Contagiousness of Varicella in Vaccinated Cases
A Household Contact Study

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Varicella is a highly infectious disease caused by the varicella zoster virus, which is spread by droplet or airborne transmission. Before the varicella vaccination program in the United States, approximately 4 million varicella cases occurred each year, resulting in 10,600 hospitalizations and 100 deaths.1-3 The majority of cases occurred in children, which reflects its highly contagious nature.

Varicella transmission has been studied in household settings using clinical observation studies, clinical trials of gamma globulin and acyclovir, and post-exposure studies of varicella vaccine. In these studies, which were conducted between 1951 and the late 1980s, the varicella secondary attack rate among susceptible children ranged from 61% to 100%.4-8 Since these studies, varicella vaccine has been licensed and recommended for routine childhood vaccination in the United States.

Postlicensure effectiveness of varicella vaccine has been studied using a variety of methods including outbreak investigations, case-control studies, and prospective cohort studies, but not household contact studies, which measure vaccine performance under the most intense conditions of exposure. Compared with unvaccinated cases, varicella cases in vaccinated persons (also known as breakthrough disease) are usually milder with fewer lesions and constitutional symptoms.9,10 Anecdotal reports and some observational studies suggest that breakthrough varicella cases are half as contagious as unvaccinated persons with varicella, although contagiousness varies with numbers of lesions.

Context Limited data are available on the contagiousness of vaccinated varicella cases.

Objectives To describe secondary attack rates within households according to disease history and vaccination status of the primary case and household contacts and to estimate varicella vaccine effectiveness.

Design, Setting, and Patients Population-based, active varicella surveillance project in a community of approximately 320,000 in Los Angeles County, California, during 1997 and 2001. Varicella cases were reported by child care centers, private and public schools, and health care clinicians and were investigated to collect demographic, clinical, medical, and vaccination data. Information on household contacts’ age, varicella history, and vaccination status was collected.

Main Outcome Measures Varicella secondary attack rate among household contacts; vaccine effectiveness using secondary attack rates in unvaccinated and vaccinated children and adolescents.

Results A total of 63,166 varicella cases were reported. Among children and adolescents aged 1 to 14 years, secondary attack rates varied according to age and by disease and vaccination status of the primary case and exposed household contacts. Among contacts aged 1 to 14 years exposed to unvaccinated cases, the secondary attack rate was 71.5% if they were unvaccinated and 15.1% if they were vaccinated (risk ratio [RR], 0.21; 95% confidence interval [CI], 0.15-0.30). Overall, vaccinated cases were half as contagious as unvaccinated cases. However, vaccinated cases with 50 lesions or more were similarly contagious as unvaccinated cases whereas those with fewer than 50 lesions were only one third as contagious (secondary attack rate, 23.4%; RR, 0.32 [95% CI, 0.19-0.53]). Vaccine effectiveness for prevention of all disease was 78.9% (95% CI, 69.7%-85.3%); moderate disease, 92% (50-500 lesions) and 100% (clinician visit); and severe disease, 100%.

Conclusions Under conditions of intense exposure, varicella vaccine was highly effective in preventing moderate and severe disease and about 80% effective in preventing all disease. Breakthrough varicella cases in household settings were half as contagious as unvaccinated persons with varicella, although contagiousness varied with numbers of lesions.
tions in outbreak settings suggest that vaccinated cases may be less contagious than unvaccinated cases. However, data are lacking that quantify the contagiousness of vaccinated varicella cases. A varicella active surveillance project in Antelope Valley, Calif, provided the opportunity to examine varicella transmission within households according to the varicella history and vaccination status of both the primary case and exposed household members and to estimate vaccine effectiveness from household secondary attack rates.

