Long-term Effectiveness of Varicella Vaccine: A 14-Year, Prospective Cohort Study

BACKGROUND: Varicella vaccine was licensed in the United States in 1995 for individuals ≥12 months of age. A second dose was recommended in the United States in June 2006. Varicella incidence and vaccine effectiveness were assessed in a 14-year prospective study conducted at Kaiser Permanente Northern California.

METHODS: A total of 7585 children vaccinated with varicella vaccine in their second year of life in 1995 were followed up prospectively for breakthrough varicella and herpes zoster (HZ) through 2009. A total of 2826 of these children received a second dose in 2006–2009. Incidences of varicella and HZ were estimated and compared with prevaccine era rates.

RESULTS: In this cohort of vaccinated children, the average incidence of varicella was 15.9 per 1000 person-years, nine- to tenfold lower than in the prevaccine era. Vaccine effectiveness at the end of the study period was 90%, with no indication of waning over time. Most cases of varicella were mild and occurred shortly after the cohort was vaccinated. No child developed varicella after a second dose. HZ cases were rare, with an average incidence of 3.8 per 1000 person-years, far lower than in the prevaccine era rates.

CONCLUSIONS: This study demonstrates the lasting effectiveness of varicella vaccine and the benefit of the second dose. Breakthrough varicella occurred soon after vaccination, varicella rates did not increase over 14 years, and there was no increase in zoster in the cohort.

WHAT’S KNOWN ON THIS SUBJECT: Varicella vaccine is known to be highly effective, with added benefit from a second dose.

WHAT THIS STUDY ADDS: This study demonstrates the lasting effectiveness of varicella vaccine and the benefit of the second dose. Breakthrough varicella occurred soon after vaccination, varicella rates did not increase over 14 years, and there was no increase in zoster in the cohort.

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KEY WORDS chicken pox, children, effectiveness, vaccine, varicella, zoster

ABBREVIATIONS CI—confidence interval HZ—herpes zoster KPNC—Kaiser Permanente Northern California PY—person-years RR—relative risk VZV—varicella virus zoster

Dr Baxter supervised data collection and analyses, drafted the initial manuscript, and approved the final manuscript as submitted; Ms Ray designed data collection instruments, coordinated interviews and data collection, performed analyses, reviewed the manuscript, and approved the final manuscript as submitted; Dr Tran assisted with analyses and the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted; Drs Black and Shinefield assisted with the original concept and design, supervised early data collection and analyses, and reviewed and approved the final manuscript as submitted; Mr Lewis assisted with the design and statistical plan, and reviewed and approved the manuscript as submitted; Dr Coplan assisted with original design and statistical plan, and reviewed and approved the manuscript as submitted; Mr Lewis assisted with the design and statistical plan, assisted with analyses, critically reviewed the manuscript, and approved the final manuscript as submitted; Dr Fireman assisted with the original concept and design, worked on analyses, critically reviewed the manuscript, and approved the final manuscript as submitted; and Dr Saddier assisted with analyses and the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted.

