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One Dose of Varicella Vaccine Does Not Prevent School Outbreaks: Is it Time for a Second Dose?

Adriana S. Lopez, MHS^a, Dalya Guris, MD, MPH^a, Laura Zimmerman, MPH^a, Linda Gladden, RN^b, Tamara Moore, RN^c, Dirk T. Haselow, PhD^b, Vladimir N. Loparev, PhD^a, D. Scott Schmid, PhD^a, Aisha O. Jumaan, PhD^a, Sandra L. Snow, MD^b

^aCenters for Disease Control and Prevention, Atlanta, Georgia; ^bArkansas Department of Health, Little Rock, Arkansas; ^cBryant Public School District, Bryant, Arkansas

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ABSTRACT

OBJECTIVES. The implementation of a routine childhood varicella vaccination program in the United States in 1995 has resulted in a dramatic decline in varicella morbidity and mortality. Although disease incidence has decreased, outbreaks of varicella continue to be reported, increasingly in highly vaccinated populations. In 2000, a varicella vaccination requirement was introduced for kindergarten entry in Arkansas. In October 2003, large numbers of varicella cases were reported in a school with high vaccination coverage. We investigated this outbreak to examine transmission patterns of varicella in this highly vaccinated population, to estimate the effectiveness of 1 dose of varicella vaccine, to identify risk factors for vaccine failure, and to implement outbreak control measures.

METHODS. A retrospective cohort study involving students attending an elementary school was conducted. A questionnaire was distributed to parents of all of the students in the school to collect varicella disease and vaccination history; parents of varicella case patients were interviewed by telephone. A case of varicella was defined as an acute, generalized, maculopapulovesicular rash without other apparent cause in a student or staff member in the school from September 1 to November 20, 2003. Varicella among vaccinated persons was defined as varicella-like rash that developed >42 days after vaccination. In vaccinated persons, the rash may be atypical, maculopapular with few or no vesicles. Cases were laboratory confirmed by polymerase chain reaction, and genotyping was performed to identify the strain associated with the outbreak.

RESULTS. Of the 545 students who attended the school, 88% returned the questionnaire. Overall varicella vaccination coverage was 96%. Forty-nine varicella cases were identified; 43 were vaccinated. Three of 6 specimens tested were positive by polymerase chain reaction. The median age at vaccination of vaccinated students in the school was 18 months, and the median time since vaccination was 59 months. Forty-four cases occurred in the East Wing, where 275 students in grades kindergarten through 2 were located, and vaccination coverage was 99%. In this wing, varicella attack rates among unvaccinated and vaccinated students were 100% and 18%, respectively. Vaccine effectiveness against varicella of any severity was 82% and 97% for moderate/severe varicella. Vaccinated cases were significantly milder compared with unvaccinated cases. Among the case patients in the East Wing, the median age at vaccination was 18.5 and 14 months among

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Dr Haselow's current address is University of Arkansas for Medical Sciences, Little Rock, AR 72205.

Dr Jumaan's current address is Agency for Toxic Substance and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA 30333.

Key Words

varicella outbreak, varicella vaccination, varicella vaccination policy, vaccine effectiveness, vaccination coverage

Abbreviations

ADH—Arkansas Department of Health
 CDC—Centers for Disease Control and Prevention
 PCR—polymerase chain reaction
 VZV—varicella zoster virus
 ORF—open reading frame
 CI—confidence interval
 gpELISA—glycoprotein-based enzyme-linked immunosorbent assay

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Address correspondence to Adriana S. Lopez, MHS, Centers for Disease Control and Prevention, 1600 Clifton Rd, Mail Stop E-61, Atlanta, GA 30333. E-mail: alopez@cdc.gov

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non-case patients. Four cases in the West Wing did not result in further transmission in that wing. The Arkansas strains were the same as the common varicella-zoster virus strain circulating in the United States (European varicella-zoster virus strain).

