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OUTBREAK OF VARICELLA AT A DAY-CARE CENTER DESPITE VACCINATION

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ABSTRACT

Background In seven studies of the effectiveness of the varicella vaccine conducted since it was licensed, the effectiveness was 71 to 100 percent against disease of any severity and 95 to 100 percent against moderate and severe disease. We investigated an outbreak of varicella in a population of children with a high proportion of vaccinees who were attending a day-care center in a small community in New Hampshire.

Methods Using standardized questionnaires, we collected information about the children's medical and vaccination history from parents and health care providers. The analysis of the effectiveness of the vaccine and of risk factors for vaccine failure was restricted to children who were enrolled in the day-care center continuously during the outbreak and attended for one week or more and who were cared for in the building that represented the epicenter of the outbreak, since transmission was not documented in a second building.

Results Varicella developed in 25 of 88 children (28.4 percent) between December 1, 2000, and January 11, 2001. The index case occurred in a healthy child who had been vaccinated three years previously and who infected more than 50 percent of his classmates who had no history of varicella. The effectiveness of the vaccine was 44.0 percent (95 percent confidence interval, 6.9 to 66.3 percent) against disease of any severity and 86.0 percent (95 percent confidence interval, 38.7 to 96.8 percent) against moderate or severe disease. Children who had been vaccinated three years or more before the outbreak were at greater risk for vaccine failure than those who had been vaccinated more recently (relative risk, 2.6 [95 percent confidence interval, 1.3 to 5.3]).

Conclusions In this outbreak, vaccination provided poor protection against varicella, although there was good protection against moderate or severe disease. A longer interval since vaccination was associated with an increased risk of vaccine failure. Breakthrough infections in vaccinated, healthy persons can be as infectious as varicella in unvaccinated persons. (N Engl J Med 2002;347:1909-15.)

SINCE the licensure of the varicella vaccine in 1995, seven investigations of the effectiveness of the vaccine have been published.[1-6] Effectiveness ranged from 71 to 100 percent against varicella disease of any severity and 95 to 100 percent against moderate-to-severe varicella disease. Those findings are similar to results from prelicensure trials that used both the currently formulated vaccine and other formulations of the Oka-strain varicella virus to immunize children.[7-14] In the United States, there is clear evidence from three active surveillance sites that the incidence of varicella disease and the rate of related hospitalizations have declined by 80 percent since the introduction of the vaccine.[15]

Although the vaccine affords excellent protection against moderate and severe varicella, a modified form of varicella develops in some vaccinated persons after exposure to someone with an infectious case. By definition, these breakthrough cases occur more than 42 days after vaccination and are usually caused by wild-type virus. Rashes occurring less than 14 days after vaccination are typically due to previously incubating wild-type disease, and rashes occurring 14 to 42 days after vaccination may be attributable to either strain and can be classified only by molecular typing. Breakthrough disease is typically mild, with fewer lesions (usually fewer than 50),[11,12,16,17] complications, and systemic symptoms.[17,18] To date, there is no evidence of an increase over time in the rate of breakthrough disease that would suggest waning immunity after vaccination. We describe an outbreak of varicella at a day-care center in New Hampshire, where vaccination coverage in 2000 was 66 percent[19] — similar to the national average of 68 percent.

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METHODS

Study Setting

The outbreak occurred in a private, licensed day-care center in a small community (population, 4500) near Concord, New Hampshire, that enrolled 92 children and employed 14 staff members. The day-care center was housed in two separate buildings approximately 20 yards apart. Building A housed children in the preschool, kindergarten, and before- and after-school programs, who mixed freely and shared common air flow. Building B, which housed the younger children, provided less opportunity for transmission, since children spent most of the day in one of four separate classrooms. Occasionally, parents with children in both buildings would have one child with them when they collected a sibling in the other building.