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Varivax (Oka/Merck varicella vaccine live [Merck Sharp & Dohme Corp, Whitehouse Station, NJ]), based on the Oka strain developed by Takahashi et al in the 1970s,1 was licensed in the United States in 1995 and recommended soon after by the Advisory Committee on Immunization Practices for routine administration to all immunocompetent children.2 Before that time, varicella virus zoster (VZV) infection was ubiquitous, with >90% of people experiencing infection by the age of 20 years, and resulting in thousands of hospitalizations with ∼100 deaths annually in the United States.3–6 After introduction of the vaccine in the United States, disease incidence fell markedly.7,8 Efficacy of 1 dose of vaccine was high in clinical trials,9 and the vaccine’s effectiveness was confirmed in post-licensure studies to be 80% to 94%10,11 in preventing chicken pox and highly effective in preventing moderate to severe disease. However, breakthrough disease was noted and outbreaks still occurred,12–14 leading to a recommendation by the Advisory Committee on Immunization Practices in 2006 for a second dose of the vaccine at 4 to 6 years of age.15 Since implementation of the second dose, studies have reported that varicella incidence has declined further.11,16 Effectiveness of the 2-dose series was calculated to be 98% in 2 separate studies, a randomized, prospective study11 and a case-control study.17 The effect of varicella vaccination programs on the incidence of herpes zoster (HZ) in the general population is not well known. HZ risk was found to be lower in vaccinated children aged <10 years than in unvaccinated children of the same age with a history of varicella.18,19 However, concerns arose that widespread vaccination of children could decrease VZV immune-boosting opportunities and lead to an increase in HZ in adults.20–23 In the current study, we prospectively followed up a cohort of children for 14 years who received varicella vaccine in their second year of life (in 1995) to assess the long-term effectiveness of the vaccine and the impact on the epidemiology of varicella and HZ. We also observed the impact of the second dose of varicella vaccine introduced in 2006. This study was conducted as a post-licensure commitment to health authorities, initially in the United States and then worldwide.

METHODS

Study Population

The study was conducted at multiple sites in Kaiser Permanente Northern California (KPNC), an integrated health care delivery system serving 3.2 million members. The membership reflects the racial and economic diversity of the general population in the northern California region, although it under-represents the low end of the economic spectrum.24–26 Members obtain almost all their medical care at KPNC facilities. KPNC databases store detailed information on all health care encounters, which are linked by using the patient’s unique medical record number.

Parents or guardians of children 12 to 23 months of age, who received varicella vaccine between June and November 1995 as a part of routine care, were contacted by telephone interviewers 6 months after receipt of the vaccine and asked to participate in a long-term follow-up study of varicella. Parents of 7585 vaccinated children consented to participate.

Data Collection

Telephone interviews were scheduled every 6 months for 14 years, from vaccination through 2009. At each contact, parents were asked about the occurrence of varicella and zoster since the last interview. Parents were provided a toll-free telephone number to report new varicella in their child between interviews or to ask questions. During each interview, parents were reminded about the clinical features of varicella and zoster, and instructed to call immediately if signs or symptoms of either of these arose.

Outcomes Definitions

Breakthrough varicella cases were based on parental report; no medical confirmation of the diagnosis was required. Parents were asked whether there were ≤50 lesions (mild); 51 to 300 lesions (moderate); or >300 lesions (severe). Cases occurring within 6 weeks of vaccination were excluded to avoid including vaccine-related rash/varicella or wild-type disease that may have been contracted before vaccination. For the description of rates of varicella after the second dose, only children with continuous KPNC membership from June 2006 (when the second dose was recommended) to November 2009 (the end of the study) were included to ensure reliable vaccine information. Cases of HZ required a diagnosis by a medical provider; confirmed by chart review, but did not require any laboratory confirmation. No testing was done to determine whether HZ cases were due to wild-type or vaccine-derived virus.

Analyses

Varicella

We measured the incidence of breakthrough varicella in vaccinees every 6 months and estimated annual rates. The person-time denominator was the total follow-up time contributed since the last interview by subjects who completed the interview for that phase. The primary analysis was based on the first occurrence of varicella, and person-time was censored at the time of the first episode, ignoring subsequent
episodes. We also measured total varicella incidence including recurrent cases after the first occurrence of varicella and all of the available person-time of follow-up.

Because the entire cohort was vaccinated, we used historical varicella incidence rates as the comparator to estimate varicella vaccine effectiveness, based on published studies conducted before vaccine licensure. Two of the published studies were population based, used parent-reported varicella, and provided age-specific incidence rates of varicella in children. We used susceptibility-adjusted rates, based on only susceptible individuals, from these published studies. To obtain the average historical varicella incidence rate over the duration of the study for comparison, we calculated a weighted average historical incidence rate, assuming all children were vaccinated at 18 months of age (the midpoint of the second year) and using the contribution of each age group to the total follow-up of the study cohort as the weight (Table 1).

