Persistence of Immunity to Live Attenuated Varicella Vaccine in Healthy Adults

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The varicella vaccine was approved in 1995 for use in healthy varicella-susceptible children and adults. Long-term immunity in 461 healthy adults who were enrolled in varicella vaccine trials in 1979–1999 were studied. Forty vaccinees (9%), including 19 (21%) of 89 vaccinees with household exposure (HHE) to chickenpox, developed breakthrough chickenpox 8 weeks to 11.8 years (mean, 3.3 years) after vaccination. The median number of skin lesions among the 36 untreated vaccinees was 20 (range, 1–240 lesions), and the number of lesions was essentially the same with time since vaccination. Breakthrough chickenpox was mild, even among vaccinees who did not have seroconversion or those recipients who lost detectable antibody. Lower varicella-zoster virus (VZV) antibody titers measured within 3 months of vaccination as well as at the time of HHE were associated with an increased risk of breakthrough disease. This study demonstrated that the varicella vaccine was effective in providing adults with long-term protection from serious VZV disease.

Varicella-zoster virus (VZV) is an α-herpesvirus that causes chickenpox in susceptible individuals. Before licensure of the varicella vaccine in 1995, 90% of American children developed chickenpox by 10–14 years of age [1]. Although the majority of children recover from chickenpox, the illness can be severe and sometimes fatal. In contrast with chickenpox in children, chickenpox in adults is associated with greater morbidity and mortality. Adults develop more skin lesions and have increased rates of such complications as pneumonia and death [2]. Varicella is highly contagious, and historically, attack rates among susceptible individuals who have had household exposure (HHE) to this herpesvirus are as high as 90%, with nonimmune individuals developing an average of 300–500 skin lesions [3, 4].

In 1995, the US Food and Drug Administration approved the use of the varicella vaccine in healthy, varicella-susceptible children and adults. To date, >25 million doses of the vaccine have been distributed in the United States. In sentinel areas, there has been a significant decrease in the incidence of chickenpox since licensure of the vaccine [5, 6]. Nevertheless, in ~10%–20% of children, mild breakthrough chickenpox, which is characterized by the development of a few lesions that last only briefly, may occur after vaccination [7–11].

Although >95% of children have seroconversion after receiving a single dose of vaccine, the seroconversion rate in adults is not as high [12]. It is therefore recommended that susceptible adults receive 2 doses of varicella vaccine at a 4–8-week interval. Children have been studied for up to 20 years after vaccination, and most have maintained cellular and humoral immunity to VZV [10, 13, 14]. However, the duration of immunity after vaccination of adults has not been adequately studied. Thus, we performed a study of long-term immunity to varicella in healthy VZV-susceptible adults who were enrolled in varicella vaccine trials. We determined the attack rate and severity of breakthrough chickenpox over time for vaccinees, including those...
with HHE to chickenpox. We also assessed long-term immunity by analyzing the persistence of VZV antibodies since vaccination.

**SUBJECTS AND METHODS**

**Study subjects and immunization regimens.** Study subjects were healthy adults who had no history of chickenpox, who had negative results of varicella serologic testing for varicella, as measured by fluorescent antibody to membrane antigen (FAMA) examination [15], and who were participating in vaccine trials in 1979–1999. Subjects were mostly health care workers or parents of young children who were considered to be at high risk of developing chickenpox. Certain aspects of some of these subjects have been described elsewhere [12, 16].

After informed consent was obtained, subjects received 1, 2, or 3 doses of the live attenuated varicella (Oka) vaccine produced by either Merck or SmithKlineBeecham. The number of doses varied by protocol; one study used a placebo to determine rates of seroconversion for patients receiving 1 versus 2 doses. This placebo-controlled study was conducted before licensure of the varicella vaccine and before the Advisory Committee on Immunization Practices and the Hospital Infection Control Practices Advisory Committee recommended the use of 2 doses for adults [17]. When 2 doses of vaccine were administered, the second dose was provided 3 months after the first dose. A third dose was administered to some vaccinees who did not have seroconversion after receiving 2 vaccine doses. Different production lots (for Merck, CL 303, CL 306, CL 308, L 716, CL 803, CL 805, 851, 867, CR 319, CR 452, CR 562, CT 683, CT 684, and CT 685; for SmithKlineBeecham, lots 5, 17, 18, 58, C-W 591, and C-W 592) and vaccines of different potency (range for Merck vaccines, 1500–3000 plaque-forming units; range for SmithKlineBeecham vaccines, 10,000 plaque-forming units) were administered.

