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Chickenpox Outbreak in a Highly Vaccinated School Population

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ABSTRACT. *Objective.* **We investigated a chickenpox outbreak that started in an Oregon elementary school in October 2001, after public schools began phasing in a varicella vaccination requirement for enrollment. We sought to determine the rate of varicella vaccination and effectiveness and risk factors for breakthrough disease.**

Methods. **A chickenpox case was defined as an acute maculopapulovesicular rash without other explanation occurring from October 30, 2001 through January 27, 2002 in a student without a prior history of chickenpox. We reviewed varicella vaccination records and history of prior chickenpox, and we calculated vaccine effectiveness. We evaluated the effects of age, gender, age at vaccination, and time since vaccination on risk of breakthrough disease (ie, chickenpox occurring >42 days after vaccination).**

Results. **Of 422 students, 218 (52%) had no prior chickenpox. Of these, 211 (97%) had been vaccinated before the outbreak. Twenty-one cases occurred in 9 of 16 classrooms. In these 9 classrooms, 18 of 152 (12%) vaccinated students developed chickenpox, compared with 3 of 7 (43%) unvaccinated students. Vaccine effectiveness was 72% (95% confidence interval: 3%–87%). Students vaccinated >5 years before the outbreak were 6.7 times (95% confidence interval: 2.2–22.9) as likely to develop breakthrough disease as those vaccinated ≤5 years before the outbreak (15 of 65 [23%] vs 3 of 87 [3%]).**

Conclusions. **A chickenpox outbreak occurred in a school in which 97% of students without a prior history of chickenpox were vaccinated. Students vaccinated >5 years before the outbreak were at risk for breakthrough disease. Booster vaccination may deserve additional consideration.** ***Pediatrics*** **2004;113:455–459;** ***chickenpox, chickenpox vaccine, disease outbreaks, risk factors.***

ABBREVIATIONS. MMR, measles, mumps, and rubella; CI, confidence interval.

Before the 1995 approval of the live, attenuated varicella vaccine in the United States, chickenpox was a nearly universal disease of childhood. Since then, several reports of chickenpox outbreaks occurring among children in day care and elementary school have been published.[1–6] Outbreaks of vaccine-preventable disease occur because of primary vaccine failure (ie, when vaccine fails to induce a protective immune response from the outset), secondary vaccine failure (ie, when vaccine-induced protective immunity is subsequently lost), failure to vaccinate, or loss of vaccine potency.[7,8] Previous investigations of breakthrough chickenpox after vaccine licensure have identified possible risk factors for primary vaccine failure, including vaccination at <14 months[5] and ≤15 months[4] of age; nonsimultaneous administration of the varicella vaccine and the measles, mumps, and rubella (MMR) vaccine within 30 days of each other;[9] and history of asthma.[1] Evidence for secondary vaccine failure was provided in a recent outbreak investigation that identified longer time since vaccination as a risk for breakthrough disease.[6] Varicella vaccine effectiveness in outbreaks has ranged from 44% to 100%, and the rate of vaccination among eligible children without a history of chickenpox in these outbreaks has ranged from 30% to 87%.[1–6] Because varicella is highly contagious, high rates of vaccination would likely be necessary to eliminate transmission.

In September 2000, Oregon began to phase in a requirement for varicella vaccination of children attending day care, kindergarten, and seventh grade who had no history of chickenpox. On October 30, 2001, a chickenpox outbreak started among students in an Oregon elementary school (grades kindergarten through 6), with several cases occurring in vaccinated students. Because of the immunization requirement, the rate of vaccination in this population was expected to be high. The outbreak was investigated to determine the rate of vaccination and vaccine effectiveness and to evaluate risk factors associated with breakthrough disease.

METHODS

Varicella Immunity Status

To determine each student's immunity to varicella at the beginning of the outbreak, we verified vaccination dates using immunization records collected by the school district. We also sent a questionnaire (survey A) to each student's parents to determine whether the student had a history of chickenpox or varicella vaccination before the outbreak and the dates (month and year) of these events; nonrespondents were telephoned. If a vaccination date could not be provided by the parent or school district record, we contacted the students' medical clinics for the information. Vaccination dates for case students were obtained by medical clinic record review.

Students were classified as "vaccinated" if they had received varicella vaccination before October 30, 2001 or "susceptible" if they had neither varicella vaccination nor a history of chickenpox before this date. Students were excluded from the analysis if they

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were vaccinated during the outbreak, because their immune status could not be classified reliably.