**METHODS**

Active surveillance for varicella has been conducted in Antelope Valley (2000 Census population of 318,670) since varicella became a reportable disease in Los Angeles County, California, in 1995. Collection of public health surveillance data does not require institutional review board approval or informed consent from the patients. This study used data collected during 1997 through 2001, which included information on household members of varicella cases. The methods for this active surveillance have been previously described. A varicella case is defined as an illness characterized by acute onset of a diffuse papulovesicular rash without other known cause, recognizing that the rash in vaccinated persons may be atypical with few or no vesicles. Reports of varicella cases are collected every 2 weeks from a variety of sources including child care centers, private and public schools, physicians, hospitals, public health clinics, health maintenance organizations, correctional facilities, homeless shelters, and employers with more than 500 employees. All reported cases were investigated primarily by telephone interview by experienced project staff, who collected detailed demographic, clinical, medical, and vaccination data on every case. As one measure of clinical severity, data were collected on estimated number of skin lesions: less than 50 lesions, 50 to 500 lesions, and more than 500 lesions. In addition, as part of the case investigation, all household members of varicella cases were enumerated and information was collected on age, varicella history, and receipt of varicella vaccine. If previously unreported cases in the household were identified, they were investigated. To capture secondary and later cases in households, follow-up telephone calls were performed at 3-week intervals until no new cases in the household occurred.

Vaccination status of cases with dates of vaccination was obtained from clinicians, school, or other immunization records for 81% to 84% of cases each year except 2001 (75%); otherwise, vaccination status was based on parental recall. Vaccination status of household contacts was obtained from immunization records or parental recall.

**Household Secondary Attack Rate**

We defined a primary case as the first case within a household according to date of onset of the rash. Coprimary cases were those with rash onset 0 through 9 days after the primary household case. Secondary cases were cases with rash onset 10 through 21 days after the primary case. If the first 2 cases in the household occurred on the same day, we assigned one primary status and the other coprimary status. To determine if transmission within households changed with increasing vaccine coverage in the community (and therefore a higher proportion of vaccinated cases in households), we analyzed the secondary attack rate by year; finding no trend, we conducted subsequent analyses for the 5-year period. We first analyzed secondary attack rate by age; subsequent analyses were according to disease, vaccination history, and disease severity were restricted to children and adolescents aged 1 to 14 years due to the low predictive value of a negative varicella history in predicting varicella susceptibility among adults and the possibility of maternally acquired antibody affecting the secondary attack rate among infants.

The secondary attack rate was calculated as the proportion of secondary cases that occurred among household contacts exposed to the primary household case. For these analyses, we classified the primary cases and exposed household contacts into groups according to their history of varicella disease and vaccination status: (1) unvaccinated (and negative disease history), (2) vaccinated (and negative disease history), and (3) positive disease history (and unvaccinated). We also described secondary attack rate by the number of reported lesions of the primary case. We examined the effect that existence of a coprimary case had on secondary attack rates in a household; finding no effect, we included families with coprimary cases in the analysis.

**Vaccine Effectiveness**

Vaccine effectiveness for prevention of all varicella disease among household contacts of primary unvaccinated varicella cases was calculated as:

\[
\text{Vaccine effectiveness} = \left[ \frac{\text{secondary attack rate in unvaccinated contacts} - \text{secondary attack rate in vaccinated contacts}}{\text{secondary attack rate in vaccinated contacts}} \right] \times 100.
\]

Infants were not included in these analyses because varicella vaccine is not recommended before age 12 months. For calculating vaccine effectiveness for prevention of moderate and severe disease, we used the number of cases with moderate or severe disease as numerators for the attack rate calculations.

We used different definitions for moderate disease (50–500 lesions and an illness associated with a complication requiring a health care clinician visit) and severe disease (>500 lesions and an illness with complications resulting in hospitalization or death).

We used Excel software (version 5.0, Microsoft Corporation, Redmond, Wash) and SAS statistical software (version 6.12, SAS Institute Inc, Cary, NC) for data analysis. Differences between proportions were calculated by using \(\chi^2\) tests; \(P\) values were 2-sided and considered significant at the .05 level. Secondary attack rates were used to calculate risk ratios (RR) and the 95% confidence intervals (CIs) were calculated using the log rate of the SE of the ratio.
CONTAGIOUSNESS OF VARICELLA

RESULTS

Household Secondary Attack Rate

During 1997 and 2001, a total of 6316 verified varicella cases were reported; 1602 households with primary cases and 5912 contacts of all ages were used in our calculations of secondary attack rate. For calculations of secondary attack rate according to disease history and vaccination status of the primary case and contacts aged 1 to 14 years, 2732 contacts were included in the analysis.

