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Second Varicella Infections: Are They More Common Than Previously Thought?

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ABSTRACT. *Objective.* **To describe the epidemiology and clinical characteristics of varicella reinfections reported to a surveillance project.**

Methods. **We investigated varicella cases reported to a surveillance project between January 1, 1995, and December 31, 1999—with more extensive investigation of cases reporting previous varicella with onset between January 1, 1998, and September 30, 1998—to provide a more detailed description of first and second varicella infections. A simple decision tree was used to assess the likelihood that reported first and second infections were varicella.**

Results. **Among varicella cases reported to the surveillance project, 4.5% of cases in 1995 and 13.3% of cases in 1999 reported previous varicella. More than 95% of first infections were physician diagnosed, epidemiologically linked to another case, or had a rash description consistent with varicella; the same was true for reported second infections. People who reported reinfections were generally healthy. There was a family history of repeat infections in 45% of people who reported reinfections.**

Conclusions. **Clinical varicella reinfections may occur more commonly than previously thought. Additional studies of the predictive value of a positive varicella history and laboratory studies of reported reinfections are indicated to guide varicella vaccination policy.** ***Pediatrics* 2002;109:1068–1073; *varicella, reinfection, surveillance, vaccination, immunity.***

ABBREVIATION. VZV, varicella-zoster virus.

The assumption that natural varicella confers lifelong immunity plays a key role in current US vaccination policy. A history of varicella, a rash illness easily recognized by the lay public, is considered a reliable indicator of immunity.[1,2] Varicella vaccine is recommended for all susceptible people 12 months of age or older. Currently, susceptibility is most commonly assessed on the basis of disease history, and people who report a history of varicella are not offered the vaccine.

Although cases of clinical reinfection with varicella have been reported in immunocompetent individuals,[3–6] such cases are thought to be rare. There are no population-based data on the frequency of reported second infections with varicella. A community-wide varicella active surveillance project provided the opportunity to investigate reported varicella reinfections. We describe the epidemiology and clinical characteristics of reported first and second varicella infections compared with reported "single-episode" infections and discuss the implications of these findings for varicella screening and vaccination programs.

CASE REPORTS

Patient 1

A healthy female experienced her first case of varicella at 5 years of age, developing a fever and a generalized, pruritic, vesicular rash of >500 lesions. The lesions appeared in "crops" and crusted over. A health care provider diagnosed the illness as varicella. Varicella cases were occurring at the child's school. The patient was moderately ill and reportedly missed 10 days of school. The patient's 4-year-old sister developed varicella approximately 14 days later. Eight years later, at 13 years of age, she experienced her second episode of varicella, 13 days after exposure to her 7-year-old sister, who contracted varicella after exposure at school. Two other siblings also developed varicella within 1 day of the adolescent's rash onset. Again she experienced a fever and >500 pruritic vesicular lesions over her face and trunk, which appeared in crops and crusted over. Her parents diagnosed the illness as varicella, and she was not seen by a health care provider. No school days were missed because the case occurred during summer break.

Patient 2

A healthy boy developed his first case of varicella at 2 years of age. He had a fever accompanied by a generalized, pruritic rash of >500 vesicular lesions. The lesions appeared in crops and crusted over. The case was diagnosed by his physician in the office. He had been exposed to a child with varicella in the neighborhood. Ten years later, he developed his second episode of varicella at 12 years of age, 15 days after exposure to his 5-year-old sister. He developed a temperature of 102°F and between 50 and 500 vesicular lesions, primarily spread over his face and trunk. The lesions appeared in crops and were pruritic and crusted over. His parents consulted with their family physician by telephone, and a diagnosis of varicella was made on the basis of the parents' account. He missed 6 days of school during the second episode.

METHODS

Under a cooperative agreement between the Centers for Disease Control and Prevention and the Los Angeles County Health Department of Health Services, active surveillance for varicella

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has been conducted in Antelope Valley, California, since January 1995. Antelope Valley is a health services district in eastern Los Angeles County; in 1995, the population was 303 624.