All immunized subjects were asked to report to the study team any symptoms, such as fever, rash, and upper respiratory tract infection, that occurred in the 2 months after each dose of vaccine was administered, as has been reported elsewhere [12]. According to the vaccine study protocols [12, 18], serum samples were obtained monthly for the first 3 months after each dose of vaccine was given and then every 4 months for 1 year. After the first year of follow-up, vaccinees were contacted annually by letter or by telephone to obtain serum and clinical information. All subjects were actively interviewed by telephone or in person about exposure to chickenpox or zoster, and they were also instructed to notify their doctors or study team if exposure occurred and to indicate whether that exposure occurred in their household. Serum samples were obtained at the time of exposure and 4–6 weeks later.

FAMA titers were used to assess serologic response. In this study, a FAMA titer of ≥1:2 was considered positive. The reciprocals of the FAMA titers (i.e., 1:4 = 4, 1:16 = 16, <1:2 = 1) were used to determine the geometric mean titer (GMT) [15].

If any vaccinee developed a varicella-like rash, the number of lesions was counted, a culture of a sample of a lesion was performed, and data from serologic tests were obtained. The follow-up interval was calculated from the date that the last vaccine dose was administered to the date that either the last serologic test was performed or until breakthrough chickenpox developed. Using the number of lesions as an indicator of severity of illness, we examined whether breakthrough varicella worsened with increased time since vaccination. We also compared the vaccine regimens and serologic responses of vaccinees with HHE who did develop breakthrough chickenpox with those who did not. Last, we analyzed whether there was any increase in varicella attack rates after HHE with increased time since vaccination.

**Data management and statistical analysis.** All data were entered in Microsoft Excel for analysis (Microsoft 2000). Statistical analysis included χ2 analysis with Fisher’s exact test (Epi Info version 6.0; Centers for Disease Control and Prevention) and Student’s t test.

**RESULTS**

**Crude attack rate after VZV vaccination.** A total of 40 (9%) of 461 vaccinees developed breakthrough chickenpox from 8 weeks to 11.8 years (mean, 3.3 years) after receiving their last vaccine dose. The mean age of vaccinees at the time the first dose of VZV vaccine was administered was 30 years (range, 22–41 years), and the mean age at the time breakthrough disease developed was 34 years (range, 22–47 years). Of the 461 adult vaccinees, 290 (63%) were women; 29 (73%) of 40 of the adult vaccinees with breakthrough disease were women. When compared with men, women did not have an increased risk of developing breakthrough chickenpox (OR, 1.6; 95% CI, 0.75–3.55). Of the 40 vaccinees with breakthrough disease, 10 received 1 dose, 28 received 2 doses, and 2 received 3 doses of VZV vaccine.

**Severity of breakthrough chickenpox.** Of the 40 vaccinees who developed breakthrough chickenpox, 1 received varicella-zoster immunoglobulin (VZIG) prophylactically after HHE to chickenpox, and 3 received acyclovir upon development of skin lesions. These 4 vaccinees were not included in the analysis of severity of breakthrough disease. The median number of skin lesions among the 36 untreated vaccinees with breakthrough disease was 20 lesions (range, 1–240 lesions).

The median number of skin lesions among vaccinees with breakthrough disease was essentially the same, regardless of time since vaccination (table 1; P = .15, by Mann-Whitney rank-sum test). Thus, all cases of breakthrough chickenpox,
including cases in vaccinees with no demonstrable antibodies to varicella after vaccination, were of mild to moderate severity, as defined elsewhere [19], and were without complications.

Serologic response after vaccination of vaccinees with breakthrough chickenpox. Nine (23%) of 40 vaccinees never had detectable antibodies before the development of breakthrough chickenpox was diagnosed. Untreated vaccinees who had seroconversion after the last dose of vaccine developed fewer skin lesions than did those who had never seroconversion; the 28 vaccinees with seroconversion developed a median of 12 lesions, and the 8 without seroconversion developed a median of 60 lesions ($P = .004$, by the Mann-Whitney rank-sum test). Thirty-one (78%) of 40 vaccinees with breakthrough chickenpox had seroconversion after vaccination: 18 did so after 1 dose, 12 after 2 doses, and 1 after the third dose. The last FAMA serologic examination done before development of breakthrough chickenpox demonstrated that 27 (87%) of 31 had lost detectable antibodies to VZV. The mean time between the last serologic test and breakthrough varicella was 1.7 years (range, 1 month to 6.8 years). Of the 20 vaccinees who had a serologic test performed within 1 year of development of breakthrough chickenpox, only one had detectable antibody, and this vaccine recipient developed 1 vesicle.

HHE to chickenpox. Eighty-nine (19%) of 461 vaccinees reported having exposure to a household member with chickenpox. The varicella attack rate after HHE was 21%; 19 of these 89 vaccinees developed chickenpox 8 weeks to 9 years after vaccination (mean, 3.4 years). Five (6%) of 89 vaccinees received treatment after HHE; 3 received prophylactic VZIG, and 2 received acyclovir with development of skin lesions. One of the 3 vaccinees who received VZIG developed mild breakthrough chickenpox. The attack rate and severity of illness remained unchanged if these 5 vaccinees were excluded from the analysis presented below (data not shown).

