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Varicella Vaccine Effectiveness in Preventing Community Transmission in the 2-Dose Era

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abstract

OBJECTIVES: We examined overall and incremental effectiveness of 2-dose varicella vaccination in preventing community transmission of varicella among children aged 4 to 18 years in 2 active surveillance sites. One-dose varicella vaccine effectiveness (VE) was examined in those aged 1 to 18 years.

METHODS: From May 2009 through June 2011, varicella cases identified during active surveillance in Antelope Valley, CA and Philadelphia, PA were enrolled into a matched case-control study. Matched controls within 2 years of the patient's age were selected from immunization registries. A standardized questionnaire was administered to participants' parents, and varicella vaccination history was obtained from health care provider, immunization registry, or parent records. We used conditional logistic regression to estimate varicella VE against clinically diagnosed and laboratory-confirmed varicella.

RESULTS: A total of 125 clinically diagnosed varicella cases and 408 matched controls were enrolled. Twenty-nine cases were laboratory confirmed. One-dose VE (1-dose versus unvaccinated) was 75.6% (95% confidence interval [CI], 38.7%–90.3%) in preventing any clinically diagnosed varicella and 78.1% (95% CI, 12.7%–94.5%) against moderate or severe, clinically diagnosed disease (≥ 50 lesions). Among subjects aged ≥ 4 years, 2-dose VE (2-dose versus unvaccinated) was 93.6% (95% CI, 75.6%–98.3%) against any varicella and 97.9% (95% CI, 83.0%–99.7%) against moderate or severe varicella. Incremental effectiveness (2-dose versus 1-dose) was 87.5% against clinically diagnosed varicella and 97.3% against laboratory-confirmed varicella.

CONCLUSIONS: Two-dose varicella vaccination offered better protection against varicella from community transmission among school-aged children compared with 1-dose vaccination.

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Ms Perella, Dr Wang, Dr Viner, Dr Daskalaki, Dr Schmid, Ms Lopez, Dr Newbern, and Dr Bialek conceived and designed the initial study protocol for implementation in Philadelphia, PA. Dr Civen, Ms Kuguru, Dr Tseng, and Dr Mascola adapted and revised the protocol for implementation in Antelope Valley, CA. Ms Perella, Dr Viner, and Dr Daskalaki coordinated and supervised data acquisition in Philadelphia, and Dr Civen, Ms Kuguru, and Dr Tseng were responsible for these activities in Antelope Valley. Dr Wang, Ms Perella, Dr Viner, and Ms Kuguru analyzed the study data, and all authors contributed to the interpretation of study analyses for the manuscript. Ms Perella, Dr Wang, and Dr Bialek drafted the manuscript. All authors critically revised the manuscript's content and approved the final manuscript as submitted.

WHAT'S KNOWN ON THIS SUBJECT: Declines in varicella incidence since 2006 and vaccine effectiveness estimates from outbreak investigations indicate that 2-dose varicella vaccination provides improved protection against varicella. Limited data exist on the performance of 2-dose varicella vaccination in preventing community transmission outside outbreak settings.

WHAT THIS STUDY ADDS: Two-dose varicella vaccination improved protection against community transmission of varicella among school-aged children in 2 geographically and demographically diverse areas compared with 1-dose vaccination. Our study provides more direct evidence on the protective effect of a 2-dose varicella vaccine regimen.

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Between 1995 and 2005, the 1-dose varicella vaccination program in the United States greatly reduced varicella incidence, hospitalizations, and deaths.¹⁻⁴ However, between 2001 and 2006, varicella outbreaks in school settings with high 1-dose vaccination coverage (>80% among students without varicella history) continued to be reported.⁵⁻¹¹ Clinical trial data had demonstrated that the immune response produced 6 weeks after 2-dose varicella vaccination was 12 times higher than levels after 1-dose vaccination, which translated into a threefold reduction in breakthrough varicella over a 10-year period.¹² Therefore, in 2006 the Advisory Committee on Immunization Practices recommended implementation of a routine 2-dose varicella vaccination program for children aged 4 to 6 years.¹³