The data collection methods of the surveillance system have been previously described.[7] Briefly, varicella cases are reported every 2 weeks from private and public schools, child care centers and preschools, health care providers (private physicians, hospitals, emergency departments, and public health clinics), employers with ≥500 employees, correctional facilities, and the community. A case of varicella is defined as an illness characterized by acute onset of a diffuse (generalized) papulovesicular rash without other known cause.[8] For all cases that met this definition, demographic and clinical variables and a history of a previous varicella infection are collected using a standardized case interview.

All cases reported between January 1, 1995, and December 31, 1999, were investigated, and the patients were asked whether they had experienced an earlier episode of varicella. We used these cases to describe the frequency of reports of previous varicella infections. Patients who reported current infection between January 1, 1998, and September 30, 1998, and who reported a previous varicella infection were contacted and reinterviewed about the previous infection, including age, source of infection, preexisting medical conditions, diagnosis by a health care provider, use of medications before onset of varicella, and presence of fever. For those with only a single reported infection, all data were obtained from the standard case investigation form. We compared the clinical and epidemiologic characteristics of the patients who reported 2 infections with those who reported only single infections. We also examined the above characteristics of the first and second infections among those who reported 2 infections.

We also collected additional information that is not routinely collected on the surveillance case investigation form for all episodes of varicella infections, including evidence of household or other close exposures or transmission, a history of multiple varicella infections in family members and detailed rash description including features characteristic of varicella (pruritus, vesicles, crusting, lesions arising in crops, and generalized rash), and features not characteristic of varicella (gradual fading of rash, peeling, localized or 1-sided rash).

We defined preexisting conditions reported before the varicella infection into 3 groups: high risk, defined as those immunocompromising or other conditions for which the Advisory Committee on Immunization Practices does not recommend varicella vaccination because of risk of severe varicella disease in the vaccine recipient; "other" preexisting conditions; and no preexisting conditions.

We used SAS statistical software, version 6.12 (SAS Institute, Cary, NC), to calculate differences in proportions using χ^2 or Fisher exact tests of association. Because severity of varicella is age related, we stratified these analyses by age at rash onset. We used the following hierarchy to classify reported infections as varicella: 1) health care provider diagnosis, 2) reported transmission in the household or in a close nonhousehold contact approximately 21 days before or after the occurrence of an infection (ie, an epidemiologic link), or 3) report of a pruritic rash with vesicular lesions that crusted over (most characteristic of varicella). To assess whether the second reported varicella infection was herpes zoster, we examined the clinical characteristics of the rash, such as localized and/or dermatomal distribution, and the proportion that were diagnosed by a health care provider.

RESULTS

Between January 1, 1995, and December 31, 1999, 9947 cases of varicella reported to the Antelope Valley surveillance project met the case definition. As the number of cases declined, cases among individuals who reported previous episodes declined as well, but the proportion of individuals who reported a previous varicella infection increased from 4.5% in 1995 to 13.3% in 1999 (Table 1). Of the 1472 cases with rash onset during the study period, 138 (9.5%) indicated a history of varicella, and 98 (71%) were successfully interviewed regarding their first infection. None of the individuals with repeat infections had a history of receipt of varicella vaccine, compared with 4.6% of the single-infection group.

TABLE 1. Number and Percentage of Individuals With Varicella Who Reported Previous Varicella Infections by Year, 1995 to 1999, Antelope Valley, California

Year	Verified Varicella Cases (*N*)	Individuals with Varicella Who Reported a Previous Infection (*N* [%])
1995	2934	132 (4.5)
1996	2422	121 (5.0)
1997	2219	184 (8.3)
1998	1785	169 (9.5)
1999	587	78 (13.3)

Ninety-seven percent of reported first and second infections were classified as varicella on the basis of our criteria. Among those with 2 infections, participants recalled that 70.4% of first infections and 82.3% of second infections were linked either to a case in another household member or to a close friend. Of the first infections, 60.2% were diagnosed by a health care provider and 84.6% of those without a health care provider diagnosis had an epidemiologic link, whereas 3 of the remaining 6 cases had a typical varicella rash (Fig 1A). Among second infections, fewer (35.7%) were diagnosed by a health care provider; however, 88.9% of the infections not diagnosed by a health care provider had an epidemiologic link. Of the 7 remaining cases, 4 had a typical varicella rash (Fig 1B).

