Parental Refusal of Varicella Vaccination and the Associated Risk of Varicella Infection in Children

Jason M. Glanz, PhD; David L. McClure, PhD; David J. Magid, MD, MPH; Matthew F. Daley, MD; Eric K. France, MD, MSPH; Simon J. Hambidge, MD, PhD

Objective: To quantify both the individual-level and attributable risk of varicella infection requiring medical care in children whose parents refuse varicella immunizations.

Design: Matched case-control study with conditional logistic regression analysis.


Participants: Each pediatric physician-diagnosed case of varicella (n=133) was matched to 4 randomly selected controls (n=493). Cases were matched by age, sex, and length of enrollment in KPCO.

Main Exposures: Varicella vaccine refusal.

Outcome Measures: Varicella infection.

Results: There were 7 varicella vaccine refusers (5%) among the cases and 3 (0.6%) among the controls. Children of parents who refused varicella immunizations were at a greatly increased risk of varicella infection requiring medical care (odds ratio, 8.6; 95% confidence interval, 2.2-33.3) compared with children of parents who accepted vaccinations (P=.004). In the entire KPCO pediatric population, 5% of varicella cases were attributed to parental vaccine refusal.

Conclusions: Children of parents who refuse varicella immunizations are at high risk of varicella infection relative to vaccinated children. These results will be helpful to health care providers and parents when making decisions about immunizing children.

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utable risk of varicella infection requiring medical care in children whose parents refuse varicella immunizations. Such information will be useful to physicians who have to counsel vaccine-refusing parents.

### METHODS

#### SETTING AND STUDY POPULATION

We conducted a case-control study to determine whether children who contracted varicella infection were more likely to have parents who refused varicella vaccination than a similar group of children who did not develop varicella infection. The setting was Kaiser Permanente Colorado (KPCO), a Denver-based health plan with more than 300,000 members. Members of KPCO receive full coverage of all pediatric vaccines, as recommended by the Advisory Committee on Immunization Practices. The study population included children aged 12 months to 8 years who were members of the health plan between 1998 and 2008. Currently, 95% of children in KPCO have up-to-date varicella vaccinations. During the entire study period, varicella vaccine was routinely given to children aged 12 to 18 months; after 2005, a second dose was routinely given to children aged 48 to 59 months. Children had to be continuously enrolled in KPCO for at least 6 months to be eligible for the study. The study was reviewed and approved by the KPCO institutional review board.

#### CASE DEFINITION

Potential cases of varicella were identified using the KPCO automated databases. Potential cases were selected if they had an International Classification of Diseases, Ninth Revision (ICD-9) code for varicella (052.x) or a laboratory test ordered for varicella. The laboratory tests included polymerase chain reaction, direct fluorescent antibody, isolation of varicella virus, or rise in serum varicella IgG.

The medical records of the potential cases were reviewed by a trained abstractor (Nicole Wagner, MPH) to confirm case status. The date of the ICD-9 code or laboratory test from the automated databases represented the medical encounter date. The abstractor, blinded to vaccination status, recorded details for this encounter and all encounters up to 14 days following this encounter from the medical record. The abstractor recorded presenting symptoms (eg, presence of a maculopapulovesicular rash, number of vesicular lesions, fever, malaise), laboratory results, clinical diagnoses, and complications of varicella infection (eg, secondary bacterial infection of skin lesions, encephalitis, pneumonia, ataxia, hepatitis, thrombocytopenia, optic neuritis, myocarditis, transverse myelitis, invasive group A streptococcal infection, death). Of the cases with invasive streptococcal infection, the abstractor examined the medical records for diagnoses of cellulitis, necrotizing fasciitis, septicemia, and toxic shock syndrome.

The abstractor recorded prior exposures to close contacts infected with varicella; a close contact was defined as someone at daycare, school, or home with known varicella infection. The abstractor also recorded preexisting conditions that may increase the risk of severe varicella infection including malignancies and human immunodeficiency virus or AIDS. Additional variables including birth date, sex, and medical setting of the qualifying encounter were extracted from medical records.

Patients were classified as confirmed cases if they had a physician diagnosis of varicella documented in the medical records. Confirmed cases aged between 12 months and 8 years were eligible for the final analyses. Cases diagnosed prior to 12 months were excluded because children are not immunized until they are at least 12 months of age. Cases diagnosed within 14 days of varicella vaccination were excluded because they likely represented wild-type varicella infection before a full immune response had developed to the vaccine.

#### CONTROL DEFINITION

An index date was defined for all cases and controls. The date of varicella diagnosis was the index date for the cases. Each case of varicella was then matched to 4 randomly selected controls by sex, length of KPCO enrollment in months, and age at index date (within 7 days). Each matched control had to be enrolled in KPCO on the index date. Matched controls also had to have at least the same amount of enrollment prior to the index date as the corresponding matched case. The controls were selected from a pool of pediatric members enrolled in the KPCO health plan between 1998 and 2008. Eligible controls did not have a record of varicella infection prior to the index date.