Case Definition

We defined a case of natural varicella as an illness involving a pruritic, maculopapulovesicular rash with no other apparent cause beginning from December 1, 2000, through January 11, 2001, in a child attending the day-care center who had not received varicella vaccine or who had been vaccinated less than 14 days before the onset of rash. Breakthrough disease was defined as varicella in a child who had been vaccinated more than 42 days before the onset of rash. Illness was classified as mild (fewer than 50 lesions without complications), moderate (51 to 500 lesions), or severe (more than 500 lesions or the occurrence of any serious complications, such as varicella pneumonitis, encephalitis, fever [temperature, >38.5°C] for five days, hospitalization, or death). Children were considered to have asthma if they had a reported history of asthma and were being treated with any asthma medication.

Questionnaires

A self-administered questionnaire for parents was used to collect demographic information, medical and vaccination history, and information about health care providers for all children, as well as detailed information about illnesses and exposure to varicella outside the day-care center for children in whom illness involving a rash developed on or after November 1, 2000 (one month before the onset of the index case). We distributed questionnaires to health care providers to verify the child's health status, medication and vaccination history, and remote or recent history of varicella.

Laboratory Investigations

An enzyme-linked immunosorbent assay testing for IgG antibody against whole-cell varicella–zoster virus in a filter-paper blood spot from a finger prick was offered for any child who did not have a history of either varicella disease or varicella vaccination. Children with rash were offered testing to determine whether varicella–zoster virus was present and to distinguish wild-type virus from the strain in the vaccine. Polymerase-chain-reaction analysis and restriction-fragment–length polymorphism analysis of varicella–zoster virus were performed with the use of the ORF62 primer pair according to the methods of Loparev et al.[20] and LaRussa et al.[21]

Investigation of Secondary Cases and Surveillance

The secondary attack rate from the index case was calculated as the proportion of susceptible, exposed children who were in Building A on at least one day when transmission could have occurred — that is, November 29 through December 1 — in whom varicella developed within 21 days after exposure. Enhanced surveillance for illness involving rash was continued at the day-care center until one incubation period (21 days) after the last case was identified.

Vaccine Lots, Storage, and Handling

Lot numbers were verified with the manufacturer, and the expiration date for each lot of vaccine was obtained. Information from periodic evaluations of the storage and handling of vaccine in the offices of vaccine providers, which have been conducted by the health department since 1995, were reviewed, and further evaluations were undertaken as a result of the outbreak.

Statistical Analysis

Data were entered into Epi Info (version 6.04b, Centers for Disease Control and Prevention) and analyzed with the use of SAS software (release 8.0, SAS Institute). Fisher's exact test was used for the comparison of proportions, and the exact Wilcoxon rank-sum test was used for the comparison of medians. All P values are two-sided, with a significance level of $P<0.05$. Because the numbers were small, multivariate models were unstable, and their results are not presented.

Vaccine effectiveness rates and 95 percent confidence intervals were calculated by the cohort method.[22] We excluded children with a history of varicella disease and children less than 12 months of age. We calculated the attack rates in unvaccinated children (ARU) and vaccinated children (ARV); we then estimated the percentage effectiveness of the vaccine as $[(ARU-ARV)\div ARU]\times 100$. The effectiveness of the vaccine against moderate-to-severe disease was calculated by classifying mild cases as noncases. Analysis of vaccine effectiveness and analysis of risk factors were limited to children in Building A (the epicenter of the outbreak) who were enrolled throughout the outbreak period and had attended day care for at least one week during the exposure period (from two days before the onset of rash in the index case — November 29, 2000 — to the date of the onset of rash in the last case — January 11, 2001). Children were considered to have been vaccinated if more than 42 days had elapsed since vaccination. Two children who were vaccinated on December 26, 2000, were classified as unvaccinated. Vaccination coverage at the start of the outbreak was defined as the proportion of children eligible for vaccination (at least 12 months of age and without a history of varicella) who had received the vaccine.

RESULTS

Study Subjects

Between December 1, 2000, and January 11, 2001, 92 children were enrolled in the day-care center. Four children attended for less than one week and were excluded from the analyses. Parents and health care providers returned questionnaires for 88 attendees (100 percent). Attendees ranged in age from 6 months to 8.9 years (median, 4.1 years) at the start of the outbreak; 61 of them (69.3 percent) were boys. At the start of the outbreak, vaccination coverage among children old enough to be eligible was 73.1 percent (49 of 67). Lot numbers of vaccine were verified for 93.9 percent of vaccinated children (46 of 49). Children were vaccinated during five different years (1996 to 2000) with at least 33 different lots of vaccine administered by 28 different health care providers. There was no evidence that any child had received expired vaccine.

