

Effectiveness of 2 Doses of Varicella Vaccine in Children

Eugene D. Shapiro,^{1,3,4} Marietta Vazquez,¹ Daina Esposito,¹ Nancy Holabird,¹ Sharon P. Steinberg,⁵ James Dziura,^{1,2} Philip S. LaRussa,⁵ and Anne A. Gershon⁵

¹Department of Pediatrics; ²Department of Medicine; ³Department of Epidemiology; ⁴Department of Investigative Medicine, Yale University School of Medicine and Graduate School of Arts and Sciences, New Haven, Connecticut; and ⁵Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York

Background. Because of ongoing outbreaks of varicella, a second dose of varicella vaccine was added to the routine immunization schedule for children in June 2006 by the Centers for Disease Control and Prevention.

Methods. We assessed the effectiveness of 2 doses of varicella vaccine in a case-control study by identifying children ≥ 4 years of age with varicella confirmed by polymerase chain reaction assay and up to 2 controls matched by age and pediatric practice. Effectiveness was calculated using exact conditional logistic regression.

Results. From July 2006 to January 2010, of the 71 case subjects and 140 matched controls enrolled, no cases (0%) vs 22 controls (15.7%) had received 2 doses of varicella vaccine, 66 cases (93.0%) vs 117 controls (83.6%) had received 1 dose, and 5 cases (7.0%) vs 1 control (0.7%) did not receive varicella vaccine ($P < .001$). The effectiveness of 2 doses of the vaccine was 98.3% (95% confidence level [CI]: 83.5%–100%; $P < .001$). The matched odds ratio for 2 doses vs 1 dose of the vaccine was 0.053 (95% CI: 0.002–0.320; $P < .001$).

Conclusion. The effectiveness of 2 doses of varicella vaccine in the first 2.5 years after recommendation of a routine second dose of the vaccine for children is excellent. Odds of developing varicella were 95% lower for children who received 2 doses compared with 1 dose of varicella vaccine.

The live, attenuated varicella vaccine was developed in Japan in 1974 by Takahashi [1]. Recommendation for a single dose of the vaccine as part of the schedule for routine immunization in the United States of susceptible children ages 12 months to 13 years (with 2 doses for susceptible older persons) was made after its licensure by the Food and Drug Administration in 1995 [2]. The incidence of varicella fell by 90%, mortality from varicella declined by 66%, and rates of hospitalization for varicella decreased by 80% after introduction and routine use of the vaccine [3–5]; however, a high frequency of breakthrough varicella in immunized children and continuing outbreaks of varicella in schools and in day-

care centers occurred, despite high rates of vaccination [6]. In addition, studies showed that over time the vaccine's effectiveness was $< 90\%$ [7], and in one study of healthy children the rate of seroconversion after 1 dose of the vaccine was only 76% [8]. Therefore, in June 2006, the Centers for Disease Control and Prevention (CDC) recommended routine administration of a second dose of varicella vaccine to children 4–6 years of age (or at least 3 months after the first dose was administered), as well as administration of catch-up second doses to older children [9]. Although data show that administration of 2 doses of varicella vaccine is associated with higher antibody titers (and presumably better protection from varicella) [10], there are no controlled data on the clinical efficacy of 2 doses of the vaccine in the general population. As part of an ongoing case-control study of the effectiveness of varicella vaccine, we conducted an analysis to assess the effectiveness of 2 doses of the vaccine in children 4 years of age and older.

METHODS

Methods are identical to those previously reported for this ongoing study [11, 12]. Informed consent was

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Reprints or correspondence: Dr Eugene D. Shapiro, Yale University Dept of Pediatrics, P.O. Box 208064, 333 Cedar St, New Haven, Connecticut 06520-8064 (eugene.shapiro@yale.edu).

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obtained from all subjects and/or parents, and the study was approved by Yale's Human Investigation Committee. Subjects included in this analysis were children ≥ 4 years of age enrolled after 30 June 2006 at one of the 28 pediatric practices in southern Connecticut that participated in our surveillance network. Potential case subjects, identified by active surveillance of the participating practices, were children who were thought by their practitioners to have varicella. They were excluded if they had a contraindication to varicella vaccine, had been previously diagnosed with varicella, or had received varicella vaccine in the preceding 4 weeks. On the third to fifth day of the illness, a research assistant visited the home of each potential case subject and conducted a brief interview. A suitable lesion from the rash was gently unroofed with a capillary tube that was also used to collect vesicular fluid, if present. Material also was obtained by swabbing the underlying skin with a cotton-tipped swab. A polymerase chain reaction (PCR) assay was performed on all specimens to detect the presence of DNA of varicella-zoster virus (VZV) by investigators who were blind to the vaccination status of the potential subject. Results were considered positive if the specimen was positive for DNA of VZV and all negative controls in the batch were negative. The test results were considered negative if the specimen was negative for DNA of VZV, all positive controls in the batch were positive, and the specimen was positive for the human β -globin gene (indicating the presence of fluid or tissue since there was amplifiable human DNA in the specimen). If the result was negative for DNA of both VZV and the β -globin gene, the specimen was considered inadequate.