#### VACCINATION STATUS

Varicella vaccination status for both cases and controls was assessed retrospectively from the index date. The medical records of cases and controls were reviewed by a trained medical records abstractor who was blinded to varicella case status. The medical abstractor documented the dates of varicella vaccinations received and whether varicella immunizations were refused by parents for personal, nonmedical reasons. Children were classified as vaccine refusers if it was explicitly documented in the medical record that their parents had refused 1 or more varicella immunizations for personal, nonmedical reasons. Children were classified as vaccine acceptors if they were vaccinated against varicella at the index date. Cases and controls were excluded if they had a documented medical contra-indication to vaccination (malignancy, human immunodeficiency virus or AIDS, systemic lupus erythematosus, cystic fibrosis, rheumatoid arthritis, scleroderma, and patients receiving corticosteroids or intravenous immune globulin). Cases and controls were also excluded if the reason for lack of vaccination was not explicitly documented in medical records.

#### STATISTICAL ANALYSIS

To estimate the association between vaccine refusal and varicella infection, we used conditional logistic regression to calculate matched odds ratios and associated 93% confidence intervals. In the regression model, the dependent variable was varicella case status and the main independent variable was vaccine refuser status. The matched odds ratio from the conditional logistic regression model was used to calculate the percentage of attributable risk in the vaccine refusers and the attributable risk in the total population. As a subanalysis, we ran a logistic regression model on the unmatched data, controlling for age, sex, and length of KPCO enrollment.

#### RESULTS

We identified a cohort of 86,993 children who were continuously enrolled in KPCO for a minimum of 6 months between 1998 and 2008. In this cohort, we identified 343 patients with an ICD-9 diagnostic code of varicella in-
fever in the automated administrative databases. Three of these patients (0.9%) also had a positive IgG test for varicella. One hundred twenty-two patients (36%) were excluded because the diagnosis was for a history of varicella illness rather than an acute infection. We excluded 34 patients (10%) with a varicella diagnosis prior to their 1-year well-child visit. Nine cases (3%) were excluded because they were diagnosed by telephone only. We excluded 17 patients (5%) that were diagnosed within 14 days of varicella vaccination. Twenty-six unvaccinated cases (8%) were excluded because the reason for lack of vaccination was not documented in the medical records. Two additional patients (1%) were excluded because they had medical contraindications to varicella vaccination. This resulted in a final study population of 133 confirmed cases (39%). None of the confirmed incident cases were diagnosed with a positive laboratory test; they were all diagnosed by clinical evaluation. In the final case population, 7 (5%) had parents who refused all varicella immunizations.

The mean age of the cases was 3.9 years, and 55% were female (Table 1). The incidence rate of confirmed varicella cases did not vary by year or season (quarter of year). Most cases presented in the clinic or emergency department, and 1 case (0.8%) was hospitalized (Table 2). The most common complication was secondary bacterial infection, seen in 6% of children with varicella.

### CONTROLS

Of the 532 potential controls, we excluded 39 children (7%) who did not have immunization records because the reason for lack of vaccination was not documented in the medical records. This resulted in a final study population of 493 controls. The controls had similar sex and age distributions as the cases. In the final control population, 3 children (<1%) had parents who refused 1 or more varicella immunizations (Table 1).

### RISK OF VARICELLA IN VACCINE REFUSERS

Varicella vaccine refusal was strongly associated with medical record–verified varicella illness (odds ratio, 8.6; 95% confidence interval, 2.2-33.3; P = .004). The percentage of attributable risk in the vaccine refusal population was 99.4% (95% confidence interval, 97.2%-99.9%), suggesting that all 7 of the unvaccinated varicella cases were attributed to vaccine refusal. The total population attributable risk was 4.7% (95% confidence interval, 0.7%-8.5%), suggesting that 4.7% of the varicella cases in the total population were associated with vaccine refusal.

In an unmatched analysis, none of the matching variables (age, sex, length of medical plan enrollment) were statistically significant. The odds ratio for vaccine refusal in this subanalysis was 9.1 (95% confidence interval, 2.3-35.7).

Our study found a strong association between parental varicella vaccine refusal and the risk of medically attended childhood varicella disease. Compared with vaccine acceptors, children of vaccine-refusing parents had a 9-fold increased risk of varicella illness. Overall, 5% of varicella cases in the study population were attributed to vaccine refusal. We believe these results will be helpful to health care providers and parents when discussing decisions about immunizing children.

To our knowledge, this is the first study to examine the relationship between vaccine refusal and the risk of varicella infection. Our study was conducted using individual-level clinical data on a well-defined cohort of children. We were able to minimize potential biases due to misclassification of exposure and outcome by validating both varicella vaccination status and varicella case status with a detailed medical record review.

Our results have important clinical implications. Universal immunization against varicella has significantly reduced rates of hospitalization and death due to varicella infection in children. Parents who refuse varicella immunizations place their children at risk for varicella infection requiring medical care when compared with fully vaccinated children. If the number of vaccine-refusing parents continues to increase across the US, it is likely that the incidence of severe varicella-associated complications will also increase over time.