Building A

Fifty-two of the 88 children (59.1 percent) attended the day-care center in Building A. Their median age was 5.3 years (range, 3.5 to 8.9), 32 of them (61.5 percent) were boys, and 15 of them (28.8 percent) had a history of varicella. Vaccination coverage among children who were old enough to receive the vaccine and

who had no history of varicella was 73.0 percent (27 of 37). Characteristics of children in the day-care center are summarized in Table 1.

Investigation of the Index Case

The index patient was a healthy, vaccinated, four-year-old boy who had an onset of rash on December 1, 2000, approximately three years after vaccination (November 14, 1997). He attended the day-care center on the two days before the onset of rash and briefly on the morning on which his rash erupted, before he was taken home. He was moderately ill, with a generalized rash consisting of approximately 150 vesicular lesions and a temperature of 102.5°F (39.2°C), remained bedridden for one day, and had no complications. His only known exposure to varicella–zoster virus was contact with an 11-year-old sister who did not attend the day-care center and who had herpes zoster (confirmed by Tzanck testing) on her left arm and back beginning on November 10, 2000 (21 days before the onset of rash in the index patient). The index case gave rise to 15 secondary cases in Building A, corresponding to a secondary attack rate of 48.4 percent (15 of 31) overall — 45.8 percent (11 of 24) among vaccinated children and 57.1 percent (4 of 7) among unvaccinated susceptible children.

The Outbreak

The outbreak lasted from December 1, 2000, to January 11, 2001 (Fig. 1). There were a total of 25 cases of varicella. Seventeen cases (68.0 percent) occurred in vaccinated children and eight cases (32.0 percent) in unvaccinated children at least 12 months of age. There were no cases in infants or children with a history of varicella disease. The median age of children with varicella was 4.4 years (range, 13 months to 7.6 years), and 19 of these children (76.0 percent) were boys (Table 1).

Overall, 17 cases of varicella were mild, and 8 cases were moderate or severe. No child had a severe complication of varicella or required hospitalization. As compared with unvaccinated children, those who had been vaccinated had milder disease, had new lesions on fewer days, had rash that crusted more quickly, missed fewer days of day care, and were less likely to have fever (Table 2).

The outbreak began and was centered in Building A, where 19 cases (76.0 percent) occurred. Of the six

TABLE 1. CHARACTERISTICS OF ALL CHILDREN AND CHILDREN IN BUILDING A WHO ATTENDED THE DAY-CARE CENTER FOR AT LEAST ONE WEEK DURING THE VARICELLA OUTBREAK PERIOD, DECEMBER 2000 THROUGH JANUARY 2001.*

CHARACTERISTIC	ENTIRE DAY-CARE CENTER (N=88)		BUILDING A (N=52)	
	CHILDREN WITH VARICELLA (N=25)	CHILDREN WITHOUT VARICELLA (N=63)	CHILDREN WITH VARICELLA (N=19)	CHILDREN WITHOUT VARICELLA (N=33)
Age at start of outbreak				
0–11 mo — no. (%)	0	4 (6.3)	0	0
12–23 mo — no. (%)	4 (16.0)	6 (9.5)	0	0
24–47 mo — no. (%)	5 (20.0)	24 (38.1)	3 (15.8)	4 (12.1)
48–96 mo — no. (%)	16 (64.0)	29 (46.0)	16 (84.2)	29 (87.9)
Median — mo	53	44	56	72
Range — mo	13–91	6–107	44–91	42–107
Male sex — no. (%)	19 (76.0)	42 (66.7)	13 (68.4)	19 (57.6)
Susceptibility to varicella at start of outbreak — no. (%)				
Age <12 mo	0	4 (6.3)	0	0
Age ≥12 mo				
Unvaccinated, susceptible	8 (32.0)	10 (15.9)	6 (31.6)	4 (12.1)
Vaccinated	17 (68.0)	32 (50.8)	13 (68.4)	14 (42.4)
Vaccination status unknown	0	1 (1.6)	0	0
History of varicella	0	16 (25.4)	0	15 (45.5)
Hours of day-care attendance/wk†				
Median	40	40	40	35
Range	15–50	6–50	15–50	6–50
Asthma — no. (%)	3 (12.0)	6 (9.5)	3 (15.8)	4 (12.1)
Coexisting conditions other than asthma — no. (%)	2 (8.0)	0	2 (10.5)	0