**HZ**

To compare rates of HZ in the study cohort with rates of HZ in unvaccinated children, we reviewed the literature on the incidence of HZ before vaccine licensure. We identified only 2 population-based epidemiologic studies providing incidence rates of physician-diagnosed HZ in children. We chose HZ reference rates from the only study that restricted the analysis to children who had experienced varicella (Table 2).

**Statistical Methods**

Person-time was calculated according to interview cycle. For varicella, the relative risk (RR) was calculated as the ratio of the observed versus the pre-vaccine incidence rates. Vaccine effectiveness was calculated as 1 minus the RR. For HZ, the RR was the ratio of the total number of observed HZ cases in the study cohort and the total number of expected cases in unvaccinated children of the same age with a history of naturally acquired varicella during the same period of time.

This study was approved by the KPNC institutional review board.

**RESULTS**

**Follow-up**

The parents/guardians of 9316 children 12 through 23 months of age, vaccinated between June and November 1995, were invited to participate in this study. Overall, 9.9% could not be reached by telephone, 6.2% refused to participate, and 2.5% were ineligible because of age or language barriers, yielding an initial cohort of 7585 (81.4%) patients enrolled by December 1995. Fourteen years later, at the end of November 2009, a total of 2814 reports were received, yielding 1505 breakthrough cases of varicella. Of the 1505 reports, 80 cases (2%) reported recurrent varicella. Of the 1505 reports, 80 cases (2%) reported 51 cases of HZ. The incidence rates of first episode of breakthrough varicella are presented in Table 3.

The average incidence rate of breakthrough varicella over the 14 years of follow-up was 15.9 per 1000 PY (95% confidence interval [CI]: 15.1–16.7) for varicella episodes with any number of lesions. Considering all episodes (including recurrences), the average incidence rate of breakthrough varicella was 14.6 per 1000 PY (95% CI: 13.9–15.4) for any symptoms, 3.7 per 1000 PY (95% CI: 3.4–4.1) for >50 lesions, and 0.3 per 1000 PY (95% CI: 0.2–0.5) for >300 lesions (data not shown).

Annual breakthrough rates of varicella were stable at ~26 per 1000 PY in the first 4 years after vaccination. They decreased to <20 per 1000 PY after the fourth year, to ~9 per 1000 PY at the end of 11 years of follow-up, then to 2 per 1000 in 2009, the last year of follow-up. A total of 28 first-incident
breakthrough varicella cases with >300 lesions were reported over the 14 years of follow-up, including 13 in the first 4 years after vaccination. Overall, there did not seem to be an increase in the severity of breakthrough varicella cases over time in vaccinated children (Fig 1).

**Comparison With Historical Incidence Rates of Varicella**

Based on susceptibility-adjusted historical rates of varicella for children 1 to 15 years old in the 2 reference studies, the expected average varicella incidence rates in the cohort children, had they remained unvaccinated, were 140.1 and 158.9 per 1000 PY (Table 1). The observed incidence rate of 15.9 per 1000 PY in the 1- to 15-year-old vaccinated children in the study was therefore 9 to 10 times lower than the historical rates in children of the same age in the prevaccine era. The overall vaccine effectiveness at the end of the study was 89% to 90% depending on the reference study used. Annual vaccine effectiveness ranged from 73% to 80% in 1996–1997 (the first 2 years of the study) to 80% to 90% in 2000–2009 (the last 10 years of the study).

**Racial Differences in Breakthrough Varicella Rates**

The average incidence rate of reported breakthrough varicella was slightly lower in Asian (12.4 per 1000 PY [95% CI: 10.6–14.5]) and African-American (11.5 per 1000 PY [95% CI: 9.2–14.4]) children than in white children (16.0 per 1000 PY [95% CI: 14.8–17.2]). For Hispanic children, the rate was 13.0 per 1000 PY (95% CI: 11.3–15.0), and for multiracial participants, it was 15.1 per 1000 PY (95% CI: 13.6–16.8).