High immunization rates help prevent the spread of varicella infection throughout the population, a con-

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**Table 1. Demographic Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 133)</th>
<th>Controls (n = 493)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>73 (54.9)</td>
<td>273 (55.4)</td>
</tr>
<tr>
<td>Male</td>
<td>60 (45.1)</td>
<td>220 (44.6)</td>
</tr>
<tr>
<td>Vaccine refusers</td>
<td>7 (5.3)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Mean (SD) age, y</td>
<td>3.9 (2.1)</td>
<td>3.8 (2.1)</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>55 (41.4)</td>
<td>207 (42.0)</td>
</tr>
<tr>
<td>4-6</td>
<td>47 (35.3)</td>
<td>174 (35.3)</td>
</tr>
<tr>
<td>7-8</td>
<td>31 (23.3)</td>
<td>112 (22.7)</td>
</tr>
</tbody>
</table>

**Table 2. Clinical Characteristics Documented in the Medical Records of 133 Varicella Cases**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>93 (69.9)</td>
</tr>
<tr>
<td>Vesicular lesions</td>
<td>92 (69.2)</td>
</tr>
<tr>
<td>Papules</td>
<td>73 (54.9)</td>
</tr>
<tr>
<td>Fever</td>
<td>39 (29.3)</td>
</tr>
<tr>
<td>Macules</td>
<td>18 (15.3)</td>
</tr>
<tr>
<td>Sequelae</td>
<td></td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>6 (4.5)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Impetigo</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Streptococcal infection</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>
cept known as herd immunity. Herd immunity provides protection to those who are at highest risk for severe varicella infection, including pregnant women, infants, persons with human immunodeficiency virus and other immunodeficiency disorders, those receiving chemotherapy, and patients treated with high-dose corticosteroids. Therefore, as rates of vaccine refusal increase, herd immunity wanes, and certain vulnerable populations will be at higher risk for severe varicella infection. In addition, because vaccine refusal in known to vary geographically, the associated risks for varicella infection are likely to be exacerbated in communities where vaccine refusal clusters.

Routine varicella immunization has also led to substantial health care and societal cost savings. Prior to universal varicella immunization, varicella illness was responsible annually for more than $330 million in health care costs and more than $1.5 billion in societal costs. Since licensure, universal 2-dose immunization has reduced varicella-associated health care costs by 97% and societal costs by 98%. It is therefore likely that parents who refuse to vaccinate their children place added economic burden on our nation’s health care system and society as a whole.

We would like to acknowledge several limitations of this study. First, our study population was selected from a single managed health care plan in Colorado, which may limit the generalizability of our findings. Kaiser Permanente Colorado, however, is a large integrated health care delivery system that broadly represents Colorado’s population. Moreover, the rates of varicella infection and vaccine refusal in KPCO are similar to previously published estimates.

Second, it is possible that physicians are more likely to make a diagnosis of varicella in children who are unvaccinated than in children who are vaccinated. This type of diagnostic bias would lead to an overestimate of the risk associated with vaccine refusal. However, breakthrough cases in vaccinated patients are common, in our study, 95% of varicella cases were in children who were vaccinated against varicella. For this reason, we do not believe that a diagnostic bias had a substantial effect on our results.

Third, vaccine refusal in our case-control population was uncommon; there were only 10 vaccine refusers (1.6%) of the 626 cases and controls. As a consequence, we did not have sufficient statistical power to evaluate the association between vaccine refusal and varicella infection by year from 1998 to 2008. In addition, a case-control study design does not allow for the calculation of parental vaccine refusal rates over time.

Finally, we may have missed mild cases of varicella that did not come to medical attention. If a disproportionate number of these mild cases had been vaccinated, it could have led to an overestimate of the risk associated with vaccine refusal. Conversely, vaccine refuser cases may have been underrepresented in our study because parents who refuse vaccination may be less likely to bring their children to medical attention. This behavior would result in an underestimate of the effect of vaccine refusal on the risk of varicella infection.

Parental refusal of varicella vaccination has important clinical and economic implications for children and the broader community in which they live. Our results provide details about the individual-level risk of disease owing to the refusal of varicella vaccination, the most commonly refused of all childhood immunizations. We found that children of parents who refuse varicella vaccination are at a significantly increased risk of varicella infection requiring medical care. These results provide evidence to counter the misperception among some parents that unvaccinated children are not at risk for vaccine-preventable diseases. As vaccine refusal increases in the United States, health care providers are in a uniquely trusted position to influence immunization behavior. We believe this information will be useful to physicians who counsel patients about immunizations.

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Correspondence: Jason M. Glanz, PhD, Institute for Health Research, Kaiser Permanente Colorado, PO Box 378066, Denver, CO 80237-8066 (jason.m.glanz@kp.org).

Author Contributions: Study concept and design: Glanz, McClure, Daley, France, and Hambidge. Acquisition of data: Glanz and McClure. Analysis and interpretation of data: Glanz, McClure, Magid, Daley, and Hambidge. Drafting of the manuscript: Glanz, McClure, and Magid. Critical revision of the manuscript for important intellectual content: Daley, France, and Hambidge. Statistical analysis: Glanz and McClure. Obtained funding: Glanz and Hambidge. Study supervision: Glanz, Daley, France, and Hambidge.

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REFERENCES


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