*Continuous enrollment in the day-care center was not a criterion for inclusion in this table.

†Data are for children without a history of varicella.

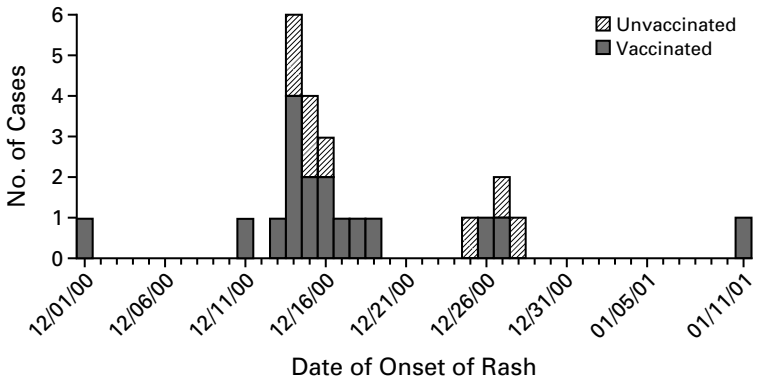

Figure 1. Cases of Varicella in a New Hampshire Day-Care Center in December 2000 and January 2001, According to the Vaccination Status of the Children and the Date of Onset of Rash.

TABLE 2. CHARACTERISTICS OF ILLNESS AMONG VACCINATED CHILDREN WITH VARICELLA AND UNVACCINATED CHILDREN WITH VARICELLA.

CHARACTERISTIC	VACCINATED CHILDREN (N=17)	UNVACCINATED CHILDREN (N=8)	P VALUE*
Severity of illness — no. (%)			
Mild	15 (88.2)	2 (25.0)	0.004
Moderate or severe	2 (11.8)	6 (75.0)	
Subjective assessment of illness — no. (%)			
Did not appear ill	10 (58.8)	1 (12.5)	0.04
Mildly to severely ill	7 (41.2)	7 (87.5)	
Person who made the diagnosis — no. (%)			
Health care provider	10 (58.8)	4 (50.0)	1.0
Other	7 (41.2)	4 (50.0)	
Presence of fever — no. (%)†			
Yes	3 (20.0)	7 (87.5)	0.006
No	12 (80.0)	1 (12.5)	
No. of days until no new lesions erupted			
Median	2	5	<0.001
Range	0–12	4–12	
No. of days until rash crusted fully			
Median	4	9	0.02
Range	0–20	5–12	
No. of days sick in bed			
Median	0	1	0.06
Range	0–2	0–4	
No. of days unable to play			
Median	0	1	0.20
Range	0–4	0–4	
No. of days of day care missed			
Median	3	5	0.04
Range	0–7	3–14	
No. of days parent or guardian missed work to care for child			
Median	1	4	0.27
Range	0–7	0–14	

*P values for severity of illness, subjective assessment of illness, person who made the diagnosis, and presence of fever were calculated by a two-sided Fisher's exact test; all other P values were calculated by an exact, two-sided Wilcoxon rank-sum test.

†Data were missing for two vaccinated children.

cases in children in Building B, three occurred within one incubation period after the index case in Building A, and two other cases were more likely to have resulted from secondary household transmission than transmission at the day-care center — evidence that little if any transmission occurred in Building B. Both cases presumed to have resulted from household transmission occurred in younger siblings of patients who attended day care in Building A, and in both cases, varicella developed 13 to 14 days after the onset of rash in the older sibling. In one family, transmission occurred between unvaccinated siblings, whereas in the other, it occurred between vaccinated siblings.