CONCLUSIONS. Although disease was mostly mild, the outbreak lasted for ~2 months, suggesting that varicella in vaccinated persons was contagious and that 99% varicella vaccination coverage was not sufficient to prevent the outbreak. This investigation highlights several challenges related to the prevention and control of varicella outbreaks with the 1-dose varicella vaccination program and the need for further prevention of varicella through improved vaccine-induced immunity with a routine 2-dose vaccination program. The challenges include: 1-dose varicella vaccination not providing sufficient herd immunity levels to prevent outbreaks in school settings where exposure can be intense, the effective transmission of varicella among vaccinated children, and the difficulty in the diagnosis of mild cases in vaccinated persons and early recognition of outbreaks for implementing control measures. The efficacy of 2 doses of varicella vaccine compared with 1 dose was assessed in a trial conducted among healthy children who were followed for 10 years. The efficacy for 2 doses was significantly higher than for 1 dose of varicella vaccine. This higher efficacy translated into a 3.3-fold lower risk of developing varicella >42 days after vaccination in 2- vs 1-dose recipients. Of the children receiving 2 doses, 99% achieved a glycoprotein-based enzyme-linked immunosorbent assay level of ≥ 5 units (considered a correlate of protection) 6 weeks after vaccination compared with 86% of children who received 1 dose. The 6-week glycoprotein-based enzyme-linked immunosorbent assay level of ≥ 5 units has been shown to be a good surrogate for protection from natural disease. Ten years after the implementation of the varicella vaccination program, disease incidence has declined dramatically, and vaccination coverage has increased greatly. However, varicella outbreaks continue to occur among vaccinated persons. Although varicella disease among vaccinated persons is mild, they are contagious and able to sustain transmission. As a step toward better control of varicella outbreaks and to reduce the impact on schools and public health officials, in June 2005, the Advisory Committee on Immunization Practices recommended the use of a second dose of varicella vaccine in outbreak settings. Early recognition of outbreaks is important to effectively implement a 2-dose vaccination response and to prevent more cases. Although the current recommendation of providing a second dose of varicella vaccine during an outbreak offers a tool for controlling outbreaks, a routine 2-dose recommendation would be more effective at preventing cases. Based on published data on immunogenicity and efficacy of 2 doses of varicella vaccine, routine

2-dose vaccination will provide improved protection against disease and further reduce morbidity and mortality from varicella.

THE IMPLEMENTATION OF a routine childhood varicella vaccination program in the United States in 1995 has resulted in a dramatic decline in varicella morbidity and mortality.¹⁻³ Although disease incidence has decreased, outbreaks of varicella continue to be reported, increasingly in highly vaccinated populations.⁴⁻⁶ Varicella disease in vaccinated persons is generally mild, with <50 lesions and atypical rash (ie, maculopapular with few or no vesicles). However, a study of varicella contagiousness among vaccinated persons in household settings found that, although varicella case patients with <50 lesions were one third as contagious as varicella in unvaccinated persons, vaccinated case patients with ≥ 50 lesions were as contagious as unvaccinated case patients.⁷

In 2000 in Arkansas, school entry requirements for varicella vaccination were implemented for entry to kindergarten. By September 2003, students in grades kindergarten through 3 were covered. School immunization surveys conducted from 2000 to 2002 indicated 99% to 100% varicella vaccination coverage among kindergarten students. In 2003, varicella vaccination coverage among children 19 to 35 months of age in Arkansas was 88%.⁸

In October 2003, the Arkansas Department of Health (ADH) was notified of a varicella outbreak in an elementary school. Because of the large number of cases among vaccinated children and the high rate of vaccination in the state, the ADH, in collaboration with the Centers for Disease Control and Prevention (CDC), investigated the outbreak to assess its extent and severity, to estimate the effectiveness of 1 dose of varicella vaccine, to identify risk factors for vaccine failure, to examine transmission patterns of varicella in this highly vaccinated population, and to implement outbreak control measures. This article summarizes findings from this investigation and discusses their implications for varicella outbreak prevention and control and vaccination policy in the United States.

METHODS

Outbreak Setting

On October 17, 2003, the ADH was notified of an outbreak of varicella in an elementary school after 15 students were sent home the same day with a rash that was later confirmed to be varicella. A total of 545 students (grades kindergarten through 5) attended the school. The school had 2 wings (East and West), with separate ventilation systems (Fig 1). With the exception of a single kindergarten classroom, all of the kindergarten

