Lack of Association between Age at Varicella Vaccination and Risk of Breakthrough Varicella, within the Northern California Kaiser Permanente Medical Care Program

Steve Black,1 Paula Ray,2 Henry Shinefield,2 Patricia Saddier,1 and Alexander Nikas1

1Department of Pediatric Infectious Diseases, Stanford University, Palo Alto, 2Kaiser Permanente Vaccine Study Center, Oakland, and 3Department of Pediatrics, University of California, San Francisco, California; 4Epidemiology Department, Merck Research Laboratories, North Wales, Pennsylvania

Background. Varicella vaccine currently is recommended for children between 12 and 18 months of age. However, rates of breakthrough varicella have been reported to be higher among children vaccinated before 14 or 15 months of age and to increase with time since vaccination.

Methods. An ongoing study at the Northern California Kaiser Permanente Medical Care Program is evaluating vaccine efficacy in 7585 children vaccinated with Varivax in 1995, when they were between 12 and 23 months of age. Cases of chickenpox are identified by telephone interviews with each child’s parent(s) every 6 months. Mean age at varicella onset and mean time from vaccination to onset were calculated on the basis of age, in months, at vaccination. Logistic regression was used to test for trend, and the \( \chi^2 \) test was used to test for differences in rates of breakthrough varicella by age.

Results. Over the first 8 years of the study, a total of 1161 cases of breakthrough varicella were reported, for an average rate of 21.7 cases/1000 person-years. Vaccine effectiveness was 83.6% at year 8. The rate of breakthrough varicella did not change for each additional month of age at vaccination (\( P = .864 \)), and no difference in the rate of breakthrough varicella was found between children vaccinated at \(<15 \text{ months of age} \) and those vaccinated at \( \geq 15 \text{ months of age} \).

Conclusions. Our data do not show a difference in vaccine effectiveness with age at vaccination and thus support the current recommendations for initial vaccination between 12 and 18 months of age.

The Oka strain–based live attenuated varicella vaccine (Varivax, Merck) was licensed for use in the United States in March 1995. In the following years, vaccine coverage has increased substantially, although it has not neared universal coverage [1], and early reports have suggested a dramatic decline in the incidence of childhood chickenpox from the historical level of 85% by 10 years of age [2, 3].

Currently, routine administration of the vaccine is recommended for children between 12 and 18 months of age [4]; however, several groups have reported that cases of breakthrough varicella among children vaccinated before 14 or 15 months of age occur at rates higher than those among children vaccinated at older ages [5–8]. In addition, it has been reported that the effectiveness of the vaccine has been reported to wane after the first year [7] or after several years [9]. We examined whether rates of breakthrough varicella vary by age at vaccination or have changed over time, within the environment of the Northern California Kaiser Permanente Medical Care Program (KPMCP), a health maintenance organization with members who are treated almost exclusively at KPMCP facilities.
METHODS

Of the 25,000 children in the KPMCP who were between 12 and 23 months of age in 1995, 9316 were vaccinated with Varivax in May, June, and July 1995 during the course of ordinary clinical practice. The families of 7585 of these children agreed to participate in a longitudinal study designed to evaluate the long-term effectiveness of the varicella vaccine, after being informed of the study procedures. The Kaiser Permanente Institutional Review Board approved this study.

Possible cases of varicella and herpes zoster (HZ) were ascertained from the parent or guardian of each child, by telephone interview, every 6 months. This report includes data obtained through 96 months of follow-up. Results from the first 4 time points (6–24 months after vaccination) have been reported previously [2].

During the interview, the parent or guardian was asked by a trained interviewer whether the child had had chickenpox or HZ during the 6 months since the last interview. If this question was answered in the affirmative for chickenpox, the parent was asked to estimate the severity of the case, as follows: a few spots (<50), scattered spots (51–100), spots on much of the body (101–300), or spots all over the body (>300). Moderate cases were defined as those with 51–300 spots, and severe cases were defined as those with >300 spots. Parental report was accepted as evidence of chickenpox.

Mean age at onset of varicella and mean time from vaccination to onset of varicella were calculated by age (in months) at vaccination. Rates of breakthrough varicella were calculated by use of the first reported occurrence of varicella during the follow-up period, with follow-up person-time data after the first occurrence excluded. Confidence intervals were calculated by means of the Blyth-Still method. A logistic regression model was fit to the data to test for trend, and the χ² test was used to test for differences in rates of reported breakthrough varicella across the 12 age groups. Vaccine effectiveness for a given time period p was defined as (1 – cumulative rate of breakthrough varicella through p) × 100.

RESULTS

We report on the first 8 years of the planned 15-year follow-up of children vaccinated against varicella. Of the 7585 children who entered the study in 1995, 7449 (98.2%) remained in the study at the 96-month time point. During this time, a total of 1161 cases of breakthrough varicella were reported by parents (table 1). The average rate of reported breakthrough varicella was 21.7 cases/1000 person-years over the 8-year follow-up period. The majority of cases of breakthrough varicella were mild; only 248 (21.4%) of the 1161 cases had >50 lesions, and only 17 cases (1.5%) had >300 lesions, of which 13 cases were in the first 4 years of the follow-up period.