Those with 2 reported infections were younger at the first infection (median age: 3 years) and older at the second infection (median age: 8 years) than those who reported no previous varicella infection (median age: 6 years). On average, 7.5 years elapsed between the first and second infections. Among those with 2 infections, 66.3% had their first infection before the age of 5 years and 11.2% had their infection before the age of 1 year. In contrast, of those with no previous infection, 31.4% had varicella before age 5 and 4.3% had varicella before age 1. Although a higher proportion of those who reported 2 infections versus 1 were male, non-Hispanic, and white, there were no statistically significant differences between the 2 groups with regard to age, race, or ethnicity (Table 2).

None of the individuals who reported repeat infections had any preexisting immunocompromising conditions, compared with 3 among individuals with no previous infection. One child (1.9% of 1- to 4-year-olds) with repeat infections had a medical condition requiring immunosuppressive medications before his infections, as compared with 4 (1.1%) among children of the same age with no previous infection. The proportions of individuals with other medical conditions (the most common of which was asthma) did not differ significantly before first and second infections when compared with the single-infection group, except that those aged 1 to 4 at first infection reported fewer other conditions (3 [5.6%]) compared with the single-infection group of the same age (50 [13.8%]; $P = .04$).

Forty-four (44.9%) of those with 2 infections re-

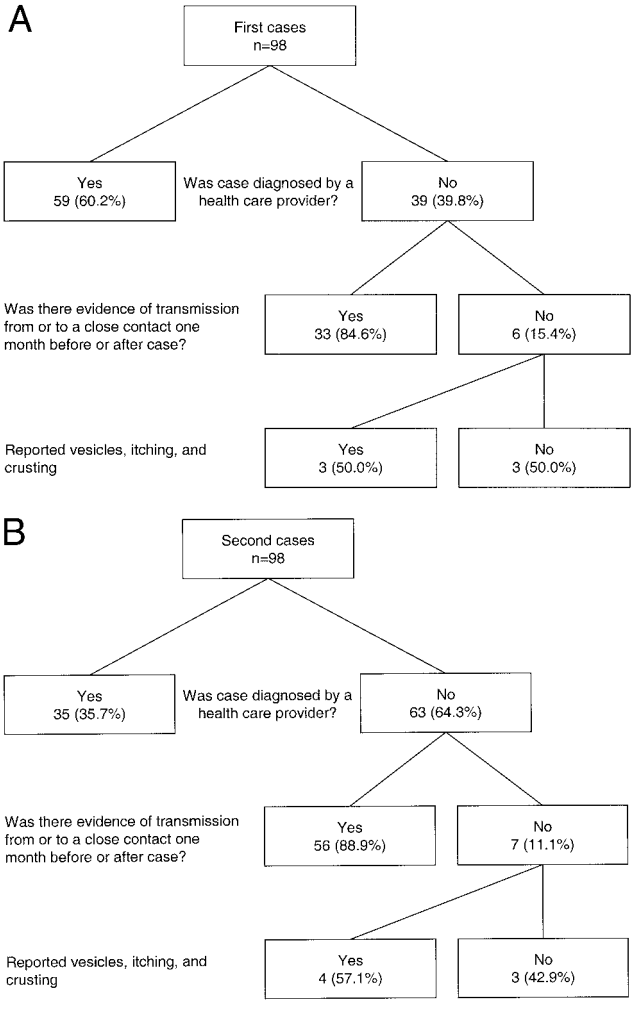

Fig 1. Tree diagram of hierarchy for deciding the likelihood of varicella, first-reported cases (n = 98).