Declines in varicella incidence reported since 2006 along with varicella vaccine effectiveness (VE) estimates from a case-control study conducted as part of active surveillance of outbreaks in West Virginia indicate that the 2-dose regimen provides improved protection against varicella.¹⁴⁻¹⁸ However, limited field data exist on the performance of a 2-dose varicella vaccination program in preventing community transmission other than in outbreak settings that may underestimate the true vaccine effectiveness.^{18,19} A community-based case-control study in Connecticut found 2-dose varicella VE was 98.3%, but no 2-dose cases were identified in the study.²⁰ As this study demonstrates, obtaining precise 2-dose varicella VE estimates is challenging because of the lower varicella incidence in the 2-dose era, particularly among recipients of both doses.

To evaluate the 2-dose varicella VE, we conducted a matched case-control study to examine the overall and incremental VE of the 2-dose varicella vaccination regimen in preventing varicella

among school-aged children (4-18 years) in 2 geographically and demographically diverse areas under active surveillance for varicella. Secondary study objectives were to estimate 1-dose VE among children aged 1 to 18 years during the 2-dose era and determine risk factors associated with breakthrough varicella among 2-dose recipients.

METHODS

Study Population and Setting

From May 2009 through June 2011, investigators from Antelope Valley (AV) and West Philadelphia Varicella Active Surveillance Project (VASP) conducted this matched case-control study in collaboration with the Centers for Disease Control and Prevention (CDC). Institutional review boards at all 3 participating institutions approved the study protocol. The target populations for case and control subject recruitment were residents aged 1 to 18 years from AV and Philadelphia. AV spans ~2200 square miles of northern Los Angeles County and has a population of >370 000 residents.²¹ Philadelphia is a large and densely populated metropolis with 1.5 million residents.²² During the study, the majority of AV residents <20 years of age were either Hispanic (51%) or non-Hispanic white (30%).²¹ Among those of same age in Philadelphia, 48% were non-Hispanic black, 28% were non-Hispanic white, and only 16% were Hispanic.²²

Case Recruitment

In AV and Philadelphia, varicella cases were identified prospectively through population-based active surveillance methods. More than 300 participating community-based sites (eg, schools, health care provider offices) in each surveillance area reported suspected varicella cases or informed project staff that no cases occurred at their facility biweekly.^{15, 23} During the 2010 to 2011 academic

year, active surveillance was expanded from West Philadelphia to include an additional 232 schools that were located in other areas of Philadelphia. Eligible case subjects in Philadelphia were also identified through citywide passive surveillance. All case reports were investigated with the standardized VASP questionnaire.^{15,23}

After investigation, a case subject was defined as a person residing in AV or Philadelphia with no previous history of varicella and acute onset of a diffuse maculopapulovesicular rash or, for previously vaccinated people, modified maculopapular rash with few or no vesicles that a medical provider definitively diagnosed as varicella without any other apparent cause.^{15,24} In May 2009 through July 2010, enrollment was limited to children aged 5 to 14 years with laboratory confirmation of varicella-zoster virus (VZV) by polymerase chain reaction (PCR) testing. During August 2010 through June 2011, enrollment was expanded to include people 1 to 18 years of age with laboratory or clinical diagnosis of varicella by a health care provider. Laboratory confirmation was expanded to include positive VZV-specific PCR, direct fluorescent antibody assay, or culture results.

Control Selection

Control subjects were selected from the Kaiser Permanente Southern California membership database and the Philadelphia Department of Public Health's Kids Immunization Database/Tracking System registry in AV and Philadelphia, respectively. Kaiser Permanente Southern California, an integrated health care system, provides comprehensive health services to 30% of AV residents aged 1 to 19 years; vaccine administration data for its members are stored in the Kaiser Immunization Tracking System and include information on vaccine doses administered by

providers inside and outside the Kaiser network or verified through school or provider records for vaccinations given before enrollment. Kaiser Permanente also was an active surveillance reporting site in AV. The Philadelphia Department of Public Health immunization registry has used health department birth records and vaccine administration reporting from health care providers to establish and maintain immunization records for all children aged ≤ 6 years in Philadelphia since 1995. The registry expanded to include children aged ≤ 18 years in 2007.