The demographic and serologic characteristics of the vaccinees with HHE who developed chickenpox ($n = 19$), compared with those of the vaccinees who did not develop chickenpox after HHE ($n = 70$), are shown in table 2. There were no differences in baseline characteristics, including the vaccine regimens received. Similarly, the attack rate among vaccinees with HHE who had received 1 dose versus either 2 or 3 doses of vaccine was 28% and 19%, respectively ($P = .3$), and the median number of skin lesions was 22 and 11, respectively ($P > .10$, by the Mann-Whitney rank-sum test).

Of the 89 vaccinees who reported HHE, seroconversion was demonstrated in 62 (70%) after 1 dose, in 17 (19%) after 2 doses, and in 1 (1%) after 3 doses of vaccine. Nine patients (10%) never had seroconversion, but only 3 patients developed mild breakthrough chickenpox. The mean duration between the last serologic examination and HHE was 1.2 years (range, 1 month to 7 years), and 28 (35%) of 80 vaccinees had lost detectable antibody to VZV. Of the 63 vaccinees who underwent testing within a year of HHE, 38 (60%) had antibodies to VZV, and only one developed mild breakthrough chickenpox. The initial seroconversion rates in a comparison of vaccinees who did and did not develop chickenpox were comparable ($P = .10$). However, within 3 months of vaccination, there was a lower GMT in vaccinees who later developed breakthrough disease ($P = .02$). Furthermore, vaccinees who lost antibodies were more likely to develop breakthrough disease than were those vaccinees who did not lose antibodies ($P < .001$).

As shown in table 3, the attack rate among the 89 vaccinees did not increase over time ($P = .6$). Although some of the 80 vaccinees who had seroconversion did lose antibodies to varicella, there was no increased loss of antibodies in vaccinees followed for 4 years, compared with vaccinees followed for <4 years.

### DISCUSSION

This study confirms that the VZV vaccine protects adults from serious disease and confers long-term immunity. In this large series of adult vaccinees with long-term follow-up, the crude attack rate of 9% in vaccinated nonimmune adults is low, compared with such rates in previously published reports. All vaccinees with breakthrough chickenpox had mild to moderate disease. The severity of breakthrough chickenpox, as measured by the number of skin lesions, was essentially the same with time since vaccination as the median number of skin lesions was 15, 32, and 42 lesions at <4 years, 4–8 years, and >8 years, respectively. In addition, we demonstrated that the severity of chickenpox and the attack rate over time did not increase after HHE, with attack rates of 19%, 35%, and 17% at <4 years, 4–8 years, and >8 years, respectively. Furthermore, breakthrough chickenpox was mild, even among vaccinees without seroconversion or vaccinees who lost detectable antibody. This suggests that VZV-specific cell-mediated immunity affords protection to vaccinees in the absence of detectable antibody response [20]. These data indicate there is no significant waning immunity to VZV in adults after vaccination.
Development of mild breakthrough chickenpox after VZV vaccination has been well described elsewhere [10, 13, 14, 21–23]. The reported crude attack rate after VZV vaccination in healthy children and children with leukemia ranges from 6% to 18% [10, 13, 14, 21–23]. In a small study of 26 adult vaccinees, the attack rate was found to be 31% [19]. However, in the present study of 461 subjects, the attack rate was 9%. Thus, in this larger study, the overall protection offered by VZV vaccination of adults appears to be similar to that noted for children.

The intensity and duration of exposure associated with HHE are higher than those associated with casual exposure, including hospital exposure. Therefore, we examined the attack rate after HHE and found that 19 (21%) of 89 vaccinees developed mild breakthrough chickenpox. The reported attack rate in vaccinated children after HHE ranges from 2% to 12% [13, 14], and the attack rate in vaccinated adults ranges from 18% to 30% [16, 24]. Thus, adults may be less well protected from chickenpox than are children.

The immunogenicity of the VZV vaccine has been well documented in children, but fewer studies—particularly long-term studies—have been performed in adults [16]. Vaccine trials in healthy children have documented that >90% of children have seroconversion after receiving 1 dose of vaccine, as assessed by a sensitive glycoprotein (gp) ELISA [14, 25]. In short-term follow-up studies of children, 34 (94%) of 36 toddlers had VZV antibodies detected by FAMA 2 years after vaccination [22], and 100% of 41 children had antibodies detected by gp ELISA 6 years after vaccination [23]. A long-term study of 25 children demonstrated that all had cellular and humoral immunity, as demonstrated by FAMA, when followed for as long as 20 years [13].