ported having another family member with repeat varicella infections. Of these, 34 (77.3%) reported 1 other family member with repeat infections and 10 (22.7%) reported 2 other members with repeat infections. We examined rash characteristics for first and second reported cases. Some of these details were not well recalled for the first infection (Table 3); however, >50% of first infections and >60% of second infections had the following rash features typical of varicella: presence of vesicles, crusting, pruritus, fever, a rash most concentrated on face/trunk, and a rash appearing in "crops." Of the first infections, 2 (2.0%) reported a localized rash and 2 (2.0%) reported a rash on 1 side of the body only. Of the second infections, 7 (7.1%) reported a localized rash and 5 (5.1%) reported a rash on 1 side of the body, which might indicate herpes zoster. However, for none of these second cases was it reported that the rash was both localized and on 1 side, and 4 were seen by a health care provider and diagnosed as varicella. We also examined the data for the 26 (26.5%) individuals who did not report vesicular lesions in their first episode and found that 15 (57.7%) were diagnosed as varicella by a health care provider and 20 (76.9%) were epidemiologically linked to another case of varicella.

First infections tended to be mild, especially among children who had onset of their first infection before 5 years of age (Table 4), and there was no pattern of second infections being more severe than single infections except among individuals older than 9 years. Of those who reported 2 infections, few reported a second infection before 5 years of age. None of the individuals with 2 infections was hospitalized (at either infection), and 11 (11.2%) reported 16 complications requiring a health care provider visit. The most frequently reported complications were pharyngitis, otitis media, severe headache, and vomiting. The complication rate among those with only 1 infection was similar; 4 (0.3%) individuals in the single-infection group were hospitalized and 130 (9.8%) had complications prompting a health care provider visit. The most frequently reported complications in this group were severe headache, otitis media, and infected lesions.

DISCUSSION

Our study provides the first population-based data on the frequency of reported clinical varicella reinfections and suggests that reinfections may occur more commonly than previously recognized. The surveillance project has also noted individuals with more than 2 reported infections of varicella, but these were not interviewed for this study. In 1998, 5 individuals reported 3 infections of varicella, 2 individuals reported 4 cases, and 1 individual reported a history of 5 infections of varicella. We concentrated our research on the more commonly occurring 2-case history. Individuals with 2 infections were generally healthy, both first and second infections were clinically and epidemiologically consistent with varicella, and second infections did not fit the clinical characteristics of herpes zoster. As varicella cases have declined in this community secondary to implementation of the vaccination program,[7] individuals with a previous reported infection constitute a greater proportion of all reported cases.

Our data suggest several possible risk factors for the occurrence of clinical varicella reinfections, including young age (younger than 12 months), having mild initial first infections, and genetic factors, which all may affect the immune response to the first infection. Early varicella infections, particularly during the first year of life, may not produce an adequate memory cell response, which may predispose a person to either a second infection or, as has been previously described, reactivation of varicella-zoster virus (VZV) as herpes zoster.[9] Our study's finding of repeated infections in family members of individuals with 2 episodes of varicella supports previous suggestions that genetic factors may be important in the development of a protective immune response to the primary infection of this herpesvirus.[4]

It is widely recognized that subclinical varicella reinfections occur in response to exposures to VZV.[10] Varicella clinical reinfections among healthy children and adults have also been previously described, although not on a population basis. Among children, laboratory-confirmed varicella infections have been described in immunocompetent children who had a

Rare de faire une 2ème varicelle entre 19 et 29 ans (2%) puis petit pics entre 30-48 ans (11%)

TABLE 2. Age at Episode 1 and Episode 2 of Varicella (n = 98) and Age of Individuals Who Reported No History of Varicella (n = 1334) and Demographic Characteristics, Antelope Valley, California, January 1 to September 30, 1998