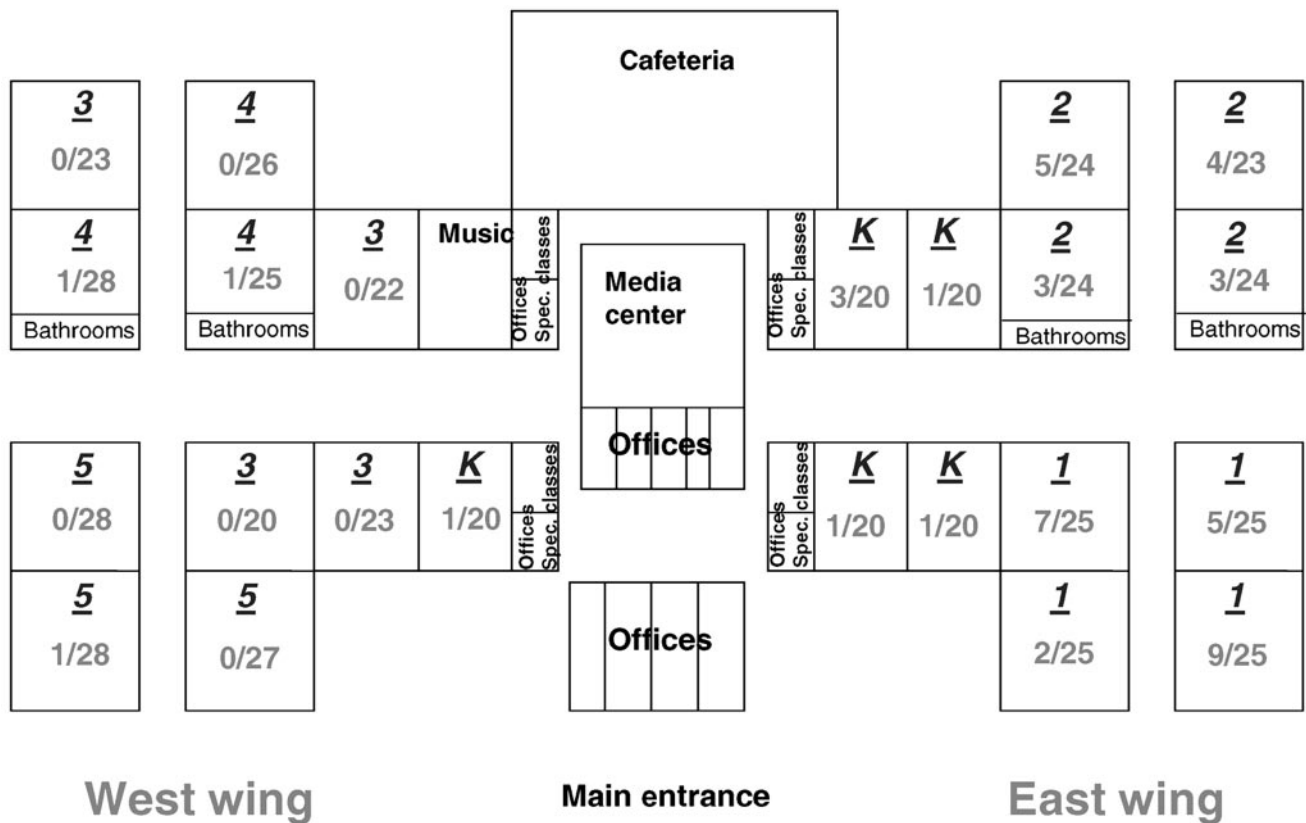


FIGURE 1
Diagram of the school, including distribution of varicella cases and students according to classroom: Arkansas, 2003.

through second grade classrooms were located in the East Wing. The remaining classrooms (1 kindergarten class and all of grades 3–5) were located in the West Wing. Mixing of students occurred in the classrooms, hallways, play areas, cafeteria, on school buses to and from school, and at after-school activities (eg, sports, dance class).

Epidemiological Investigation

Questionnaires were distributed to all of the students in the school to be completed by their parents. Information about demographics, underlying medical conditions, history of varicella disease and vaccination, health care providers, and parental consent to contact health care providers was collected. Varicella vaccination history was verified through vaccination cards, school immunization records, state immunization registry, or provider records. Parents of case patients were contacted by telephone to collect information about the possible source and setting of exposure, clinical course of illness (eg, duration of rash, number of lesions, presence of fever, complications), long-term medical conditions, and treatment of the case patient that could affect immunity, household transmission, and parental consent to collect specimens for testing.

Outbreak Control Measures

Varicella case patients were excluded from school until lesions crusted or faded. A letter was sent home to parents informing them of the outbreak and recommending vaccination for susceptible students. Susceptible, immunocompromised persons and pregnant staff were recommended for exclusion from school until 21 days after the onset date of the last identified case.

Case Definitions

A case of varicella was defined as an acute, generalized, maculopapulovesicular rash without other apparent cause in a student or staff member in the school from September 1 to November 20, 2003. Varicella among vaccinated persons was defined as varicella-like rash that developed >42 days after vaccination. In vaccinated persons, the rash may be atypical, maculopapular with few or no vesicles. Varicella disease was categorized as mild (<50 lesions), mild/moderate (50–249 lesions), moderate (250–500 lesions), and severe (>500 lesions or presence of complications or hospitalization).

Laboratory Investigation

Specimens from lesions were collected and tested by polymerase chain reaction (PCR) for confirmation of

varicella. Genotyping was done at the CDC Varicella Zoster Virus (VZV) Laboratory using methods described previously.⁹

Analyses

Data were analyzed by using Epi Info 6.0 (CDC) and SAS 8 (SAS Institute Inc, Cary, NC) software. Fisher's exact test was used to compare proportions, the Wilcoxon rank-sum test was used to compare medians, and 2-sided *P* values were reported with a significance level of *P* < .05. The analyses were restricted to students at the school. Vaccination coverage at the start of the outbreak was defined as the proportion of persons who had received varicella vaccine among those who had no history of varicella disease. Vaccine effectiveness was calculated using methods described previously.¹⁰ Persons with a previous or unknown history of varicella, unknown vaccination and history, vaccination at <12 months of age, vaccination <42 days before the start of the outbreak, or those who received 2 doses of varicella vaccine were excluded from the vaccine effectiveness calculation.