**Breakthrough Varicella in Study Participants Who Received a Second Dose**

Among the study participants who were still active in the last survey year, 4546 (62%) were continuous KPNC health plan members from June 2006 to November 2009. Of these, 2829 children (62% [or 33.6% of the study cohort]) received a second dose of varicella vaccine. No breakthrough varicella cases were reported after receipt of a second dose.

**TABLE 2 Incidence of HZ According to Age Group and Compared With Historical Rates**

<table>
<thead>
<tr>
<th>Age Groupa</th>
<th>PYb</th>
<th>Expected</th>
<th>Observed</th>
<th>RR Observed/Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Historical Rate c,d</td>
<td>No. of Expected Cases</td>
<td>Observed Cases</td>
</tr>
<tr>
<td>&lt;5 y</td>
<td>25 313</td>
<td>1.10</td>
<td>27.8</td>
<td>4</td>
</tr>
<tr>
<td>5–9 y</td>
<td>37 176</td>
<td>0.51</td>
<td>19.0</td>
<td>17</td>
</tr>
<tr>
<td>10–15 y</td>
<td>40 099</td>
<td>0.69</td>
<td>28.0</td>
<td>25</td>
</tr>
<tr>
<td>All ages (1–15 y)</td>
<td>103 098</td>
<td>0.73</td>
<td>74.8</td>
<td>48</td>
</tr>
</tbody>
</table>

a Age was estimated on interview cycle since vaccination, assuming that all children were vaccinated at 18 months of age.

b Person-time denominators were based on the total follow-up time since the last interview by subjects with completed interviews for that phase.

c Age-specific population-based rates in individuals with a history of varicella were obtained from Guess et al, 1986.

d Rate per 1000 PYs.

**TABLE 3 Incidence Rate of Breakthrough Varicella (First Episode Only) According to Year Since Vaccination (Rate per 1000 PYs): KPNC, 1996–2009**

<table>
<thead>
<tr>
<th>Years Since Vaccination</th>
<th>Follow-up in PY</th>
<th>Any Lesions</th>
<th>Mild (1–50 Lesions)</th>
<th>Moderate (51–299 Lesions)</th>
<th>Severe (&gt;300 Lesions)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rate</td>
<td>95% CI</td>
<td>n</td>
<td>Rate</td>
</tr>
<tr>
<td>1</td>
<td>6531</td>
<td>174</td>
<td>26.6 22.9–31.0</td>
<td>150</td>
<td>23.0</td>
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<tr>
<td>2</td>
<td>7311</td>
<td>157</td>
<td>21.5 18.3–25.1</td>
<td>136</td>
<td>18.6</td>
</tr>
<tr>
<td>3</td>
<td>7044</td>
<td>191</td>
<td>27.1 23.5–31.3</td>
<td>161</td>
<td>22.9</td>
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<tr>
<td>4</td>
<td>8841</td>
<td>195</td>
<td>28.2 24.5–32.5</td>
<td>153</td>
<td>22.4</td>
</tr>
<tr>
<td>5</td>
<td>8671</td>
<td>134</td>
<td>20.1 16.9–23.8</td>
<td>101</td>
<td>15.1</td>
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<tr>
<td>6</td>
<td>8505</td>
<td>113</td>
<td>17.4 14.3–20.9</td>
<td>79</td>
<td>12.1</td>
</tr>
<tr>
<td>7</td>
<td>8425</td>
<td>120</td>
<td>17.9 15.6–22.4</td>
<td>81</td>
<td>12.6</td>
</tr>
<tr>
<td>8</td>
<td>8273</td>
<td>79</td>
<td>18.7 10.1–15.8</td>
<td>52</td>
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<tr>
<td>9</td>
<td>8172</td>
<td>76</td>
<td>12.3 9.8–15.5</td>
<td>47</td>
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<td>38</td>
<td>5.9</td>
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<tr>
<td>11</td>
<td>6058</td>
<td>53</td>
<td>8.7 6.6–11.5</td>
<td>26</td>
<td>4.3</td>
</tr>
<tr>
<td>12</td>
<td>5937</td>
<td>48</td>
<td>8.1 6.0–10.8</td>
<td>27</td>
<td>4.5</td>
</tr>
<tr>
<td>13</td>
<td>5945</td>
<td>20</td>
<td>3.4 2.1–5.3</td>
<td>8</td>
<td>1.3</td>
</tr>
<tr>
<td>14</td>
<td>5886</td>
<td>12</td>
<td>2.0 1.1–3.7</td>
<td>6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