Overall, considering unvaccinated primary cases and unvaccinated household contacts, the secondary attack rate varied by age and was highest (72.0%-72.5%) among children aged 1 to 9 years and lowest (30.7%) among persons aged 15 years or older (Table 1). Analysis of secondary attack rate among contacts aged 1 to 14 years showed that rates varied according to the disease and vaccination status of the primary case and the household contacts. The secondary attack rate was highest (71.5%) for primary cases and contacts who were unvaccinated (Table 2). In contrast, vaccinated children exposed to unvaccinated cases had a secondary attack rate of 15.1% (RR, 0.21; 95% CI, 0.15-0.30). Some children with a positive varicella history (n=44; 7.1%) also contracted varicella when exposed to unvaccinated primary cases in their household. When primary cases in the household were vaccinated, 37.1% of unvaccinated contacts (RR, 0.52; 95% CI, 0.38-0.71) and 22.3% of vaccinated contacts (RR, 0.31; 95% CI, 0.21-0.46) developed varicella (Table 2).

Vaccinated secondary cases were much milder. Following exposure to an unvaccinated primary case, only 24.0% of the secondary cases in vaccinated contacts had 50 lesions or more compared with 75.6% of secondary cases in unvaccinated contacts (P<.001) and 81.8% of secondary cases in children with a history of varicella (P<.001) (Table 2). Although vaccinated secondary cases resulting from exposure to a vaccinated primary case appeared to be even milder with only 10.2% having 50 lesions or more, this proportion was not statistically significantly different from vaccinated contacts exposed to unvaccinated primary cases (24.0%; P=.69) (Table 2).

Among unvaccinated contacts, the secondary attack rate was higher (73.8%) if the unvaccinated primary case had 50 lesions or more compared with fewer than 50 lesions (67.9%; RR, 0.92 [95% CI, 0.86-0.99]) (Table 2). Following exposure to vaccinated primary cases, the secondary attack rate among unvaccinated contacts was much higher (65.2%) if the primary case had 50 or more lesions compared with fewer than 50 lesions (23.4%; P<.002). Moreover, vaccinated cases with 50 or more lesions appeared to be as contagious as unvaccinated cases with less than 50 lesions (RR, 0.96; 95% CI, 0.71-1.30). Vaccinated cases with fewer than 50 lesions were only one third as contagious as unvaccinated cases with 50 or more lesions (RR, 0.32; 95% CI, 0.19-0.53).

Vaccine Effectiveness

Among the 1499 unvaccinated contacts aged 1 to 14 years exposed to an unvaccinated varicella case, 1071 (71.5%) developed varicella compared with 25 (15.1%) of 166 vaccinated contacts (Table 2); thus vaccine effectiveness for prevention of all disease was 78.9% (95% CI, 69.7%-85.3%). For prevention of moderate disease, vaccine effectiveness was 92% (varicella with 50-500 lesions) and 100% (varicella resulting in a complication requiring a health care clinician visit); and for prevention of severe disease, 100%. Among 620 children with a varicella history, 44 developed varicella following household exposure (secondary attack rate, 7.1%) (Table 2). Therefore, varicella disease history was 90.1% effective for prevention of all disease.

COMMENT

Overall, in this study of varicella transmission in households, we found that persons with breakthrough disease (ie, persons with varicella despite receiv-

Table 1. Secondary Attack Rate of Unvaccinated Household Contacts Exposed to Unvaccinated Primary Household Cases

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>No. of Contacts</th>
<th>Secondary Attack Rate, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>164</td>
<td>97 (69.1)</td>
</tr>
<tr>
<td>1-4</td>
<td>713</td>
<td>513 (72.0)</td>
</tr>
<tr>
<td>5-9</td>
<td>615</td>
<td>446 (72.5)</td>
</tr>
<tr>
<td>10-14</td>
<td>171</td>
<td>112 (65.5)</td>
</tr>
<tr>
<td>≥15</td>
<td>368</td>
<td>113 (30.7)</td>
</tr>
</tbody>
</table>