For each varicella case identified that met study inclusion criteria, we selected potential controls using incidence density sampling by extracting age-matched (± 2 years) records for all children from the pool of eligible controls aged 1 to 18 years who did not have a previous varicella history documented in historic surveillance data or immunization registry.²⁵ A 2-year age range for controls was chosen, because the routine 2-dose varicella vaccination recommendation spans ages 4 to 6 years.¹³ Moreover, because routine 1-dose coverage reached higher levels ($>80\%$), protection from 1-dose varicella vaccination appears to remain consistent during the first few years after vaccination.¹³ Between 5 and 60 potential control subjects were randomly selected from the corresponding control pool for each incident case. To be able to analyze VE among the age groups for which the first and second doses of varicella vaccine are recommended, controls selected for cases aged 1 to 3 years had to be <4 years of age, and controls selected for cases ≥ 4 years of age had to be ≥ 4 years of age. Study staff sent an invitation letter and contacted parents or guardians of eligible control subjects via telephone. The first 3 eligible respondents who consented to participate were the controls for each incident case. Recruited controls

were eligible to be controls for subsequent incident cases, and if she or he developed varicella at a later time point, the subject was eligible for the study as a case subject.

Data Collection

Study staff obtained verbal consent and collected data from a parent or guardian of each subject by telephone by using a standard questionnaire. Given limited study resources, we did not recruit cases and controls with non-English-speaking parents or guardians who could not provide consent because of the language barrier. The questionnaires captured information on demographics, varicella vaccination history, recent VZV exposures, underlying medical conditions, and use of immunosuppressing medications. The case questionnaire, which has been described previously, included additional disease-specific questions and standardized prompts to obtain the number of lesions.²³ VASP staff scheduled home visits to collect lesion specimens from eligible cases reported before their rashes had resolved. The CDC National VZV Laboratory performed PCR testing^{26, 27} on lesion specimens collected from suspected varicella cases. For a few cases, VZV-specific testing was conducted by hospital or commercial reference laboratories. Participating families received a \$10–\$20 gift card after completion of study-related activities, and AV health care providers were offered a \$20 gift card for every case reported with lesion specimens collected.

For case and control subjects, varicella vaccination administration dates were collected from the registries used for control selection, parental records, and the subject's health care provider. Study staff made efforts to validate vaccination information for all subjects with the immunization registry or health care provider records. If a discrepancy existed between these 2 sources,

the source with the most complete information (ie, highest number of doses) was used. We considered 1-dose varicella vaccination to be valid when given 4 days before a child's first birthday or later. Second-dose varicella vaccination was considered valid when administered ≥ 4 weeks after the first dose. The last dose also needed to be given >42 days before rash onset for cases (breakthrough varicella) or the matched incident case's onset for controls. Those given doses within 42 days were excluded.

Data Analysis

For our main analysis, we combined data from both sites, because varicella vaccine coverage and risk for breakthrough varicella have not differed between sociodemographic subgroups,^{13,28} and the directions of estimates from each site were similar. We used 2 case definitions for varicella: clinically diagnosed and laboratory confirmed. Varicella severity was categorized based on the number of lesions reported as mild (<50 lesions), moderate (50–500 lesions), or severe (>500 lesions). The following VE estimates were calculated to examine protection against any varicella or moderate or severe disease alone (≥ 50 lesions): incremental 2-dose VE (2 doses versus 1 dose), overall 2-dose VE (2 doses versus unvaccinated), and overall 1-dose VE (1 dose versus unvaccinated). All VE estimates were calculated with Greenwood and Yule's formula: $VE = 1 - \text{relative risk (RR)}$.¹⁹ In our study, RR refers to the risk of developing varicella among the subgroup with the higher number of varicella vaccine doses compared with the subgroup with fewer or no doses and was estimated with an odds ratio (OR) from conditional logistic regression to account for the matching variable (age). We were able to adjust for other potential confounders when examining VE against clinically diagnosed disease