For each PCR-positive case subject, we selected 2 controls who had not had varicella, matched by both date of birth (± 1 month) and pediatric practice. Controls were selected from a list of potential controls by using a table of random numbers to select the order in which potential controls were contacted. The medical records of the subjects (both case and control) were reviewed, and all information about previous immunizations and about significant medical illnesses was recorded. Records of all health care practitioners (including previous practitioners) were reviewed. Subjects were considered vaccinated if there was written documentation that varicella vaccine had been received at least 4 weeks before the date of onset of varicella for each case subject. Only written documentation of receipt of vaccines was accepted as evidence of prior immunization.

Data were analyzed using SAS software, version 9.1.3, for Windows (SAS Institute) and LogExact statistical software packages (Cytel). Matched odds ratios (ORs), with both their associated statistical significance and their 95% confidence intervals (CIs), as well as adjustments for potential confounding, were calculated using exact conditional logistic regression. The vaccine's effectiveness was calculated as $1 - \text{the matched OR} \times 100\%$ [13]. Student *t* test or Wilcoxon rank-sum test was used as appropriate to assess statistical significance of differences

between groups in continuous variables; the χ^2 test was used to assess statistical differences between categorical values. All *P* values are 2-sided. Results were considered statistically significant if the 2-tailed *P* value was $< .05$.

RESULTS

Subjects

From 1 July 2006 to 8 January 2010 we identified 306 potentially eligible case subjects. Of these, 247 (80.7%) enrolled, 42 (13.7%) refused, and 17 (5.6%) could not be contacted. For the case subjects that were enrolled, PCR assay results were positive for 71 (28.7%), negative for 135 (54.7%), and inadequate for 41 (16.6%). Of the parents of the 187 potentially eligible matched controls whom we were able to contact, we enrolled 140 (74.9%)—for 2 of the cases, only 1 matched control was enrolled; 47 (25.1%) refused to enroll. Characteristics of the subjects are shown in Table 1.

Immunization with Varicella Vaccine

Vaccination status of the subjects is shown in Table 2. Of the 71 subjects with varicella, 5 (7.0%) had not received varicella vaccine, 66 (93.0%) had received 1 dose, and none (0%) had received 2 doses of the vaccine. By contrast, among the 140 matched controls, 1 (0.7%) had not received varicella vaccine, 117 (83.6%) had received 1 dose, and 22 (15.7%) had received 2 doses ($P < .001$). Nearly all case subjects and controls had received 2 doses of measles, mumps, and rubella (MMR) vaccine. No statistically significant demographic differences were shown between subjects who had received 2 doses of varicella vaccine and those who had received fewer doses. All of the vaccinated case subjects and controls received monovalent varicella vaccine for their first dose (combined measles-mumps-rubella-varicella

Table 1. Characteristics of the Subjects

	Case Subjects n = 71 (%)	Controls n = 140 (%)	<i>P</i> value
Age, years			.905
Mean \pm SD	10.7 \pm 2.7	10.7 \pm 2.7	
Median	11	11	
Range	4–18	4–18	
Male sex	40 (56.3)	77 (55.0)	.853
Caucasian race	62 (87.3)	126 (90.0)	.556
Parent education			.185
High school or less	22 (31.9)	48 (34.3)	
Some college	18 (25.4)	21 (15.0)	
College/postgraduate degree	31 (43.7)	71 (50.7)	
Weekday location			.015
Home	3 (4.2)	22 (15.7)	
School or day-care	68 (95.8)	118 (84.3)	
Diagnosis of asthma	4 (5.6)	17 (12.1)	.136

Table 2. Vaccination Status of Subjects

	Case Subjects n = 71 (%)	Controls n = 140 (%)	P value
Varicella vaccine			<.001
0 doses	5 (7.0)	1 (0.7)	
1 dose	66 (93.0)	117 (83.6)	
2 doses	0 (0.0)	22 (15.7)	
Months since dose 1			.151
Mean ± SD	103.2 ± 24.1	97.4 ± 28.2	
Median	106	101	
Range	35–139	17–161	
Months since dose 2			N/A
Mean ± SD	–	14.8 ± 13.3	
Median	–	12	
Range	–	0–50	
Received MMR ^a >1 dose	71 (100.0)	139 (99.3)	1.000
Received MMR 2 doses	70 (98.6)	137 (97.9)	1.000

NOTE. ^a MMR, Measles, mumps, and rubella vaccine; N/A, not applicable.

[MMRV] vaccine was not yet on the market at the time these children received their first dose of varicella vaccine). Two of the controls received their second dose as MMRV vaccine (it was no longer available beginning in late 2007).