Case Definition and Case Finding

A chickenpox case was defined as an acute maculopapulovesicular rash without other explanation occurring from October 30, 2001 through January 27, 2002 in a student without a prior history of chickenpox. Breakthrough disease was defined as chickenpox with onset >42 days after vaccination, because generalized rashes appearing after 42 days are usually due to wild-type virus.[10,11] While school was in session, school staff notified investigators when a student was absent or sent home with a chickenpox rash. Diagnosis was made on the basis of parental or physician report of disease. A questionnaire (survey B) about chickenpox occurrence during the 2-week winter break and the week after the break (December 21, 2001 through January 11, 2002) was sent to each child's parents; nonrespondents were telephoned.

In addition, parents of case students were telephoned to obtain rash onset dates; numbers of lesions (<50, 50–99, 100–249, 250–499, or ≥500); rash duration (from rash onset until all lesions were dry and crusted); other signs and symptoms (eg, fever, headache, malaise, and anorexia); history of comorbidities (eg, asthma) and regular medicine use; and information about chickenpox-related hospitalizations or complications (eg, cellulitis, pneumonia, or encephalitis).

Vaccine Effectiveness

Because students in classrooms without a case might never have been exposed, we calculated vaccine effectiveness for students without a prior history of chickenpox in classrooms attended by case students ("affected classrooms"). Vaccine effectiveness was calculated by using the equation (1 − [attack rate among vaccinated students/attack rate among susceptible students]) × 100%.

Risk Factors for Breakthrough Chickenpox

We evaluated potential risk factors for breakthrough disease among vaccinated students without a prior history of chickenpox in affected classrooms, including age at the start of the outbreak, gender, years since vaccination calculated from the start of the outbreak, and age at vaccination. For case students only, we determined whether the MMR vaccine and varicella vaccine had been administered within 30 days of, but not simultaneously with, each other by reviewing school district or medical clinic vaccine records. History of asthma or medication use provided by the parents of case students was also reviewed. From medical clinic records, we determined whether vaccinated case students shared common vaccine lot numbers.

Significance of univariate analyses was assessed by using Fisher's exact test, and P values ≤0.05 were considered significant. Using exact procedures, 95% confidence intervals (CIs) were derived (StatXact 5, Cytel Software Corporation, Cambridge, MA).[12]

This public health investigation was undertaken to control a communicable disease outbreak and, as such, was not research and not subject to approval by an institutional review board.

RESULTS

Outbreak Setting and Immune Status

During the outbreak, 422 students in 16 classrooms attended school. School district immunization records documented a history of varicella vaccination before the outbreak for 156 (37%) of the students, and information about vaccination and prior varicella illness was obtained on the remaining 266 (63%) students through survey A (or through telephone follow-up), with vaccination dates verified through medical clinics if they were not provided by the parents or school district.

Of the 422 students, 8 (2%) were vaccinated during the outbreak and excluded from the analysis. Of the remaining 414 students, 187 (45%) had a prior history of chickenpox, 7 (2%) had had both chickenpox and varicella vaccination, and 2 (<1%) had an unknown history (Fig 1). The remaining 218 students had no prior history of chickenpox; these students were aged 5 to 12 years (median: 7 years), and 116 (53%) were male. Of these 218 students, 211 (97%) had been vaccinated before the outbreak. The vaccinated students had been immunized a median of 4.8 years before the outbreak.

Case Descriptions

During the outbreak period, 21 cases of chickenpox occurred. Case students were aged 5 to 11 years (median: 7 years); 14 (67%) were male. Cases occurred in all grades (kindergarten through a com-