TABLE 1 Demographic and Vaccination Characteristics of Clinically Diagnosed Varicella Case and Control Subjects From Philadelphia, Pennsylvania and Antelope Valley, California, 2009–2011^a

	Aged 1–3 y			Aged ≥4 y		
	Cases (n = 32), n (%)	Controls (n = 103), n (%)	P	Cases (n = 93), n (%)	Controls (n = 305), n (%)	P
Median age	2.1 (1.0–3.9)	2.2 (1.1–3.9)	.53	9.5 (4.0–18.9)	9.3 (4.1–18.9)	.58
Surveillance site			.68			.48
Antelope Valley, CA	9 (28.1)	33 (32.0)		56 (60.2)	171 (56.1)	
Philadelphia, PA	23 (71.9)	70 (68.0)		37 (39.8)	134 (43.9)	
Vaccination status			<.001			<.001
Unvaccinated	9 (28.1)	4 (3.9)		8 (8.6)	8 (2.6)	
1-dose	22 (68.8)	98 (95.1)		40 (43.0)	50 (16.4)	
2-dose	1 (3.1)	1 (1.0)		45 (48.4)	247 (81.0)	
Race			.09			.43
White	12 (37.5)	46 (44.7)		59 (63.4)	171 (56.1)	
African American	9 (28.1)	40 (38.8)		25 (26.9)	95 (31.1)	
Other	11 (34.4)	17 (16.5)		9 (9.7)	39 (12.8)	
Ethnicity			.18			.20
Hispanic	14 (45.2)	33 (32.0)		40 (43.0)	109 (35.7)	
Non-Hispanic	17 (54.8)	70 (68.0)		53 (57.0)	196 (64.3)	
Gender			.41			.87
Male	16 (50.0)	60 (58.3)		47 (50.5)	157 (51.5)	
Female	16 (50.0)	43 (41.7)		46 (49.5)	148 (48.5)	
Born in United States			>.999			>.999
Yes	31 (100.0)	103 (100.0)		91 (97.8)	296 (97.0)	
No	0 (0.0)	0 (0.0)		2 (2.2)	9 (3.0)	
Immunosuppressing condition			>.999			>.999
Yes	0 (0.0)	0 (0.0)		0 (0.0)	2 (0.7)	
No	32 (100.0)	103 (100.0)		92 (100.0)	303 (99.3)	
Asthma			.99			.26
Yes	6 (18.8)	19 (18.6)		19 (20.4)	47 (15.5)	
No	26 (81.3)	83 (81.4)		74 (79.6)	257 (84.5)	
Attend day care			.62			.03
Yes	13 (40.6)	47 (45.6)		6 (4.5)	47 (15.4)	
No	19 (59.4)	56 (54.4)		87 (93.5)	258 (84.6)	

^a Missing and unknown responses excluded. Valid percentages presented.

using the combined site data. Changes in VE by time since vaccination (rash onset date minus the date of most recent varicella vaccination) were calculated via previously described methods.²⁵ The distribution of categorical or continuous variables between cases and controls was examined with Mantel–Haenszel χ^2 test, Fisher’s exact test, Mann–Whitney *U* test, or Kruskal–Wallis test where appropriate. All analyses were conducted in SAS 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Case and Control Subject Characteristics

A total of 125 clinically diagnosed varicella cases and 408 matched

controls were enrolled. Of the 44 (35.2%) cases that had lesion specimens tested for VZV, 29 were laboratory-confirmed cases (all PCR positive), 11 were PCR negative (median lesion collection day: 5 [range: 2–21]), 2 had inadequate specimens, and 2 were culture negative. The median age of clinically diagnosed cases was 2.1 years among those aged <4 years and 9.5 years among those aged ≥4 years (Table 1). For each case, 2 to 7 matched controls (median = 3) were recruited after we approached a median of 5 (range: 5–15) and 29 (range: 5–60) eligible people in AV and Philadelphia, respectively. The distribution of demographic characteristics did not differ significantly between clinically diagnosed case and control subjects,

except day care attendance among those aged ≥4 years (*P* = .03). Most controls aged ≥4 years from AV and Philadelphia had received ≥1 dose of varicella vaccine (98.8% vs 95.5%, *P* = .05), and the majority in each site had received 2 doses (78.5% vs 83.6%, *P* = .31). Although the proportion of vaccinated cases aged ≥4 years from each site was similar (91% to 92%), the proportion of cases aged ≥4 years who were 2-dose recipients was slightly lower in AV than Philadelphia (41.1% vs 59.5%, *P* = .08).