RESULTS

Study Population

Of the 545 students attending the school during the outbreak, 479 (88%) completed the questionnaires, and response rates ranged by grade from 82% to 96%. Vaccination and disease history information were obtained from school records for 529 (97%) and 485 (89%) of the 545 students, respectively. Fifty-three percent (288 of 540) of the students were female. The West Wing had 270 students, and the East Wing had 275 students. Kindergarten through second grades shared recess, whereas third through fifth grades shared recess; lunch was shared by 2 grades at a time: kindergarten and 1, 2 and 3, and 4 and 5.

The proportion of students by grade at the start of the outbreak who had a history of varicella disease ranged between 7% and 57% (Fig 2). Among children with a

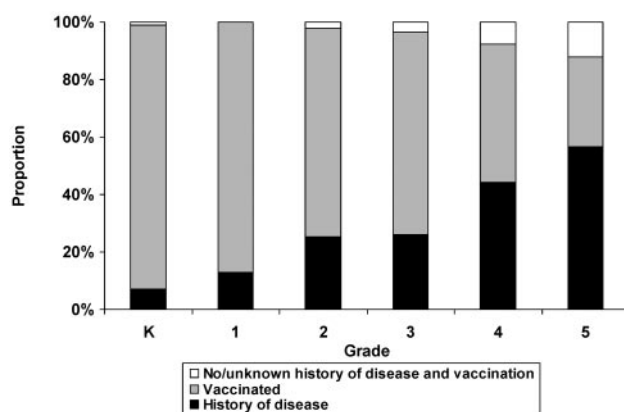


FIGURE 2

The proportion of students according to grade and varicella disease and vaccination history before the outbreak: Arkansas, 2003. ■, students with history of varicella disease regardless of vaccination status; ▒, students with history of varicella vaccination and a negative history of disease; and □, students with a negative or unknown history of varicella disease and/or vaccination.

negative disease history, the overall vaccination coverage was 96% and ranged by grade from 79% to 100%. The median age at vaccination of vaccinated students in the school was 18 months (range: 4–99 months), and the median time since vaccination was 59 months (range: 0–101 months). Fourteen of the students had received 2 doses of varicella vaccine. One (7%) of 14 had received their first dose at <12 months of age; the remaining 13 (93%) received their first dose at ≥12 months of age and their second dose >3 months after the first dose.

Students in the East Wing were younger than those in the West Wing (median age: 6 years (range: 5–8 years) vs 9 years (range 5–12 years); *P* < .001) and less likely to have a history of varicella disease (15% [42 of 275] vs 40% [107 of 270]; *P* < .001). Among those without previous disease, a higher proportion were vaccinated in the East Wing compared with the West Wing (99% [230 of 233] vs 92% [123 of 133]; *P* < .001; Table 1).

TABLE 1 Distribution of Students, Cases, and Disease and Vaccination History by Wing: Arkansas, 2003

Variable	West Wing	East Wing	<i>P</i>
Total number of students	270	275	NA
Median age of students, y (range)	9 (5–12)	6 (5–8)	<.001
Had history of disease ^a	40%	15%	<.001
Had history of vaccination ^b	92%	99%	<.001
No or unknown disease and vaccination history ^{a,c}	7%	1%	.0004
No. of varicella cases	4	44	NA
Overall varicella attack rate	2%	16%	<.001
AR among students without disease history ^d	3%	19%	<.001
AR by classroom among students without disease history, range	0–14%	7–41%	NA

AR indicates attack rate; NA, not applicable.

^a Before the start of the outbreak.

^b Had no previous history of disease.

^c Children who had: (1) no history of disease and no history of vaccination, (2) no history of disease and unknown vaccination history, (3) unknown history of disease and no vaccination history, or (4) unknown history of disease and vaccination.

^d Four case patients had previous history of disease.

Outbreak

Between September 24 and November 19, a total of 49 cases of varicella were identified (Fig 3): 48 students and 1 teacher. The median age of the student case patients was 6 years (range: 5–11 years); 46% (22 of 48) were female.

Forty three (90%) of the student case patients were vaccinated. Of these, 41 received 1 dose of varicella vaccine and 1 received 2 doses, both at age ≥ 12 months and >3 months apart, and 1 received 2 doses, the first of which was administered at <12 months of age. Of the 41 case patients who had received 1 dose of varicella vaccine, 2 also had a history of disease before vaccination. Of the 5 (10%) unvaccinated case patients, 2 had a previous history of disease.