Table 2. Secondary Attack Rate and Lesion Severity of Secondary Cases Among Household Contacts Aged 1 to 14 Years by Vaccination and Varicella History Status of Primary Cases and Household Contacts, Antelope Valley, Calif, 1997-2001

<table>
<thead>
<tr>
<th>Primary Varicella Cases</th>
<th>Secondary Varicella History</th>
<th>No. of Cases</th>
<th>No. of Contacts</th>
<th>Secondary Attack Rate, No. (%)</th>
<th>RR (95% CI)</th>
<th>Lesions of Secondary Cases, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>1088</td>
<td>No</td>
<td>1499</td>
<td>1071 (71.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>112</td>
<td>No</td>
<td>166</td>
<td>25 (15.1)</td>
<td>0.21 (0.15-0.30)</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>397</td>
<td>Yes</td>
<td>620</td>
<td>44 (7.1)</td>
<td>0.10 (0.07-0.13)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>54</td>
<td>No</td>
<td>70</td>
<td>26 (37.1)</td>
<td>0.52 (0.38-0.71)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>59</td>
<td>No</td>
<td>94</td>
<td>21 (22.3)</td>
<td>0.31 (0.21-0.46)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>27</td>
<td>Yes</td>
<td>38</td>
<td>1 (2.6)</td>
<td>0.04 (0.01-0.25)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>56</td>
<td>No</td>
<td>65</td>
<td>29 (44.6)</td>
<td>0.62 (0.48-0.82)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>13</td>
<td>Yes</td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>86</td>
<td>No</td>
<td>161</td>
<td>26 (16.1)</td>
<td>0.23 (0.16-0.32)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, risk ratio.
Vaccinated... et al,10 who described an attack rate of 12% among vaccinated siblings after exposure to a vaccinated household case. Transmission between vaccinated children and adolescents raises the potential for sustained varicella transmission in group settings, such as schools, even when vaccine coverage is high.17

Due to the intensity and duration of exposure, household contact studies are an ideal method for studying vaccine effectiveness and represent the most intense test of vaccine performance. Therefore, our study provides reassuring evidence of the extremely high effectiveness of varicella vaccine in preventing moderate or severe disease under the most adverse circumstances. For prevention of all disease, we found varicella vaccine effectiveness to be within the range of effectiveness described from other postlicensure studies.15-22

We also confirmed previous findings that the varicella secondary attack rate varies according to age.8 For infants, maternally acquired antibodies likely contribute to their lower secondary attack rate. The lower attack rate among persons aged 15 years or older reflects high immunity gained through natural varicella infection and reaffirms the low-predictive value of a negative history in predicting susceptibility.6,23 The secondary attack rate of 71.5% among unvaccinated children and adolescents with a negative disease history is similar to previous studies among susceptible children (defined by negative disease history) in England (65%)11 and in the United States (86%-87%).3,8 Secondary attack rates as high as 100% have been described in seronegative children who were placebo recipients in household varicella vaccine postexposure studies.6,7 Not all children with a negative disease history are seronegative and the likelihood will decrease with increasing age. In a study of children aged 7 to 12 years with negative varicella history, 9% of 7-year-olds, 23% of 9-year-olds, and 33% of 12-year-olds had serological evidence of immunity.24 Other reasons for differences in secondary attack rate across studies include definitions of the length of the incubation period, which varied from between 8 and 21 days4 to between 10 and 23 days.3

Our finding that some children and adolescents with a positive history of varicella contracted disease mirrored findings by Ross,3 who also described a 7% secondary attack rate among siblings with a positive disease history. Secondary varicella infections have been described in a small case series with laboratory confirmation for both cases25 and previously in our surveillance area.26 These cases may represent true second cases of varicella or an erroneous history of varicella. The fact that 82% of such cases had 50 or more lesions—a similar proportion of moderate or severe disease as unvaccinated cases (76%)—may be more suggestive of erroneous disease history. Alternatively, a small proportion of the population may not develop immunity sufficient to prevent or modify disease following their first varicella infection. As the varicella vaccination program continues with further declines in disease in all age groups, the likelihood will decrease that persons with positive disease history will actually have had varicella, which may prompt consideration of whether persons should receive varicella vaccine irrespective of their disease history.