Among clinically diagnosed cases ≥4 years of age, rash severity and characteristics differed significantly by vaccination status, with the majority of breakthrough cases reporting mild and mostly

TABLE 2 Varicella Disease Severity by Vaccination Status for Clinically Diagnosed Varicella Case-Subjects Aged ≥ 4 y in Philadelphia, Pennsylvania and Antelope Valley, California, 2009–2011^a

	Varicella Vaccination Status			Overall <i>P</i>	2- vs 1-Dose <i>P</i>
	Unvaccinated (<i>n</i> = 8), <i>n</i> (%)	1-Dose (<i>n</i> = 40), <i>n</i> (%)	2-Dose (<i>n</i> = 45), <i>n</i> (%)		
Rash severity ^b				.01	.81
Mild (<50 lesions)	1 (12.5)	26 (65.0)	31 (68.9)		
Moderate or severe (50–500 lesions)	6 (75.0)	13 (32.5)	14 (31.1)		
Severe (>500 lesions)	1 (12.5)	1 (2.5)	0 (0.0)		
Fever				.36	.11
Yes	2 (25.0)	16 (41.0)	11 (24.4)		
No	6 (75.0)	23 (59.0)	34 (75.6)		
Most lesions are vesicular				<.001	.01
Yes	3 (60.0)	9 (23.1)	2 (4.5)		
No	2 (40.0)	30 (76.9)	42 (95.5)		
Days of fever: median (IQR)	2 (0–3)	1.5 (1–2.5)	2 (1–2)	.86	.57
Rash duration				.01	.01
<1 wk (<7 d)	2 (25.0)	10 (25.6)	24 (53.3)		
≥ 1 wk (≥ 7 d)	6 (75.0)	29 (74.4)	21 (46.7)		
School missed				.17	.89
≤ 1 school wk (≤ 5 d)	2 (33.3)	3 (8.6)	3 (7.7)		
>1 school wk (>5 d)	4 (66.7)	32 (81.4)	36 (82.3)		

IQR, interquartile range.

^a Missing and unknown responses excluded. Valid percentages presented.

^b Rash severity was defined as follows: <50 or the total number of spots could be counted in 30 s; 50–249 or you could place the child's hand between the spots without touching a spot; 250–500 or you could *not* place a child's hand between the spots without touching a spot; or >500 spots or the spots were so close you could hardly see normal skin.

maculopapular rashes, whereas most unvaccinated cases had 50–500 lesions that were mostly vesicular (Table 2). There was no severe varicella among 2-dose cases. Only 2 cases had >500 lesions; both were otherwise healthy adolescents, of whom, 1 was a 1-dose recipient and the other unvaccinated. None of the cases were hospitalized due to varicella or developed complications of varicella. Among breakthrough cases aged ≥ 4 years, 2-dose cases were more likely to have rashes that resolved in <1 week ($P = .01$) and were less likely to have vesicular rashes ($P = .01$) than 1-dose cases. Presence and duration of fever did not differ significantly between breakthrough and unvaccinated cases.

Varicella Vaccine Effectiveness

Among all unvaccinated and 1-dose participants, the effectiveness of 1-dose of varicella vaccine compared with no vaccine was 75.6% (95% confidence interval [CI], 38.7%–90.3%) against all clinically diagnosed varicella and

78.1% (95% CI, 12.7%–94.5%) against moderate or severe disease (Table 3). The effectiveness of 2 doses of varicella vaccine compared with no vaccine among subjects aged ≥ 4 years was 93.6% (95% CI, 75.6%–98.3%) against all clinically diagnosed varicella and 97.9% (95% CI, 83.0%–99.7%) against moderate or severe varicella. The incremental effectiveness of 2-dose varicella vaccination compared with 1-dose among participants ≥ 4 years of age was 87.5% (95% CI, 74.9%–93.7%) in preventing any clinically diagnosed varicella and 94.1% (95% CI, 72.4%–98.8%) in preventing moderate or severe clinically diagnosed disease.