The first identified case patient had rash onset on September 24. The case patient was a vaccinated second grade student who had ~ 15 vesicular lesions and did not have fever or appear sick. No varicella exposure before illness was reported.

Most of the cases (44 of 48 [92%]) occurred among students in the East Wing, with the highest attack rates among first and second graders, 26% and 19%, respectively. The highest attack rate occurred in a first grade classroom where all of the students had been previously vaccinated and 41% developed varicella. Among the case patients in the East Wing, the median age at vaccination was 18.5 months (range: 12–79 months) and 14 months (range: 12–90 months) among non-case patients ($P = .15$). Four (8%) cases occurred in the West Wing. Three of these case patients had siblings in the East Wing. No secondary transmission occurred in the West Wing.

Secondary transmission to household members was reported for 2 vaccinated student case patients from the East Wing. Both vaccinated student case patients had vesicular rashes in the mild/moderate severity range (50–249 lesions) and transmitted to vaccinated siblings, aged 3 and 4 years, who had rash onset 14 to 15 days, respectively, after rash onset of the student case patients.

Laboratory Investigation

Four (67%) of 6 specimens collected and tested by the Arkansas State Laboratory were positive by PCR for VZV DNA. The 2 case patients with negative PCR results had been taking antiviral medication for varicella. The 3 specimens confirmed and characterized at the CDC were the same wild-type strain. The genetic profile included *BglI* + (open reading frame [ORF] 54), *PstI* + (ORF 38), and *SmaI* – (ORF62). The Arkansas strains were the same as the common VZV strain circulating in the United States (European VZV strain) based on variability of the ORF 22 region.

Outbreak Control Measures

One student was vaccinated during the outbreak. Another student, who had contraindications for vaccination and was immunocompromised, was excluded from school through 21 days after the last case was identified. A pregnant substitute teacher was referred to her obstetrician for postexposure options.

Disease Severity

Most of the vaccinated case patients experienced mild disease, with 89% having <50 lesions, parents reporting that 94% did not appear sick, and missing only a median of 2 days of school because of illness (Table 2). However, 2 of the vaccinated case patients reported skin infections. No hospitalizations were reported.

Vaccine Effectiveness and Risk Factors

Analyses of vaccine effectiveness and risk factors for vaccine failure were limited to students in the East Wing. Forty-three students were excluded from the vaccine effectiveness calculation because they had an unknown or positive history of disease. Fourteen students were excluded because they were vaccinated with 2 doses of varicella vaccine (10 students, including 1 case patient), vaccinated at <12 months of age (3 students, including 1 case patient), or were vaccinated <42 days before the start of the outbreak (1 student). The attack rate among

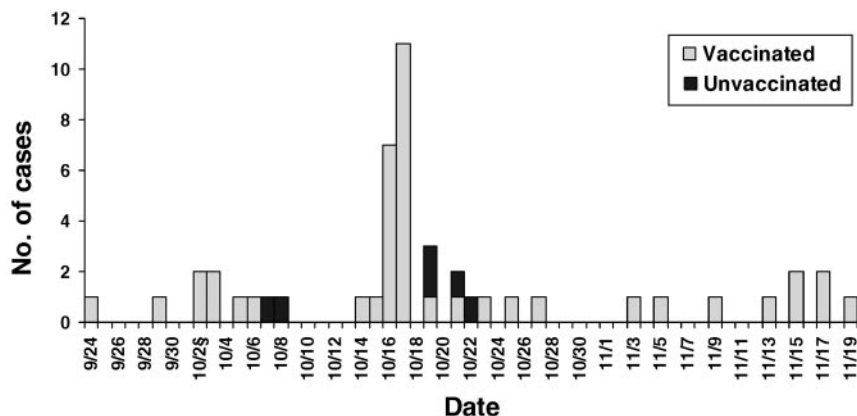


FIGURE 3

Reported varicella cases according to rash onset date, grade, and vaccination status ($n = 49$): Arkansas, 2003. The onset date for 1 child was unknown. Onset dates (October 2) for 2 student cases were estimated based on the date they were first identified.