DISCUSSION

When stratified by age at vaccination (in months), the rates of breakthrough varicella ranged from 20.0 to 24.0 cases/1000 person-years (table 1). A test for trend revealed no change in the rate of reported breakthrough varicella for each additional month of age at vaccination (monthly incidence rate ratio, 1.001; P = .86), and no significant difference in the rate of reported breakthrough varicella was found across the 12 age groups (χ² 11 = 3.4; P = .98).

Several studies have reported significant differences in rates of breakthrough varicella when age at vaccination was dichotomized into <15 months and ≥15 months [6–8]. However, for children vaccinated at <15 months of age versus those vaccinated at ≥15 months of age, we did not find differences in rates of breakthrough varicella during the first year after vaccination or during 8 years of follow-up (table 2). Age at vaccination also did not affect the time between vaccination and the onset of breakthrough varicella, which ranged from 38 to 48 months (mean, 43 months). Rates of breakthrough varicella were fairly steady, at an average of ~26 cases/1000 person-years, for the first 4 years after vaccination and started to decrease thereafter, to ≤20 cases/1000 person-years. At 8 years after vaccination, the proportion of vaccinees who had remained disease free was 83.6%.

Table 1. Reported rates of breakthrough varicella, by age at vaccination, within the Northern California Kaiser Permanente Medical Care Program.

<table>
<thead>
<tr>
<th>Age at vaccination, months</th>
<th>No. of children vaccinated</th>
<th>Rate of breakthrough varicella No. of cases</th>
<th>Cases/1000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1014</td>
<td>150</td>
<td>20.7</td>
</tr>
<tr>
<td>13</td>
<td>526</td>
<td>90</td>
<td>24.0</td>
</tr>
<tr>
<td>14</td>
<td>649</td>
<td>95</td>
<td>21.0</td>
</tr>
<tr>
<td>15</td>
<td>1463</td>
<td>229</td>
<td>22.2</td>
</tr>
<tr>
<td>16</td>
<td>649</td>
<td>102</td>
<td>22.5</td>
</tr>
<tr>
<td>17</td>
<td>505</td>
<td>75</td>
<td>20.9</td>
</tr>
<tr>
<td>18</td>
<td>651</td>
<td>94</td>
<td>20.5</td>
</tr>
<tr>
<td>19</td>
<td>381</td>
<td>54</td>
<td>20.0</td>
</tr>
<tr>
<td>20</td>
<td>369</td>
<td>53</td>
<td>20.1</td>
</tr>
<tr>
<td>21</td>
<td>433</td>
<td>66</td>
<td>21.6</td>
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<tr>
<td>22</td>
<td>417</td>
<td>71</td>
<td>24.0</td>
</tr>
<tr>
<td>23</td>
<td>528</td>
<td>82</td>
<td>22.2</td>
</tr>
<tr>
<td>Total</td>
<td>7585</td>
<td>1161</td>
<td>21.7</td>
</tr>
</tbody>
</table>

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breakthrough disease over the first 8 years after vaccination in a cohort of children vaccinated, in 1995, in their second year of life. We further examined the rates of breakthrough varicella when data were stratified by age at vaccination.

The incidence of breakthrough varicella in each year of this study was comparable to that seen in clinical trials of the vaccine [10–12]. In our study, as in others [11, 13–15], cases of breakthrough varicella generally were milder than cases of natural varicella. In natural varicella, the median number of cutaneous lesions is at least 300 [16, 17]; in this study, the majority of cases of breakthrough varicella (79%) had <50 lesions, and a very small minority of cases (1.5%) had >300 lesions. The variation in varicella severity may be correlated with the immune response to vaccination [18].

There was no evidence that age at vaccination affected the extent or duration of protection. Rates of breakthrough varicella among toddlers vaccinated at <15 months of age and those vaccinated at ≥15 months of age were similar. Overall, the rate of breakthrough varicella was highest during the first 4 years after vaccination, after which it declined steadily, suggesting that immunity had not waned over the 8 years of follow-up. Although it has been suggested that immunity may decline within 3 years after vaccination [7, 9], other studies have found long-term persistence of antibodies to VZV or of immunity against chickenpox [10, 11, 19, 20] or even an increase in antibody titers over time [19, 21]. In Japan, where the Oka strain-based vaccine has been in use for almost 30 years, varicella vaccine appears to provide substantial protection against varicella. In natural varicella compared with breakthrough varicella after immu-

### Table 2. Reported rates of breakthrough varicella within 1 year or 8 years after vaccination, within the Northern California Kaiser Permanente Medical Care Program: vaccination at <15 months of age vs. vaccination at ≥15 months of age.

<table>
<thead>
<tr>
<th>Time since vaccination</th>
<th>Vaccination at &lt;15 months of age</th>
<th>Vaccination at ≥15 months of age</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>Cases/1000 person-years</td>
<td>No. of cases</td>
<td>Cases/1000 person-years</td>
<td></td>
</tr>
<tr>
<td>Within 1 year</td>
<td>52</td>
<td>27.5</td>
<td>122</td>
<td>26.3</td>
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<tr>
<td>Within 8 years</td>
<td>335</td>
<td>21.6</td>
<td>826</td>
<td>21.7</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval. *a* Calculated by the Blyth-Still method.

### Acknowledgments

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### References


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