	First Episode (N [%])	Second Episode (N [%])	No Previous Varicella (N [%])
Age group (y)			
<1	11 (11.2)*	0 (0)	57 (4.3)
1–4	54 (55.1)*	7 (7.1)*	361 (27.1)
5–9	30 (30.6)*	58 (59.2)	723 (54.2)
10–19	2 (2.1)*	20 (20.4)*	141 (10.6)
20–29	0 (0)	2 (2.1)	22 (1.6)
30–39	0 (0)	6 (6.1)*	23 (1.7)
≥40	1 (1.0)	5 (5.1)	7 (0.5)
Median (y)	3	8	6
Mean (y)	3.5	11.5	6.9
Range (y)	0–45	3–48	0–52
Gender			
Male		53 (54.1)	653 (49.0)
Female		45 (45.9)	681 (51.0)
Race			
White		82 (83.7)	1066 (80.0)
Black		11 (11.2)	205 (15.4)
Asian/Pacific Islander		4 (4.1)	55 (4.1)
American Indian		0 (0.0)	5 (0.3)
Unknown		1 (1.0)	3 (0.2)
Ethnicity			
Hispanic		26 (26.5)	432 (32.4)
Non-Hispanic		72 (73.5)	902 (67.6)

* Proportion significantly different ($P < .05$) using χ^2 or Fisher exact test of association when compared with 1998 cases with no previous history in same category.

TABLE 3. Presence of Fever and Description of Rash at the First and Second Reported Episodes of Varicella (n = 98), Antelope Valley, California, January 1 to September 30, 1998

	First Episode			Second Episode		
	Yes (n [%])	No (n [%])	Unknown/Missing (n [%])	Yes (n [%])	No (n [%])	Unknown/Missing (n [%])
Typical of varicella						
Fever	63 (64.3)	17 (17.3)	18 (18.4)	70 (71.4)	28 (28.6)	0 (0.0)
Macular rash	18 (18.4)	55 (56.1)	25 (25.5)	24 (24.5)	73 (74.5)	1 (1.0)
Papular rash	48 (49.0)	31 (31.6)	19 (19.4)	65 (66.3)	32 (32.7)	1 (1.0)
Vesicular rash	55 (56.1)	26 (26.5)	17 (17.4)	79 (80.6)	18 (18.4)	1 (1.0)
Rash crusted over	51 (52.0)	27 (27.6)	20 (20.4)	74 (75.5)	21 (21.4)	3 (3.1)
Pruritic rash	59 (60.2)	15 (15.3)	24 (24.5)	87 (88.8)	11 (11.2)	0 (0.0)
Rash appeared in crops	49 (50.0)	26 (26.5)	23 (23.5)	77 (78.6)	17 (17.3)	4 (4.1)
Rash was most concentrated on the face/trunk	53 (54.1)	31 (31.6)	14 (14.3)	61 (62.2)	37 (37.8)	0 (0.0)
Rash was generalized	21 (21.4)	63 (64.3)	14 (14.3)	27 (27.6)	71 (72.4)	0 (0.0)
Yes to 4, 5, 6	38 (38.8)	37 (37.8)	23 (23.4)	62 (63.2)	33 (33.7)	3 (3.1)
Not typical of varicella						
Localized rash	2 (2.0)	56 (57.2)	40 (40.8)	7 (7.1)	68 (69.4)	23 (23.5)
Rash on 1 side of the body	2 (2.0)	58 (59.2)	38 (38.8)	5 (5.1)	66 (67.3)	27 (27.6)
Rash peeled	1 (1.0)	84 (85.7)	13 (13.3)	1 (1.0)	94 (95.9)	3 (3.1)

La 2ème varicelle est typique dans 80% des cas contre seulement 60% pour la1ère!