TABLE 2 Clinical Severity of Student Case Patients According to Vaccination Status: Arkansas, 2003

Clinical Characteristics	Vaccinated Case Patients (n = 43)	Unvaccinated Case Patients (n = 5)	P
Median number of days with rash, n (range)	4 (1–8)	7 (5–7)	.009
<50 lesions, n (%)	32 (89) ^a	0 (0)	<.001
Itchy rash, n (%)	32 (89) ^a	5 (100)	NS
Developed scabs, n (%)	29 (83) ^b	5 (100)	NS
Generalized rash, n (%)	34 (94) ^a	5 (100)	NS
Fever, n (%); median maximum temperature °F, (range)	18 ^c (47); 99.8 (99.2–102.4)	4 (80); 100.8 (100–102)	.04, NS
Did not appear sick vs appeared moderately sick, n (%)	34 (94) ^a	2 (40)	.009
Median number days child missed school, n (range)	2 (0–5)	5 (3–5)	.002
Median number days adult missed work, n (range)	0 (0–5)	2 (0–5)	NS

Clinical severity was not available for all cases. NS indicates not significant.

^a For vaccinated case patients, total n = 36.

^b For vaccinated case patients, total n = 35.

^c For vaccinated case patients, total n = 38.

vaccinated students in the East Wing was 18% compared with 100% among unvaccinated students. The overall vaccine effectiveness was 82% (95% confidence interval [CI]: 76%–87%) for varicella of any severity and 97% (95% CI: 94%–99%) for moderate/severe varicella.

None of the risk factors for varicella in vaccinated persons that have been identified previously (ie, age at vaccination, time since vaccination, presence of asthma, or use of steroid inhalers)^{5,11–14} were statistically significant in our analyses.

DISCUSSION

We documented a varicella outbreak that lasted ~2 months in an elementary school where vaccination coverage in the 12 classrooms most affected by the outbreak was 99%. One dose of varicella vaccine was 82% effective against preventing varicella of any severity. Although disease was mostly mild, transmission was sustained for 2 months, confirming that varicella in vaccinated persons is contagious, and with an 82% effective vaccine, 99% coverage was not sufficient to prevent the outbreak.

This investigation highlights several challenges related to the prevention and control of varicella outbreaks with the 1-dose varicella vaccination program and the need for improved protection through a 2-dose program. The first challenge is that the effectiveness of 1 dose of varicella vaccine is not adequate to provide sufficient herd immunity levels to prevent outbreaks in school settings where exposure can be intense. Varicella morbidity and mortality have declined significantly^{1–3} as vaccination coverage has increased in the United States (2004: 88% among children 19–35 months of age).¹⁵ The majority of postlicensure 1-dose varicella vaccine effectiveness estimates have been in the range of prelicensure estimates of 70% to 90%, with higher estimates for protection against severe disease. However, varicella continues to be an endemic disease in the United States, with outbreaks, albeit smaller than previously, occurring among populations with varying levels of coverage.

From 2001 to 2003, several outbreaks were reported in schools with high varicella vaccination coverage (96%–100%) and vaccine effectiveness between 72% and 85%.^{4,5,16} The outbreaks occurred in elementary schools, the highest attack rates occurred among the younger students, each outbreak lasted ~2 months, and vaccinated students played important roles in the transmission of disease. Overall attack rates among vaccinated children ranged between 11% and 17%. Despite high vaccination coverage, sufficient levels of susceptibility among vaccinated students resulted in sustained transmission.

The second challenge is the effective transmission of VZV among vaccinated children.⁷ Varicella is transmitted from person to person by direct contact with persons with varicella or herpes zoster or through airborne spread from respiratory secretions. Varicella transmission was substantially different in the East Wing versus the West Wing of the school. Most cases occurred in the East Wing; despite mixing of students between the East and West Wings, only 4 cases occurred in the West Wing and did not result in further transmission. A number of reasons could account for this discrepancy. First, contact between the younger students in the East Wing may have been more intense compared with contact among the older students in the West Wing. Second, the separate ventilation systems in the 2 wings could have contributed to the transmission pattern. Airborne transmission of varicella has been documented previously in health care settings.^{17,18} Finally, students in the West Wing were more likely to have disease-induced immunity (West Wing, 40% vs East Wing, 15%). Although it is uncertain how much disease-induced immunity may have played a role in the prevention of transmission in the West Wing, we speculate that this may have been an important factor.

The third challenge is the difficulty in diagnosing mild cases in vaccinated persons and early recognition of outbreaks for implementing control measures. This outbreak was recognized after the first generation of cases.

No index case was identified. Disease could have been missed in the index case if presentation was mild. Because vaccinated cases are mild, recognition or exclusion may be difficult, resulting in more opportunities to infect others. Education of physicians, school officials, and parents about the appearance of varicella in vaccinated persons and laboratory confirmation of suspected cases are important for early recognition of outbreaks. Because varicella disease in vaccinated persons is contagious, it should be treated similarly to varicella in unvaccinated persons. CDC recommends exclusion or isolation of all cases, regardless of their vaccination status, until all lesions crust or fade.