Vaccine Effectiveness

The cumulative attack rate among continuously enrolled, unvaccinated, susceptible children at least 12 months of age who had attended day care for at least one week was 85.7 percent (6 of 7) in Building A and 18.2 percent (2 of 11) in Building B. When corrected for transmission occurring outside of the building, the attack rate in Building B was 9.1 percent (1 of 11). The attack rate among vaccinated children in Building A was 48.0 percent (12 of 25). Vaccine effectiveness for children in Building A was 44.0 percent (95 percent confidence interval, 6.9 to 66.3 percent) against disease of any severity and 86.0 percent (95 percent confidence interval, 38.7 to 96.8 percent) against moderate-to-severe disease (which occurred in two vaccinated and four unvaccinated children in Building A).

Risk Factors for Vaccine Failure

Two continuous variables — time since vaccination and age at vaccination — were associated with the risk of vaccine failure (Table 3). Children vaccinated three or more years before the start of the outbreak had more than twice the risk of disease found among those vaccinated within three years before the outbreak (relative risk, 2.6 [95 percent confidence interval, 1.3 to 5.3]). Age at vaccination did not remain significantly associated with vaccine failure when it was dichotomized into vaccination at less than 14 months of age and vaccination at older ages ($P=0.59$).

Laboratory Analysis

Two cases were confirmed by laboratory testing, and the remainder were epidemiologically linked. Wild-type varicella was cultured from an unvaccinated child in Building A with an onset of rash on December 25, 2000, and wild-type varicella was detected by polymerase-chain-reaction analysis of a papule from the vaccinated child in Building B who had the last case in the outbreak.

Reliability of the Absence of a History of Varicella

Seven children who did not have varicella were reported by parents to be susceptible to it. All four whose parents agreed to serologic testing were seronegative, including the only child in Building A whose history suggested susceptibility but in whom varicella did not develop.

TABLE 3. RISK FACTORS FOR FAILURE OF VARICELLA VACCINE AMONG VACCINATED CHILDREN IN BUILDING A CONTINUOUSLY ENROLLED AND IN ATTENDANCE FOR AT LEAST ONE WEEK DURING THE VARICELLA OUTBREAK.

VARIABLE	CHILDREN WITH VARICELLA (N=12)	CHILDREN WITHOUT VARICELLA (N=13)	P VALUE*
Age at start of outbreak — mo			
Median	54.0	53.7	0.73
Mean	57.3	56.6	
Sex — no. (%)			
Male	8 (66.7)	7 (53.8)	0.69
Female	4 (33.3)	6 (46.2)	
Age at vaccination			
<14 mo — no. (%)	2 (16.7)	1 (7.7)	0.59
≥14 mo — no. (%)	10 (83.3)	12 (92.3)	
Median — mo	18.4	24.7	0.04
Mean — mo	21.8	32.2	
Time since vaccination			
<36 mo — no. (%)	6 (50.0)	12 (92.3)	0.03
≥36 mo — no. (%)	6 (50.0)	1 (7.7)	
Median — mo	35.7	29.0	0.02
Mean — mo	35.5	24.5	
Asthma — no. (%)	1 (8.3)	2 (15.4)	1.0

*P values for age at the start of the outbreak, median age at vaccination, and median time since vaccination were calculated by an exact, two-sided Wilcoxon rank-sum test. All other P values were calculated by a two-sided Fisher's exact test.

Storage and Handling of Vaccine

Periodic evaluation of the storage and handling of vaccine in the offices of vaccine providers, conducted by the state health department since the licensure of the vaccine, did not identify substantial problems. The vaccine is distributed directly from the manufacturer to the clinics and offices that provide vaccination without reliance on redistribution centers.

DISCUSSION

In this outbreak, the effectiveness of the varicella vaccine was 44 percent against disease of any severity and 86 percent against moderate and severe disease — significantly lower than that found in any previous investigation. We found an increased risk of vaccine failure among children vaccinated three or more years previously. The index patient was a healthy vaccinated child who infected more than 50 percent of susceptible classmates, indicating that breakthrough disease can be highly infectious.