Effectiveness of the Vaccine

The distribution of vaccination by matched groups is shown in Table 3. The effectiveness of 1 dose of the vaccine was 86.0% (95% CI: –44.5%–99%; $P = .124$). The effectiveness of 2 doses of the vaccine was 98.3% (95% CI: 83.5%–100%; $P < .001$). The matched odds ratio for 2 doses versus 1 dose of the vaccine was 0.053 (95% CI: 0.002–0.320; $P < .001$), indicating that, in the first 2.5 years after introduction of the second dose, the odds of developing varicella for children who had received 2 doses of the varicella vaccine were 95% lower than for those who had received 1 dose. Results of all of the analyses were virtually unchanged after adjusting for potential confounding (ie, site of week-day care, home vs school or day care).

Table 3. Receipt of Varicella Vaccine by Dose and Matched Groups

Doses Received by Case Subject	Doses Received by Matched Control Subjects					
	Neither Control Received Vaccine	One Control Received 1 Dose	One Control Received 2 Doses ^a	Both Controls Received 1 Dose	One Control Received 1 Dose, One 2 Doses	Both Controls Received 2 Doses
0	0	0	1	3	1	0
1	0	1	1	48	13	3
2	0	0	0	0	0	0

NOTE. Matched odds ratio, 1 dose vs 0 dose of vaccine: 0.14 (95% CI: 0.003–1.445; $P = .124$)

Matched odds ratio, 2 doses vs 0 dose of vaccine: 0.017 (95% CI: 0–0.165) $P < .001$

Matched odds ratio, 2 doses vs 1 dose of vaccine: 0.053 (95% CI: 0.002–0.320; $P < .001$)

^a Both cases in this category had only one control.

DISCUSSION

Results from this controlled study of the effectiveness of 2 doses of varicella vaccine indicate that administration of 2 doses was highly effective in preventing varicella in the first 2.5 years after implementation of the 2-dose schedule to prevent disease. There has been controversy about whether the suboptimal effectiveness of a single dose of varicella vaccine is due to primary vaccine failure, waning immunity, or both [8, 12,14–16]. Whatever the cause, however, initial assessment indicates that administration of 2 doses of the vaccine has been highly effective in preventing varicella; none of the 71 children with PCR-confirmed varicella had received 2 doses of the vaccine, although many had received 1 dose.

The effectiveness of a vaccine is defined as 1 – the odds of disease in vaccinated vs unvaccinated individuals $\times 100\%$ [13]. In a matched analysis, only groups in which there is discordance in the number of doses of vaccine between the case subjects and any of the controls contribute information to the analyses [17]. Because of the small number of discordant groups in which subjects had received either no dose or 1 dose of the vaccine, our statistical power to assess the effectiveness of 1 dose of the vaccine was poor. Consequently, the confidence interval around this estimate is wide, although the point estimate is similar to previous estimates of the effectiveness of 1 dose of the vaccine [7, 12]. By contrast, we were able to show that administering 2 doses of the vaccine was very effective and that the odds of developing disease after 2 doses were significantly lower than after 1 dose. No similar difference was seen between subjects and controls in receipt of the MMR vaccine—nearly all subjects and controls had received 2 doses of this vaccine. Since MMR vaccine is recommended to be administered at the same ages as varicella vaccine, this demonstrates the specificity of our results and suggests that they are not attributable to selection bias [18].

The United States was the first country to recommend universal immunization with 1 dose of varicella vaccine, and the first to introduce a 2-dose schedule. Two doses were recommended although there were no data to demonstrate that administering 2 doses would reduce the incidence of breakthrough varicella, though one uncontrolled study suggested there might

be a decrease in incidence after 2 doses [10]. Currently, many other countries, including Australia, Japan, China, and Spain, are carrying out universal immunization programs with a single dose of the vaccine.

The experience in the United States demonstrated that although a single dose of the vaccine had a substantial impact on the burden of disease, breakthrough varicella continued to occur. Breakthrough varicella is generally a much milder illness than varicella in unimmunized children and may be difficult to differentiate from other common skin conditions such as insect bites or impetigo. This likely is the explanation for the lower proportion of potential subjects with a positive VZV PCR result in this study than in our previous reports [11–12]. However, breakthrough varicella still can be transmitted to other susceptible individuals and has often led to outbreaks in settings in which children are in close contact, such as schools and day-care centers [6, 7, 9]. A second dose of vaccine may be important not only to prevent breakthrough varicella and continuing transmission of the virus, but also to potentially lower the subsequent risk of developing zoster by decreasing latent infection with wild-type VZV. It will be important to continue to monitor the effectiveness of 2 doses of varicella vaccine over time. The effects of this 2-dose policy in the United States will also have important implications for national immunization programs in other countries that use varicella vaccine.

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