These challenges highlight the need for further prevention of varicella through improved vaccine-induced immunity. The efficacy of 2 doses of varicella vaccine compared with 1 dose was assessed in a trial conducted among healthy children who were followed for 10 years. The efficacy for 2 doses was significantly higher than for 1 dose of varicella vaccine (98% vs 94%, respectively; $P < .001$).¹⁹ This higher efficacy translated into a 3.3-fold lower risk of developing varicella >42 days after vaccination in 2- vs 1-dose recipients. Of the children receiving 2 doses, 99% achieved a glycoprotein-based enzyme-linked immunosorbent assay (gpELISA) level of ≥ 5 units (considered a correlate of protection) 6 weeks after vaccination compared with 86% of children who received 1 dose.¹⁹ The 6-week gpELISA level of ≥ 5 units has been shown to be a good surrogate for protection from natural disease.^{20,21} Furthermore, the proportion of children with gpELISA levels of ≥ 5 units in the 1-dose group correlates better to values found for vaccine effectiveness during field investigations (80%–85%). In addition, in 2 subsets of children, 2 dose recipients had higher levels of cell-mediated immune response 6 and 52 weeks after vaccination compared with 1-dose recipients.^{22,23} Therefore, it is expected that a 2-dose regimen would provide better protection against disease than the current 1-dose regimen. During this outbreak, 1 of the 13 children who had received 2 adequate doses (3 months apart and ≥ 12 months of age) had varicella. However, the number of 2-dose recipients was too small to accurately interpret the significance of this finding.

Varicella in vaccinated persons may occur from failure to develop adequate immune response to vaccine (primary vaccine failure) or loss of immunity acquired after vaccination (secondary vaccine failure). Multiple studies and investigations have identified several risk factors for varicella vaccine failure, including: age at vaccination, time since vaccination, presence of asthma, or use of steroid inhalers.^{5,11–14} Improper vaccine storage and handling has also been suggested to result in vaccine failure but has not been identified as a risk factor in any study or investigation. None of these risk factors were identified during this study. As shown in clinical trials,¹⁹ a second dose of varicella vaccine provides greater pro-

tection 6 weeks after vaccination. Therefore, the routine use of a second dose of varicella vaccine will help catch those without adequate response to a first dose and could decrease the number of secondary vaccine failures by providing a booster. Although data are insufficient to conclude whether 2 doses of varicella vaccine will prevent all varicella outbreaks, we expect that 2 doses will decrease the susceptibility levels and increase herd immunity among school-aged children, the age group with the most cases, and thereby substantially decrease the number of varicella outbreaks.

The timing of administration of the second dose of varicella vaccine has also been studied to determine the immunogenicity based on timing. A study where the second dose was given 4 to 6 years after the first dose found a large increase in the antibody levels during the 7 to 10 days after the second dose, indicating an anamnestic response (geometric mean titer on the day of second dose: 25.7 and on day 7 to 10 after second dose: 143.6).²⁴ However, the antibody levels after 2 doses administered 4 to 6 years apart were comparable to those levels seen when 2 doses were administered 3 months apart.^{19,24}

Ten years after the implementation of the varicella vaccination program, disease incidence has declined dramatically, and vaccination coverage has increased greatly. However, varicella outbreaks continue to occur among vaccinated persons. As a step toward better control of varicella outbreaks and to reduce the impact on schools and public health officials, in June 2005, the Advisory Committee on Immunization Practices recommended the use of a second dose of varicella vaccine in outbreak settings. If this policy would have been implemented during the outbreak in Arkansas, we estimate that ~6 cases could have been prevented, resulting in a shorter duration of the outbreak. Early recognition of outbreaks is important to effectively implement a 2-dose vaccination response and prevent more cases. Although varicella disease among vaccinated persons is mild, the case patients are contagious and able to sustain transmission. These children may pose a risk for those who are at high risk for severe disease and have contraindications for vaccination (eg, susceptible pregnant women, immunocompromised persons). School outbreaks cause disruptions for students, teachers, parents, and public health authorities. Although the current recommendation of providing a second dose of varicella vaccine during an outbreak offers a possible tool for controlling outbreaks, a routine 2-dose recommendation would be more effective at preventing cases. Based on published data on immunogenicity and efficacy of 2 doses of varicella vaccine, routine 2-dose vaccination will provide improved protection against disease and further reduce morbidity and mortality from varicella.