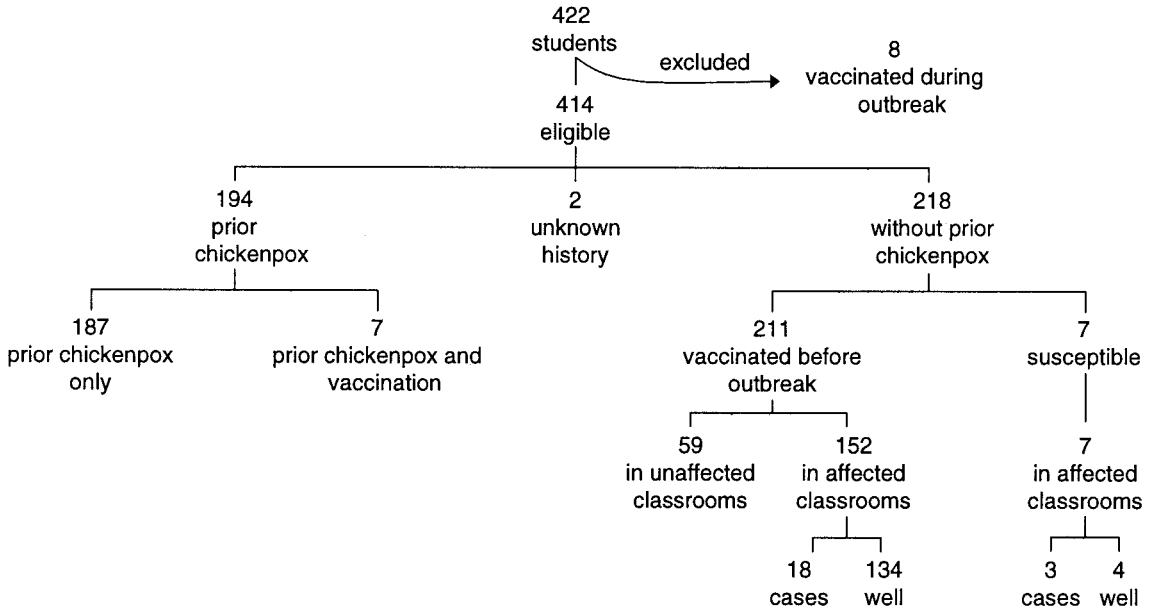

Fig 1. Classification of students in an Oregon elementary school with a chickenpox outbreak: 2001. Students were classified as susceptible if they had neither varicella vaccination nor a history of chickenpox before October 30, 2001.

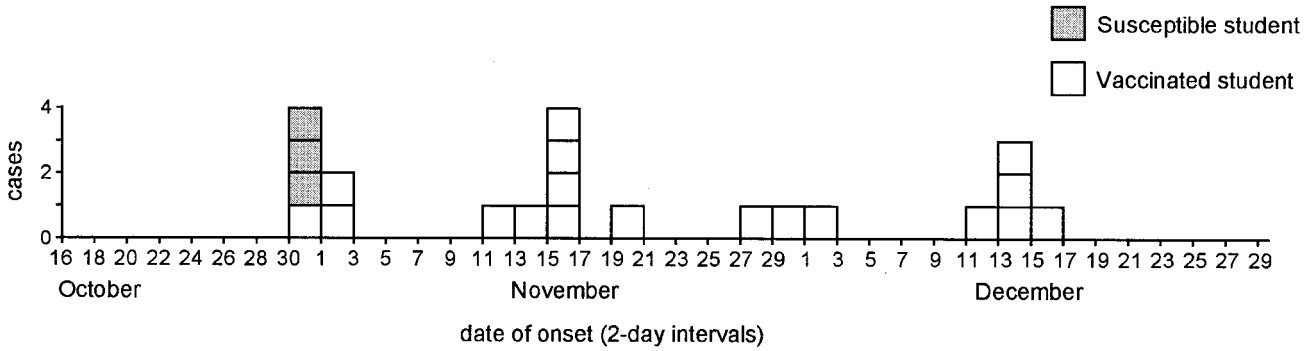

Fig 2. Onset of chickenpox cases in an elementary school by 2-day intervals (Oregon, 2001). Students were classified as vaccinated if they had received varicella vaccination before October 30, 2001 or susceptible if they had neither varicella vaccination nor a history of chickenpox before this date.

bined fifth/sixth grade); 9 of 16 classrooms were affected. Eighteen cases (86%) occurred in previously vaccinated students (breakthrough cases) and 3 cases (14%) in susceptible students. Three vaccinated case students were exposed to their siblings, also vaccinated case students, and developed chickenpox within 1 incubation period.

The first 3 recognized cases occurred in susceptible students; their symptoms were first observed on October 30 (Fig 2). The source of these initial cases was not identified. All subsequent cases were among vaccinated students and occurred in 3 waves at ~2-week intervals. Each wave included students from multiple classrooms. The last case occurred on December 16.

Parents of 214 (51%) of the students returned survey B regarding occurrence of chickenpox during and 1 week after winter break; the remaining 208 (49%) were telephoned. Parents reported rashes in 2 students during the winter break, but they each had a prior history of chickenpox and therefore did not meet the case definition. In addition, 2 vaccinated students were reported to have rashes with onset dates of January 31 and February 11, 2002. These occurred later than 2 incubation periods after the last case and therefore were not included as cases in this outbreak.