The following limitations should be considered when interpreting our data. First, cases were clinically diagnosed rather than laboratory confirmed. However, varicella is an easily recognized disease (even by the public) and laboratory diagnosis is not the standard of care. Moreover, a clustering of secondary cases 2 weeks after primary cases (data not shown) is consistent for the incubation period for varicella. Second, because susceptibility was defined in terms of negative disease (and vaccination) history rather than negative serological status, we are likely to have underestimated secondary attack rate among unvaccinated children because a proportion will be immune. This, in turn, would underestimate vaccine effectiveness. Finally, because vaccination status of contacts was based on parental recall as well as immunization record, there may have been misclassification of vaccination status, which could affect

Table 3. Secondary Attack Rate of Unvaccinated Household Contacts Aged 1 to 14 Years by Vaccination Status and Number of Lesions of the Primary Cases

<table>
<thead>
<tr>
<th>Primary Cases</th>
<th>Unvaccinated</th>
<th>Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥50 Lesions</td>
<td>&lt;50 Lesions</td>
</tr>
<tr>
<td>Primary cases, No.</td>
<td>654</td>
<td>434</td>
</tr>
<tr>
<td>Contacts, No.</td>
<td>907</td>
<td>592</td>
</tr>
<tr>
<td>Secondary cases, No.</td>
<td>669</td>
<td>402</td>
</tr>
<tr>
<td>Secondary attack rate, %</td>
<td>73.8</td>
<td>67.9</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>0.92 (0.86-0.99)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, risk ratio.
vaccine effectiveness estimates in either direction.

Since implementation of the varicella vaccination program in the United States, varicella cases have declined dramatically. In sentinel surveillance sites, varicella cases and hospitalizations declined by approximately 80% by 2000. A similar downward trend is indicated from passive surveillance data through state notifications to the National Notifiable Disease Surveillance System in 2001 and by the number of varicella deaths reported to the Centers for Disease Control and Prevention. It appears likely, therefore, that the 2010 Healthy People goals for more than 90% reduction in varicella cases will be met ahead of schedule. As cases and the severe health burden from varicella further decline, monitoring age, severity, and vaccination status of the remaining varicella cases will become increasingly important. It is expected that with continuing increases in vaccine coverage, a higher proportion of cases will occur in vaccinated children. Further understanding of the severity and contagiousness of these cases in the community as well as in household settings will assist with future vaccine policy decisions.

A recent study reported a 4% increase in varicella vaccine efficacy (and therefore a lower risk of breakthrough disease) among 2-dose compared with 1-dose vaccine recipients. However, the efficacy of 1 dose of varicella vaccine in this study (94.4%) was considerably higher than that in our study and in the majority of postlicensure vaccine effectiveness studies. Studies of transmission of breakthrough cases and the effectiveness of 2 doses of varicella vaccine in community settings are needed. If vaccinated cases are sufficiently contagious to enable ongoing transmission, especially in child care, school, and university settings, a re-evaluation of the goal of the varicella vaccination program (elimination of endemic disease transmission vs disease control) and appropriate strategies for achieving the program goal, including a 2-dose varicella vaccine policy, may need to be considered.

Author Contributions: Dr Seward had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Seward, Mascola, Jumaan.

Acquisition of data: Seward, Zhang, Maupin, Mascola.

Analysis and interpretation of data: Seward, Zhang, Jumaan.

Drafting of the manuscript: Seward, Zhang, Mascola.

Critical revision of the manuscript for important intellectual content: Maupin, Jumaan.

Statistical analysis: Zhang, Jumaan.

Obtained funding: Mascola.

Administrative, technical, or material support: Seward, Zhang, Maupin, Jumaan.

Study supervision: Seward, Mascola.

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