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REFERENCES

1. 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
2. Davis MM, Patel MS, Gebremariam A. Decline in varicella-related hospitalizations and expenditures for children and adults after introduction of varicella vaccine in the United States. *Pediatrics*. 2004;114:786–792
3. 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
4. Centers for Disease Control and Prevention. Outbreak of varicella among vaccinated children: Michigan, 2003. *MMWR Morb Mortal Wkly Rep*. 2004;53:389–392
5. Tugwell BD, Lee LE, Gillette H, Lorber EM, Hedberg K, Cieslak PR. Chickenpox outbreak in a highly vaccinated school population. *Pediatrics*. 2004;113:455–459
6. Lee BR, Feaver SL, Miller CA, Hedberg CW, Ehresmann KR. An elementary school outbreak of varicella attributed to vaccine failure: policy implications. *J Infect Dis*. 2004;190:477–483
7. Seward JF, Zhang JX, Maupin TJ, Mascola L, Jumaan AO. Contagiousness of varicella in vaccinated cases: a household contact study. *JAMA*. 2004;292:704–708
8. Centers for Disease Control and Prevention. Estimated vaccination coverage with individual vaccines and selected vaccination series among children 19–35 months of age by state: U.S., National Immunization Survey, 2003. Available at: www.cdc.gov/nip/coverage/nis/03/tab03_antigen_state.xls. Accessed June 8, 2005
9. Loparev VN, McCaustland K, Holloway BP, Krause PR, Takayama M, Schmid DS. Rapid genotyping of varicella-zoster virus vaccine and wild type strains with fluorophore-labeled hybridization probes. *J Clin Microbiol*. 2000;38:4315–4319
10. Orenstein WA, Bernier RH, Dondero TJ, et al. Field evaluation of vaccine efficacy. *Bull World Health Organ*. 1985;63:1055–1068
11. Izurieta HS, Strebel PM, Blake PA. Postlicensure effectiveness of varicella vaccine during an outbreak in a child care center. *JAMA*. 1997;278:1495–1499
12. Dworkin MS, Jennings CE, Roth-Thomas J, Lang JE, Stukenberg C, Lumpkin JR. An outbreak of varicella among children attending preschool and elementary school in Illinois. *Clin Infect Dis*. 2002;35:102–104
13. Galil K, Lee B, Strine T, et al. Outbreak of varicella at a day-care center despite vaccination. *N Engl J Med*. 2002;347:1909–1915
14. Verstraeten T, Jumaan AO, Mullooly JP, et al. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. *Pediatrics*. 2003;112(2). Available at: www.pediatrics.org/cgi/content/full/112/2/e98
15. Centers for Disease Control and Prevention. National, state, and urban area vaccination coverage among children aged 19–35 months: United States, 2004. *MMWR Morb Mortal Wkly Rep*. 2005;54:717–721
16. Reuer J, Harpaz R, Gladden L, et al. Brisk onset of a varicella outbreak in a well-vaccinated school population with no identified source: how did it start? [abstract: 1029]. In: *42nd Annual Meeting of the Infectious Diseases Society of America*. Alexandria, VA: Infectious Diseases Society of America; 2004
17. Leclair JM, Zaia JA, Levin MJ, Congdon RG, Goldmann DA. Airborne transmission of chickenpox in a hospital. *N Engl J Med*. 1980;302:450–453
18. Gustafson TL, Lavelly GB, Brawner ER, Hutcheson RH Jr, Wright PF, Schaffner W. An outbreak of airborne nosocomial varicella. *Pediatrics*. 1982;70:550–556
19. Kuter B, Matthews H, Shinefield H, et al. Ten year follow-up of healthy children who received 1 or 2 injections of varicella vaccine. *Pediatr Infect Dis J*. 2004;23:132–137
20. White CJ, Kuter BJ, Ngai A, et al. Modified cases of chickenpox after varicella vaccination: correlation of protection with antibody response. *Pediatr Infect Dis J*. 1992;11:19–23
21. Li S, Chan IS, Matthew H, et al. Inverse relationship between 6 week postvaccination varicella antibody response to vaccine and likelihood of long term breakthrough infection. *Pediatr Infect Dis J*. 2002;21:337–342
22. Ngai AL, Staehle BO, Kuter BJ, et al. Safety and immunogenicity of 1 vs. 2 injections of Oka/Merck varicella vaccine in healthy children. *Pediatr Infect Dis J*. 1996;15:49–54
23. Watson B, Boardman C, Laufer D, et al. Humoral and cell-mediated immune responses in healthy children after 1 or 2 doses of varicella vaccine. *Clin Infect Dis*. 1995;20:316–319
24. Watson B, Rothstein E, Bernstein H, et al. Safety and cellular and humoral immune responses of a booster dose of varicella vaccine 6 years after primary immunization. *J Infect Dis*. 1995;172:217–219

One Dose of Varicella Vaccine Does Not Prevent School Outbreaks: Is it Time for a Second Dose?

Adriana S. Lopez, Dalya Guris, Laura Zimmerman, Linda Gladden, Tamara Moore, Dirk T. Haselow, Vladimir N. Loparev, D. Scott Schmid, Aisha O. Jumaan and Sandra L. Snow

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