VE estimates were higher but not significantly in AV than Philadelphia. Among subjects aged ≥ 4 years from AV, 2-dose VE and incremental VE against any clinically diagnosed varicella were 98.4% and 92.4%, respectively. In Philadelphia, 2-dose VE and incremental VE among subjects ≥ 4 years old were 92.7% and 79.8%, respectively. Two-dose VE estimates did not differ significantly between sites ($P =$

0.20); however, the small number of unvaccinated cases (≤ 5) and controls (≤ 6) may have led to unstable VE estimates by site.

Among the 26 laboratory-confirmed cases aged ≥ 4 years and their matched controls, 2-dose varicella VE was 95.9% (95% CI, 23.2%–99.8%), and incremental VE was 97.3% (95% CI, 88.9%–100%). Because data were sparse, we could not assess effectiveness of 1-dose of varicella vaccine against laboratory-confirmed varicella.

Risk Factors for Breakthrough Varicella Among 2-Dose Varicella Vaccine Recipients

Among 2-dose varicella vaccine recipients, there was no association between time since receiving dose 2 and breakthrough varicella ($P = .17$; Table 4). However, those who received the second dose after 6 years of age were 60% less likely to have breakthrough varicella than those who had received the second dose at an earlier age ($P = .009$). A longer time interval

TABLE 3 Varicella VE Against All Varicella and Moderate or Severe Varicella in Philadelphia, Pennsylvania and Antelope Valley, California, 2009–2011

	Unvaccinated and 1-Dose Participants Regardless of Age			Participants ≥ 4 y Old ^a		
	Cases <i>n</i> = 79	Controls <i>n</i> = 160	VE (95% CI)	Cases <i>n</i> = 93	Controls <i>n</i> = 305	VE (95% CI)
VE against any clinically diagnosed varicella						
Unvaccinated	17 (21.5)	12 (7.5)	Reference	8 (8.6)	8 (2.6)	Reference
1-dose	62 (78.5)	148 (92.5)	75.6 (38.7–90.3)	40 (43.0)	50 (16.4)	49.1 (0–85.7)
2-dose	—	—	—	45 (48.4)	247 (81.0)	93.6 (75.6–98.3)
Incremental VE (2-dose vs 1-dose)	—	—	—	—	—	87.5 (74.9–93.7)
VE against moderate or severe clinically diagnosed varicella (≥ 50 lesions)	<i>n</i> = 28	<i>n</i> = 49	—	<i>n</i> = 35	<i>n</i> = 119	—
Unvaccinated	10 (35.7)	6 (12.2)	Reference	7 (20.0)	5 (4.2)	Reference
1-dose	18 (64.3)	43 (87.8)	78.1 (12.7–94.5)	14 (40.0)	20 (16.8)	64.2 (0–93.1)
2-dose	—	—	—	14 (40.0)	94 (79.0)	97.9 (83.0–99.7)
Incremental VE (2-dose vs 1-dose)	—	—	—	—	—	94.1 (72.4–98.8)

—, no value for category available.

^a Adjusted for ethnicity given significant differences between cases and controls aged ≥ 4 y in Philadelphia. Although day care attendance differed between cases and controls aged ≥ 4 y, only a small proportion of each group attended day care (<16%), and adding this variable to the model produced VE estimates similar to those presented.