All 3 susceptible students, but only 10 of 18 vaccinated students, experienced fever. The median duration of illness was 6 days in vaccinated students and 7 days in susceptible students. Fewer than 50 lesions occurred in 2 of 3 susceptible students and 11 of 18 vaccinated students; the remainder experienced 50 to <500 lesions. One vaccinated case student, who had a history of asthma and inhaled steroid use, developed a bacterial skin superinfection; no students were hospitalized.

Vaccine Effectiveness

Vaccine effectiveness was calculated for the 159 students who were in the 9 affected classrooms and had no prior history of chickenpox. Of these students, 152 (96%) had been vaccinated before the outbreak, and 7 (4%) were susceptible. The attack rate among vaccinated students was 12% (n = 18), and the attack rate among susceptible students was 43% (n = 3); vaccine effectiveness was 72% (95% CI: 3%–87%).

Risk Factors for Breakthrough Chickenpox

Among vaccinated students who had no prior history of chickenpox in affected classrooms, attack rates were dramatically increased among students vaccinated >5 years before the start of the outbreak (Table 1). Therefore, we chose this 5-year point for additional comparison. Cases occurred in 15 of 65 (23%) students vaccinated >5 years before the outbreak, and in 3 of 87 (3%) students vaccinated ≤5 years before the outbreak (relative risk: 6.7; 95% CI: 2.2–22.9).

Early age at vaccination (≤15 months) was not associated with the development of chickenpox. Of 36 students vaccinated at ≤15 months of age, 5 (14%) contracted chickenpox, compared with 13 of 116 (11%) vaccinated at >15 months of age (P = .77). The risk of chickenpox among vaccinated students did not vary significantly by age at the start of the outbreak or by gender.

All the vaccinated case students had received the varicella vaccine and the MMR vaccine either simultaneously or >30 days apart. Only 1 vaccinated case student had a history of asthma and intermittent inhaled steroid use. The 18 vaccinated case students had been vaccinated at 8 different medical clinics with vaccine from 15 different lots. The 15 case students vaccinated >5 years before the outbreak had been vaccinated at 7 different medical clinics.

TABLE 1. Chickenpox Attack Rate by Years Since Vaccination: Oregon Elementary School Outbreak

Years Since Vaccination	Cases	Total Students	Attack Rate, %
≤2	1	28	3.6
>2–3	0	12	0
>3–4	1	15	6.7
>4–5	1	32	3.1
>5–6	9	39	23.1
>6	6	26	23.1
Total	18	134	12

The table includes only vaccinated students without a prior history of chickenpox in classrooms attended by case students.

Outbreak Control

Students with chickenpox were excluded from school until lesions had crusted, and all susceptible students were offered vaccine. Eight students were vaccinated after the outbreak began (7 without prior chickenpox history and 1 with an unknown history). Seven of the 8 students remained free of chickenpox. The other student was vaccinated 3 days after his susceptible sibling developed a chickenpox rash with 250 to 499 lesions. He developed chickenpox 9 days after vaccination.

DISCUSSION

A chickenpox outbreak erupted and propagated for 3 subsequent generations in a school despite vaccination of nearly all (97%) students without a prior history of chickenpox—the highest such rate of vaccination documented in an outbreak to date.[1–6] Because the rate of vaccination was so high, disease transmission was probably facilitated by vaccine failure. Theoretically, a rate of vaccination of >97% might eliminate transmission, but such a rate would be difficult to achieve. Therefore, if the goal is to eliminate transmission, then improvement of vaccine effectiveness or reduction of vaccine failure is necessary. In this outbreak, effectiveness was 72%, similar to that seen in most other postlicensure investigations of breakthrough chickenpox,[1–5,13] but 1 other investigation found effectiveness to be as low as 44%.[6]

All vaccines have an intrinsic primary failure rate even in the setting of clinical trials.[7] In this investigation, we have no reason to believe that primary vaccine failure was greater than expected. Vaccination at ≤15 months of age was not related to disease in this outbreak; no vaccinated case students had nonsimultaneous administration of MMR vaccine and varicella vaccine <30 days apart, and only 1 vaccinated case student had a history of asthma and steroid use. These factors had been implicated in vaccine failure in other investigations.[1,4,5,9] In addition, in the current outbreak, case students had been vaccinated in multiple clinics with a variety of vaccine lots, making it less likely that a "bad lot," improper vaccine storage and handling, or loss of vaccine potency would explain the degree of breakthrough disease that we observed.