physician-diagnosed history of varicella.[4,5] The largest case series summarized 38 infections that occurred among 14 generally immunocompetent children. During follow-up, 3 children demonstrated loss of cellular immunity or antibody over time.[4] Weller, the "father of VZV research," described 2 varicella infections in his own son at ages 6 months and 6 years.[11] Other reports have described second varicella infections after VZV exposures in adults, including health care workers who had serologic evidence of immunity before their second infection.[3,5,6,12–14] Wallace et al[15] tested for VZV immunoglobulin G antibodies in stored sera taken on average 1 year earlier from 19 military personnel who had a current case of varicella and reported a previous varicella infection and found no antibodies in any of the sera. Although the authors' conclusion was that histories were incorrect, waning immunity may be an alternative, albeit less likely, explanation for the findings. With the high levels of varicella immunity and low incidence among adults in the United States, it is unlikely that waning immunity after varicella disease is an epidemiologically significant problem. However, a small proportion of the population may not be fully protected after their first varicella infection. Abendroth and Arvin[16] pointed out the ability of VZV to evade immune response. In the prevaccine era, the likelihood of exposure to VZV during childhood is likely to have ensured that by adulthood essentially all individuals were immune, including

TABLE 4. Comparison of Lesion Grading of First and Second Episodes of Varicella (n = 98) to Individuals Who Reported No Previous Varicella (n = 1334) by Age Group, Antelope Valley, California, January 1 to September 30, 1998

Age (Years)	Mild (<50) (n [%])	Moderate (50–500) (n [%])	Severe (>500) (n [%])	Unknown/ Undefined (n [%])	Total in Age Group
<1					
First episode	9 (81.8)*	1 (9.1)	0 (0.0)	1 (9.1)	11 (100.0)
Second episode	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (100.0)
Singular episode	27 (47.4)	25 (43.8)	5 (8.8)	0 (0.0)	57 (100.0)
1–4					
First episode	38 (70.4)*	11 (20.4)*	1 (1.8)	4 (7.4)	54 (100.0)
Second episode	1 (14.3)	6 (85.7)	0 (0.0)	0 (0.0)	7 (100.0)
Singular episode	150 (41.6)	187 (51.8)	24 (6.6)	0 (0.0)	361 (100.0)
5–9					
First episode	15 (50.0)	12 (40.0)	1 (3.3)	2 (6.7)	30 (100.0)
Second episode	28 (48.3)	28 (48.3)	2 (3.4)	0 (0.0)	58 (100.0)
Singular episode	269 (37.2)	401 (55.5)	53 (7.3)	0 (0.0)	723 (100.0)
≥10					
First episode	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)	3 (100.0)
Second episode	11 (33.3)	12 (36.4)*	10 (30.3)*	0 (0.0)	33 (100.0)
Single-episode	45 (23.3)	123 (63.7)	25 (13.0)	0 (0.0)	193 (100.0)

* Proportion significantly different ($P < .05$) using χ^2 or Fisher exact test of association when compared with 1998 cases with a single episode in same age group/category of severity.

Plus on est **vieux** plus la varicelle est **sévère** **à chaque fois**. Plus on est jeune, moins elle est sévère et plus on est à **risque de la refaire**...

the proportion of individuals who may have acquired varicella more than once.

Data from previous studies reporting on the severity of reinfections have not shown a consistent pattern.[3–6,12,14,15] Our findings of milder disease among first infections was consistent with disease severity data described by Junker et al,[4] who reported on a small group of children for whom this information was available that 4 of the 6 children had 50 or fewer lesions in the first infections. In another report, a physician who kept records of the children in his practice with very mild varicella infections noted that children with second infections frequently had first cases that were very mild. He queried whether adequate immune responses occurred after very mild infections and whether such children may benefit from varicella vaccination.[17] In this respect, it is notable that in our study, the first infections did not confer partial protection, because most of the second infections were average or severe cases of disease. In contrast, varicella cases that occur >42 days after vaccination (breakthrough disease) are usually mild with fewer than 50 lesions that may be atypical.[18–20]