TABLE 4 Risk Factors Associated With Breakthrough Varicella Among 2-Dose Varicella Vaccinees Aged ≥ 4 y

	Cases, <i>n</i> (%) (<i>n</i> = 45)	Controls, <i>n</i> (%) (<i>n</i> = 247)	OR (95% CI)	<i>P</i>
Time since 2-dose varicella vaccination				
<1 y	6 (13.3)	46 (18.6)	Reference	
1–3 y	19 (42.2)	118 (47.8)	1.2 (0.5–3.3)	.67
>3 y	20 (44.4)	83 (33.6)	1.8 (0.7–4.9)	.22
Age at receiving 2-dose varicella vaccine				
≤ 6 y	33 (73.3)	128 (51.8)	Reference	
>6 y	12 (26.7)	119 (48.2)	0.4 (0.2–0.8)	.009
Time interval between receiving 1- and 2-dose varicella vaccine				
≤ 5 y	34 (75.6)	144 (58.3)	Reference	
>5 y	11 (24.4)	103 (41.7)	0.5 (0.2–0.9)	.03

between receiving 1- and 2-dose varicella vaccine (>5 vs ≤ 5 years) was associated with lower odds of developing breakthrough varicella (OR = 0.5, *P* = .03; Table 4). Subjects receiving dose 2 after 6 years of age were older than those receiving the second dose varicella vaccine earlier (12.7 vs 7.0 years, *P* < .001), as were subjects with a time interval between 1- and 2-dose varicella vaccine >5 years compared with those having a shorter interval between doses (13.0 vs 7.4 years, *P* < .001).

DISCUSSION

During the first 5 years after implementation of 2-dose varicella

vaccination program, we found that 2 doses conferred significantly better protection against varicella disease from community transmission among school-aged children compared with the 1-dose regimen. By 2010, AV and West Philadelphia reported >60% 2-dose varicella vaccination coverage among 5-year old children and 67% to 78% reductions in overall varicella incidence since 2006.¹⁵ Our study provides more direct evidence of the protective effect of a 2-dose regimen of varicella vaccine for children. Incremental effectiveness of the 2-dose varicella vaccination regimen among all subjects aged ≥ 4 years was 88% to 97% against all forms of disease and also highly protective against moderate and severe varicella (94%). The reduction

in community circulation of VZV as a result of high 2-dose coverage will also protect children who are immunocompromised and not eligible for varicella vaccination. Additional benefits of routine childhood varicella vaccination may include reduced risk of herpes zoster among vaccinated children.²⁹

In 2006, concerns about the effectiveness of the 2-dose regimen were raised after a varicella outbreak in an Arkansas elementary school with 97% 1-dose varicella vaccination coverage and 41% 2-dose coverage.³⁰ Consistent with our findings, incremental effectiveness estimates from all but 1 subsequent outbreak investigation and epidemiologic studies in the United States have been much higher (>90% vs 28% from the Arkansas outbreak).^{18,20,31,32} Incremental effectiveness estimates from school varicella outbreak surveillance in Indiana and West Virginia during 2009 to 2010 were 86% and 64%, respectively.^{18,32} Among ~2800 patients who were recruited into a prospective cohort study in 1995 at 2 years of age and received a second dose through catch-up vaccination, no cases of breakthrough varicella were observed through 2009.³¹

Similarly, no 2-dose breakthrough varicella cases were identified in a community-based case-control study conducted by Shapiro et al²⁰ between 2006 and 2010.

Given the excellent protection provided by the 2-dose regimen in preventing moderate and severe disease, it is not surprising that the majority of 2-dose breakthrough cases (69%) had mild rashes with <50 lesions, and none had severe varicella. These findings were consistent with 2-dose era active surveillance data and other epidemiologic studies.^{15,18,20,31} No cases in our study were hospitalized or fatal. Likewise, additional declines in varicella-related hospitalizations since implementation of the 2-dose varicella vaccination era have also been documented in the literature.^{15,33} Although there was no difference in rash severity observed between 1- and 2-breakthrough cases, average illness duration for 2-dose breakthrough cases was slightly shorter than for 1-dose cases, and fewer 2-dose cases developed mostly vesicular rashes. The shorter duration of mild breakthrough illness among 2-dose recipients may add to the cost savings from use of this regimen, and infectiousness may be lowered, given the lower proportion of vesicular rashes among 2-dose breakthrough cases.