Students vaccinated >5 years before the outbreak had a higher incidence of breakthrough disease. In 1 other outbreak investigation, children vaccinated ≥3 years before the outbreak were at higher risk of breakthrough disease, compared with those vaccinated more recently.[6] In at least 1 clinical trial in the United States, the number of breakthrough cases increased between the fourth and sixth years after immunization but did not increase thereafter.[11] Our finding is suggestive of waning immunity, although this cannot be proven in the absence of immunologic testing. The likelihood of breakthrough disease has been shown to correlate inversely with 6-week postvaccination antibody titers,[14] and thus an alternate explanation to our finding is that risk of breakthrough disease may have been related to a limited initial immune response. However, there is nothing to explain why those vaccinated >5 years before the outbreak would be more likely to have developed a limited initial immune response.

Although immunity has been shown to endure for 6 to 10 years after varicella vaccination in clinical trials in the United States (and for up to 20 years in Japan), these studies were conducted in the setting of well-documented subsequent exposure of subjects to natural chickenpox, which may have resulted in immunologic boosting.[15–20] According to the National Immunization Survey, the rate of varicella vaccination of 19- to 35-month-old Oregon children (unadjusted for history of varicella illness) increased from 29% in 1997 to 74% in 2001,[21] and circulation of varicella zoster virus therefore has presumably decreased. Immunologic boosting, which may occur through exposure to wild-type virus,[22] may decrease as the rate of vaccination increases.

Immunologic boosting through a second dose of varicella vaccination for children deserves additional consideration. Watson et al[23] demonstrated that a second dose of varicella vaccine in children induced stronger humoral and cell-mediated immune responses than did a single dose. A second vaccination should decrease the rates of both primary and secondary vaccine failure, if present.[24]

This investigation had some limitations. To gather information expeditiously while the outbreak was occurring, case finding and data collection relied on multiple sources. Chickenpox histories were not obtained for all vaccinated students, and thus a few vaccinated students who also had a prior history of chickenpox may have been included in the calculation of vaccine effectiveness, resulting in an overestimation of vaccine effectiveness. Reliance on school staff to notify us of potential cases may have led to incomplete case ascertainment. Failure of staff or parents to recognize mild cases of breakthrough disease may also have led to an overestimation of vaccine effectiveness. On the other hand, if the case definition was not sufficiently specific, with other unexplained rashes misclassified as chickenpox and presumably occurring at equivalent rates among the vaccinated and unvaccinated populations, vaccine effectiveness would have been underestimated.[25]

Inclusion of only affected classrooms in the calculation of vaccine effectiveness may have led to an underestimate if the vaccine was more protective in the unaffected classrooms. However, we chose to include only affected classrooms in our calculation of vaccine effectiveness because we could not be certain that exposure to the virus had taken place outside of those classrooms. Because there were no susceptible students in unaffected classrooms in this outbreak, had we included all classrooms in our analysis, susceptible students would have had a higher likelihood of exposure relative to vaccinated students, and thus vaccine efficacy would have been overestimated.[25]

Although questions remain regarding the optimal number of doses, several benefits of varicella vaccination are noteworthy. In areas in which surveillance for chickenpox after vaccine licensure has been conducted, varicella vaccination has been associated

with dramatic reductions in chickenpox cases.[26] Parents should be reminded that, although uncommon, breakthrough cases are expected to occur but are usually milder than wild-type chickenpox. In this outbreak, vaccine was effective in preventing disease, and most case students had <50 lesions. Although differences in disease severity between vaccinated and susceptible students could not be examined statistically due to small numbers, other studies have shown that varicella vaccine is effective in preventing moderate to severe disease.[1–3,5,6,13] For these reasons, the routine use of varicella vaccine should be encouraged as recommended by the Advisory Committee on Immunization Practices.[27,28]

If the interval between vaccination and exposure is significantly associated with breakthrough disease in future outbreak investigations, routine booster vaccination for children might be warranted. Studies regarding the effectiveness and cost-benefit of such a strategy would still be needed.[24] Since this outbreak, we have received reports of several other chickenpox outbreaks in Oregon schools. We have initiated limited school surveillance for outbreaks of chickenpox to follow its changing epidemiology in the vaccine era.

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