The following limitations should be considered when interpreting our results. First, we relied on clinical and epidemiologic data to classify cases as varicella infection; no cases were laboratory confirmed. Although reliance on clinical diagnosis may result in misclassification of some cases, it is thought to be generally accurate. Although varicella is a distinctive rash illness easily recognized by health care providers and parents, other diseases, including scabies, herpes simplex, rickettsial diseases, or some enteroviral infections, may occasionally be mistaken for varicella. (However, the majority of first and second cases were pruritic, suggesting that these were not misdiagnosed enteroviral infections, only rarely associated with itchiness.) A recent study found that 5.4% of the nonvaccinated individuals with varicella in clinical practice settings were negative for VZV antigen when tested using polymerase chain reaction methods,[21] and Dunkle et al[22] found that 3.3% of children with physician-diagnosed varicella did not seroconvert using florescent antimembrane antibodies testing in a trial for acyclovir treatment, suggesting that physician diagnoses are not 100% accurate.

A second limitation is that 29% of individuals who reported previous varicella infections could not be located and reinterviewed regarding their first infections. These individuals may have differed from the individuals we interviewed. Third, problems with recall of past infections that occurred on average 7.5 years before the interview limited comparisons of rash descriptions because, on average, 20% of participants could not recall some aspect of the clinical details of illness. Fourth, detailed rash description and information on epidemiologic link to other cases were not available on individuals who reported a single infection; data for these cases were obtained from the standard investigation of all varicella cases reported to the surveillance project. It was not considered feasible to reinterview 1334 individuals. Finally, it is possible that families that report >1 infection have recall problems or overreport infections as a result of family and/or cultural beliefs that varicella reinfections are common in their families. As the surveillance project does not collect information on socioeconomic factors such as educational level that may be related to accuracy of reporting, we were unable to examine whether these factors differed between those who did and did not report 2 infections.

Although our study provides description of the disease experience of the largest number of cases of reported repeat infections to date, the practical application of our study to identify individuals who may be likely to develop repeat infections in the clinical setting is limited, as cases that occur at early ages and with mild disease are common in the general population. The finding of a history of repeat infections in family members of 45% of cases was striking, however, and may serve this purpose.

Although our findings cannot definitively provide

evidence that repeat varicella infections are occurring regularly in our population without laboratory confirmation, they raise issues about the value of a positive history of varicella in predicting protective immune status, which in turn has important public health implications for varicella vaccination programs. Although infrequently obtained, serologic evidence of immunity is considered the "best" evidence of immunity, followed by a physician diagnosis and then a reliable parent history.[1,2] Studies among adults have shown that 97% to 99% of those with a positive history of varicella have serologic evidence of immunity.[23,24] Among children, data are sparse. Ross reported an attack rate of 7% among children who had positive histories and were exposed in a household setting, indicating either that a positive varicella history may not be 100% predictive of immunity or that some children acquire 2 varicella infections.[25]

Our results suggest the need for additional studies on the predictive value of a positive history of varicella, especially among children, to guide future policy for varicella vaccination. Experience with varicella vaccine has shown it to be approximately 85% effective in preventing clinical varicella.[21] Data are needed on the protective efficacy of a positive disease history that may be lower than 100%. On the basis of data reported from this surveillance area, 13.3% of reported varicella cases that occurred in 1999 were not preventable because children with a history of varicella are not offered vaccine. Routine use of laboratory confirmation of immunity may become more realistic as disease burden decreases; alternatively, at least among children, vaccination irrespective of disease history may be indicated. However, because clinical reinfection has been demonstrated to occur, although rarely, in individuals with VZV-specific antibodies before the second infection,[3,6] determining antibody levels that correlate with protection against disease will be important. In addition, because waning immunity is also a possibility at least in a subgroup of individuals with previous varicella, immunologic studies to determine whether natural varicella infection always confers lifelong immunity are also suggested. As the varicella vaccination program continues in the United States, accurately determining who is susceptible to VZV infection and achieving high VZV immunity through vaccination will be crucial to attaining public health goals of reduction in varicella cases and their attendant morbidity and mortality.

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