The reasons for the poor performance of the vaccine are not apparent. The thermolability of the vaccine raised concern about lapses in vaccine storage and

handling, although no substantial deficiencies were detected over time or after the outbreak was recognized. Furthermore, we found no clustering of breakthrough cases according to the lot number of the vaccine used, the year of vaccination, the clinic, or the medical provider that might suggest the use of an ineffective lot of vaccine or problems with storage, handling, or administration.

Univariate analysis identified time since vaccination as a risk factor for vaccine failure. Children vaccinated three or more years before the start of the outbreak had a risk of breakthrough disease that was more than twice as high as that among children vaccinated more recently. A younger age at vaccination (less than 14 months), which has previously been identified as a risk factor,[5,6] was not associated with an increased risk of vaccine failure, nor did we detect an association with asthma or other coexisting conditions. However, in Building A, only three children were vaccinated at less than 14 months of age, three children with varicella had asthma, and two children with varicella had coexisting conditions (one had IgA deficiency, and the other had epilepsy).

We used data from Building A to estimate vaccine effectiveness and determine risk factors for vaccine failure. The cumulative attack rate among unvaccinated, susceptible children 12 months of age or older was approximately 86 percent in Building A and 9 percent in Building B. The low attack rate in Building B suggests that most children in this building were never exposed to varicella. Since the calculation of vaccine effectiveness relies on an assumption of equal exposure to disease, data from children in Building B were excluded from the calculations. The cases in children in Building B probably resulted from contact that occurred outside the classroom or from household exposure.

This outbreak began with disease in a vaccinated child who infected more than half his classmates who had no history of varicella. His attendance at day care for two days before the onset of rash and only brief attendance on the morning on which his rash erupted suggest that transmission occurred by airborne spread. Our findings also suggest that it is not possible to identify in advance persons who could be highly infectious were they to have breakthrough disease, a fact of particular concern in hospitals and other settings that rely on vaccine-derived immunity to protect against the acquisition and transmission of varicella. It is possible that vaccinated persons in whom a large number of vesicular lesions develop when they are exposed to a patient with an infectious case of varicella or herpes zoster may be more infectious than persons who have nonvesicular lesions or fewer lesions overall, although this question requires further study.

There are a number of limitations to our study. This outbreak and others that come to the attention of public health officials may represent extreme situations and result in underestimates of the effectiveness of the vaccine.[23] Even so, the upper confidence limit of our estimate was below the lower limit of the expected range of effectiveness for varicella vaccine. We relied on reports of rash by parents or physicians for diagnosis in most cases, a method that may have resulted in an overestimate or underestimate of the effectiveness of the vaccine. Incorrect diagnosis of conditions commonly mistaken for breakthrough disease (such as insect bites or enteroviral infections) could have falsely lowered the estimate of vaccine effectiveness, although these conditions occur infrequently in midwinter. Subtle presentations of breakthrough disease that were not clinically recognized could have led to a false elevation of the estimate of vaccine effectiveness. Finally, the small number of children in the day-care center limited our ability to explore the independent effects of the time since vaccination and the age at vaccination in multivariate analyses.

Although policy cannot be established on the basis of one outbreak, the findings in this investigation raise concern that the current vaccination strategy may not protect all children adequately. Further investigations are needed to define more clearly the range of effectiveness of the vaccine and risk factors for vaccine failure. In a number of prelicensure studies, persons who did not have an adequate immune response after vaccination were revaccinated,[13] excluded from the analysis of vaccine efficacy,[10,14] or analyzed separately,[11] potentially inflating the estimate by the removal of persons who had primary vaccine failure.

Although the vaccine provided suboptimal protection against varicella in this outbreak, it provided robust protection against moderate and severe varicella and has reduced the incidence of varicella dramatically in the United States.[14] Given the approximately 11,000 hospitalizations[24] and 100 deaths[25] due to varicella that occurred annually in the era before vaccination, vaccination remains the most effective strategy for protecting children and adults against illness and death due to varicella.

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