protection over time or may represent an increased risk of exposure (and force of infection) in older compared to younger age groups.[2,33] Between 1995 and 2010, the median age of varicella increased from 3–5 years to 7–9 years among vaccinated cases and from 5–6 years to >15 years among unvaccinated cases.[2,16] This changing epidemiology confounds analysis of vaccine effectiveness by time since vaccination. More data are needed to better understand the duration of protection in children after varicella vaccination, although this is increasingly challenging to investigate as disease circulation and risk of exposure has declined so substantially since vaccine introduction. Given the small number of cases and controls receiving 2-dose varicella vaccine >5 years before enrollment in our study, it was not possible to produce a reliable estimate on varicella 2-dose VE after 5 years since vaccination. The lack of differences in 2-dose VE by age at vaccination or length of time between receiving first and second doses reinforces the importance of catch-up vaccination at any age as an effective way to induce protection.

Similar to findings reported from clinical trials,[19,25] 2-dose recipients with breakthrough varicella appear to present with fewer lesions than in the 1-dose recipients, and none with severe rash was identified. The failure to detect statistically significant differences in rash severity between 1-dose and 2-dose breakthrough cases may be due to the rarity of severe breakthrough varicella and/or the small number of breakthrough cases enrolled. Given the limitations of current laboratory assays for confirming varicella, especially in mild breakthrough varicella in the 2-dose varicella vaccination era, ascertaining the full spectrum of breakthrough disease will be challenging. As a greater proportion of cases present with <50 lesions among breakthrough cases,[25] it may be informative to collect more precise data on the numbers of lesions from cases with mild disease. Understanding the extent to which very mild breakthrough varicella cases are contagious[34] and present a risk to susceptible individuals is important for ensuring that implementation of varicella control efforts is effective as well as the need to exclude such cases from work and school.

Several limitations should be considered in interpreting the current findings. This study relied on a clinical case definition that did not require laboratory confirmation and may underestimate VE. The mild clinical manifestations in 1-dose and 2-dose breakthrough cases make misclassification possible and may lead to overreporting or underreporting of varicella. It can be challenging to confirm varicella by laboratory testing due to difficulties in collecting adequate specimens from maculopapular rashes.[35] The categorization of rash severity used in this study was based on reports from a large number of school nurses, and there may have been variation in accuracy of their observations

In conclusion, both 1-dose and 2-dose varicella vaccine regimens are highly effective in preventing varicella, but 2-dose vaccination induces higher protection than the 1-dose regimen. The clinical manifestations of breakthrough varicella among 2-dose vaccinees may be milder than among 1-dose vaccinees, but more data are needed to better understand this as well as whether VE wanes over time. Full implementation of the routine 2-dose varicella vaccination program should result in further reductions in varicella incidence and outbreaks.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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TABLE 1

Demographic and Vaccination Characteristics Among Cases and Controls in Public School Students of West Virginia, 2010–2011

	Cases (N = 133), n (%)	Controls (N = 365), n (%)	*P* Value
Age in years: mean (range)	10.8 (5.3–18.0)	10.5 (5.4–18.7)	0.27
Years since last dose of varicella vaccine: mean (range)	7.5 (0.7–14.4)	5.7 (0.1–14.7)	<0.001
Age in months at receipt of first dose varicella vaccine: mean (range)	24.0 (12.2–139.5)	29.1 (12.0–165.1)	0.12
Age in years at receipt of second dose of varicella vaccine: mean (range)	6.2 (2.6–13.4)	8.2 (1.5–15.3)	0.007
Years between first and second dose: mean (range)	4.9 (1.6–12.1)	6.1 (0.2–13.4)	0.09
Sex			0.58
Male	70 (52.6)	182 (49.9)	
Female	63 (47.4)	183 (50.1)	
Vaccination status			<0.001
Unvaccinated	57 (42.9)	36 (9.9)	
1-dose	56 (42.1)	181 (49.6)	
2-dose	20 (15.0)	148 (40.6)	
Received first dose of varicella vaccine at <15 months of age	42 (55.3)	158 (48.0)	0.31
Received second dose of varicella vaccine at age <6 years	12 (60.0)	49 (33.1)	0.03

TABLE 2

Varicella Vaccine Effectiveness Against All Varicella and Moderate/Severe Varicella in Public School Students of West Virginia, 2010–2011

	Cases, n (%)	Controls, n (%)	VE (95% CI)	*P* Value
All varicella cases and matched controls	N = 133	N = 365		
Unvaccinated	57 (42.9)	36 (9.9)	Reference	
1-dose	56 (42.1)	181 (49.6)	83.2 (69.2–90.8)	<0.001
2-dose	20 (15.0)	148 (40.6)	93.9 (86.9–97.1)	<0.001
Incremental (1-dose recipients as reference)			63.6 (32.6–80.3)	0.001
Moderate/severe cases and matched controls	N = 77	N = 216		
Unvaccinated	43 (55.8)	24 (11.1)	Reference	
1-dose	28 (36.4)	107 (49.5)	88.2 (72.7–94.9)	<0.001
2-dose	6 (7.8)	85 (39.4)	97.5 (91.6–99.2)	<0.001
Incremental (1-dose recipients as reference)			78.6 (40.9–92.3)	0.003

VE indicates vaccine effectiveness; 95% CI, 95% confidence interval.

TABLE 3

One-Dose and Two-Dose Varicella Vaccine Effectiveness Against All Varicella by Time Since Vaccination in Public School Students of West Virginia, 2010–2011

	Cases, n (%)	Controls, n (%)	VE (95% CI)	*P* Value	*P* Value
Unvaccinated	57 (50.4)	36 (16.6)	Reference		
Years since receipt of first dose of varicella vaccine	N = 56	N = 181			
<5 years	4 (3.5)	31 (14.3)	93.0 (75.0–98.1)	<0.001	Reference
5–9 years	31 (27.4)	93 (42.9)	88.0 (72.4–94.8)	<0.001	0.36
≥10 years	21 (18.6)	57 (26.3)	81.8 (57.8–92.1)	<0.001	0.15
Years since receipt of second dose of varicella vaccine	N = 20	N = 148			
<3 years	7 (9.7)	65 (90.3)	92.8 (72.4–98.1)	<0.001	Reference
3–5 years	11 (12.5)	77 (87.5)	87.8 (65.1–95.8)	<0.001	0.240
>5 years	2 (25.0)	6 (75.0)	50.7 (0–97.5)	0.64	<0.001

VE indicates vaccine effectiveness; 95% CI, 95% confidence interval.

TABLE 4

Association of Rash Severity With Vaccination Status in Varicella Cases Identified in Public School Outbreaks of West Virginia, 2010–2011[a]

	Vaccination Status				
	Unvaccinated, n (%)	**1-Dose, n (%)**	**2-Dose, n (%)**	**Overall *P* Value**	***P* Value (1-Dose vs. 2-Dose Cases)**
Number of lesions	N = 57	N = 55	N = 20	<0.001	0.38
<50	14 (24.6)	27 (49.1)	14 (70.0)		
50–249	19 (33.3)	23 (41.8)	5 (25.0)		
250–500	19 (33.3)	3 (5.5)	1 (5.0)		
>500	5 (8.8)	2 (3.6)	0 (0.0)		

[a]One case had missing information on rash severity.