Previous studies in adults have demonstrated that 2 doses of vaccine are needed to achieve seroconversion rates comparable to those noted in children [12, 24, 26]. In this study, seroconversion rates of 90% were achieved in vaccinees with HHE, as determined by FAMA. Long-term persistence of VZV antibodies was also demonstrated: 5 (71%) of 7 vaccinees had VZV antibodies >8 years after vaccination. We also examined the relationship of GMT and the loss of VZV antibody with breakthrough disease and disease severity. A lower GMT measured within 3 months of vaccination as well as at the time of

Table 2. Clinical characteristics and serologic responses of adult varicella vaccinees with household exposure who did or did not develop breakthrough chickenpox.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No chickenpox (n = 70)</th>
<th>Chickenpox (n = 19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean years (range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At vaccination</td>
<td>31 (20–44)</td>
<td>33 (28–46)</td>
<td>.24a</td>
</tr>
<tr>
<td>At HHE</td>
<td>33 (20–44)</td>
<td>37 (28–46)</td>
<td>.10a</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>49 (70)</td>
<td>13 (68)</td>
<td>.60</td>
</tr>
<tr>
<td><strong>No. of vaccine doses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18 (26)</td>
<td>7 (37)</td>
<td>.10</td>
</tr>
<tr>
<td>2</td>
<td>52 (74)</td>
<td>11 (58)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td><strong>Seroconversion rates with</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>51 (73)</td>
<td>11 (58)</td>
<td>.10</td>
</tr>
<tr>
<td>2 doses</td>
<td>63 (90)</td>
<td>16 (84)</td>
<td></td>
</tr>
<tr>
<td>3 doses</td>
<td>NA</td>
<td>17 (89)</td>
<td></td>
</tr>
<tr>
<td><strong>GMT, FAMA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 3 months of vaccinationb</td>
<td>4.7</td>
<td>2.4</td>
<td>.02a</td>
</tr>
<tr>
<td>Before HHE</td>
<td>5.8</td>
<td>1.4</td>
<td>&lt;.05a</td>
</tr>
<tr>
<td><strong>Interval (mean years) between HHE and</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last dose</td>
<td>6</td>
<td>5</td>
<td>.60a</td>
</tr>
<tr>
<td>Last FAMA serologic examination</td>
<td>1</td>
<td>1.3</td>
<td>.50a</td>
</tr>
<tr>
<td>Interval between last dose and HHE, mean years</td>
<td>3.2</td>
<td>3.3</td>
<td>.74a</td>
</tr>
<tr>
<td>Detectable antibody before HHE</td>
<td>48 (69)</td>
<td>2 (11)</td>
<td>&lt;.05a</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of vaccinees, unless otherwise indicated. FAMA, fluorescent antibody to membrane antigen; GMT, geometric mean titer; HHE, household exposure; NA, not available.

a As analyzed by paired t test.

b Some vaccinees only received 1 dose of vaccine.
HHE was associated with increased risk of breakthrough disease. Similar observations have been reported in children; vaccinated children with lower VZV antibody titers 6 weeks after immunization were more likely to develop breakthrough chickenpox [10]. The authors of this article also demonstrated that loss of detectable antibody was associated with increased risk of breakthrough disease [16]. Conversely, in this and another study [12], adults with a positive FAMA finding within a year of HHE had a very low risk of developing chickenpox. Although, overall, 35% of vaccinees lost detectable antibody to VZV, this did not increase with time or lead to an increase in disease severity.

Additional VZV vaccine doses increased seroconversion rates, but results from this study as well as others suggest that administration of >1 vaccine dose to adults does not necessarily provide better protection [16, 19]. In this study, vaccinees who had received a single dose did not have a higher attack rate or more skin lesions, compared with vaccinees who had received 2 or 3 doses of vaccine; however, only a small number of vaccinees were studied.

There were many limitations to this study. This was not a randomized, controlled vaccine trial that used vaccine versus placebo in nonimmune adults. The vaccinees were enrolled in different vaccine protocols and therefore received a different number of doses as well as different vaccine strengths. However, the attenuated virus used for the vaccine is derived from the Oka strain of VZV. That HHEs were self-reported introduces the element of bias in reporting. Some vaccinees or their household contacts with chickenpox were evaluated by primary-care physicians and not the study team. Finally, neither FAMA nor gp ELISA is available in most clinical serologic laboratories to screen for VZV antibodies, and the commercially available assays have decreased sensitivity and specificity when compared with these research assays [16].

Despite these limitations, this study demonstrated that the varicella vaccine was effective in protecting adults from serious VZV disease. Vaccinees who never had seroconversion or who lost detectable antibody were still protected from severe disease. In addition, immunity to varicella was persistent and did not wane with time. Antibodies were present in most vaccinees long after vaccination, and the attack rate and disease severity did not increase with time since vaccination.

### References