In our study and as reported by others,^{1,18,34} breakthrough varicella generally has a modified appearance with few or no vesicular lesions, making it challenging to diagnose clinically. PCR testing of lesion specimens to detect VZV is highly sensitive and specific.³⁵ However, as demonstrated during the investigation of a suspected varicella outbreak in a Texas school district in 2011, the utility of VZV-specific PCR testing can be limited when only macular lesions are present or lesion specimens are not collected early in the course of illness. In the absence of better laboratory tools,

clinical and epidemiologic data will remain necessary to support the confirmation of varicella disease.³⁶ In the Texas outbreak, the incremental effectiveness of 2-dose varicella vaccination against any form of clinically diagnosed varicella varied widely across the 2 involved schools (21% and 72%).³⁶ We therefore chose to examine 2-dose varicella VE by using 2 different case definitions for breakthrough varicella: one based on clinical and epidemiologic criteria and the other using laboratory confirmation alone. Both definitions produced similar estimates for 1-dose and 2-dose varicella VE when unvaccinated people were used as the comparison group. Although incremental effectiveness against laboratory-confirmed disease was slightly higher compared with the incremental effectiveness against clinically diagnosed disease (97% vs 88%), both estimates demonstrate that the 2-dose varicella vaccine regimen is highly effective in preventing varicella due to sporadic VZV circulation in the community.

Data on risk factors for 2-dose breakthrough varicella are limited. Similar to Thomas et al,¹⁸ we did not find a significant association between time since 2-dose vaccination and the development of breakthrough varicella; however, in both studies findings may have been affected by the low number of varicella cases among 2-dose recipients. We were surprised that those who were older at time of 2-dose varicella vaccination or had >5 years between dose 1 and dose 2 had lower likelihood of breakthrough varicella. These findings may reflect a lower risk of VZV exposure or shorter exposure durations among older subjects in middle school and high school, because they are less likely to spend several hours with the same class of students throughout the school day.

Our findings are subject to the following limitations. Given high

1-dose varicella vaccine coverage among children ≥ 4 years of age,¹⁵ very few unvaccinated subjects were identified, which resulted in wide confidence intervals for our estimates of varicella VE. Similarly, the small number of laboratory-confirmed 2-dose breakthrough varicella cases limited our ability to identify risk factors for or describe the characteristics of breakthrough disease in 2-dose vaccinees. Lastly, although we used the best available sources of case and control subjects for our study, ascertainment of mild varicella cases was probably incomplete. The data source used to identify controls in the Antelope Valley area represented only 30% of the source population, and the response rate among potential controls selected from the immunization registry was low in Philadelphia because of incomplete or outdated contact information. Despite these potential limitations, the distributions of demographic characteristics (ie, gender, race, and ethnicity) among control subjects were similar to population estimates for residents <18 years of age in each site. In AV, 2-dose varicella vaccination coverage was moderately high (84%) among kindergarten students during the 2009 to 2010 school year and 98% to 99% among Kaiser members aged 5 to 6 years in 2010.¹⁵ The use of Kaiser members only as controls probably did not affect 2-dose varicella VE but may have resulted in slightly higher incremental effectiveness estimates.

With superior protection provided by the 2-dose varicella vaccination compared with the 1-dose regimen as demonstrated in our study and others, it will be important to expand school immunization requirements to include 2-dose varicella vaccination. By 2012, 36 states had a 2-dose varicella vaccination elementary school entry requirement, and 2-dose varicella vaccine coverage among

7-year-olds in 6 sentinel sites had reached moderate to high levels (79.9%–92.0%).³⁷ Catch-up varicella vaccination will be particularly important for 1-dose vaccinees at increased risk for exposure to people with varicella or herpes zoster (ie, international travelers, health care workers). Continued monitoring of 2-dose varicella VE is also warranted, to ensure that protection is sustained over time.

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ABBREVIATIONS

AV: Antelope Valley
CDC: Centers for Disease Control and Prevention
CI: confidence interval
OR: odds ratio
PCR: polymerase chain reaction
RR: relative risk
VASP: Varicella Active Surveillance Project
VE: vaccine effectiveness
VZV: varicella zoster virus

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