All years (0–14) 89 685 1425 15.9 15.1–16.7 1063 11.9 11.2–12.6 334 3.7 3.3–4.2 28 0.3 0.2–0.5

Breakthrough episodes were defined as any reported varicella with onset of symptoms occurring >6 weeks after vaccination.
Incidence and Characteristics of HZ Cases Confirmed by Physician Diagnosis

There were 113 cases of HZ reported over the 14 years of follow-up, 99 of which were seen at KPNC and records were available. Ninety of these reviewable cases occurred after vaccination and were seen by a physician. Forty-six (51%) of the 90 cases had HZ confirmed by the physician. The 46 cases occurred over 103,098 PY of follow-up, resulting in an incidence rate of 0.45 per 1000 PY (95% CI: 0.33–0.60). The incidence of HZ increased slightly over time, as expected with increasing age (Table 2).

Of the 46 confirmed HZ cases, 18 (39%) were male subjects, and the mean age at HZ diagnosis was ~10 years (range: 2.0–15.0 years). Among the 46 HZ cases, 27 (59%) had HZ-related pain identified in their medical charts, 20 with documentation regarding pain severity. Of these 20 cases, 6 were recorded as mild and 14 as moderate. No postherpetic neuralgia was reported. Of the 46 HZ cases, 40 resolved without sequelae, 5 had unknown outcome, and 1 was unresolved. The average time between varicella vaccination and HZ diagnosis was 8.4 years. Twenty of the confirmed HZ cases had a previous report of breakthrough varicella. The average time interval between the reported breakthrough varicella and HZ was 6.1 years (range: 0.9–11.5 years). No cases of HZ were reported after a second dose.

Comparison With Historical Incidence Rates of HZ in Children

Based on the historical rates of HZ after naturally acquired varicella, ~75 cases of HZ were expected in the study cohort over the 14 years of follow-up, corresponding to an average incidence of 0.73 per 1000 PY. At the end of the study, the calculated RR was 0.61 (95% CI: 0.43–0.89), suggesting an ~40% decreased HZ incidence in vaccinated children over the first 14 years after vaccination compared with that in unvaccinated children of the same age in the prevaccine era. This rate resulted in an overall vaccine effectiveness of ~90% (ranging from ~75% to 90%), consistent with previous studies in the United States and Europe.

The incidence rate of breakthrough varicella steadily decreased over time, and no increase was observed during the 14 years of follow-up. Few breakthrough cases were severe (only 28 of 7585 children over 14 years had >300 lesions), whereas in the prevaccine era, most children presented with >300 lesions. Prevention of moderate to severe disease was achieved with 1 dose of varicella vaccine, with 14 years of active surveillance of both patient-reported varicella and physician-diagnosed HZ. Retention was excellent, with >97% of the 7585 children initially enrolled in the cohort completing the study.

Over the entire follow-up period, the incidence rate of varicella (any disease, regardless of severity) in this cohort of vaccinated children was 9 to 10 times lower than corresponding rates in unvaccinated children of the same age in the prevaccine era. This rate resulted in an overall vaccine effectiveness of ~90% (ranging from ~75% to 90%), consistent with previous studies in the United States and Europe.

DISCUSSION

To our knowledge, this is the largest and longest follow-up study of varicella vaccine, with 14 years of active surveillance of both patient-reported varicella and physician-diagnosed HZ.
reflecting the likelihood of early vaccine
c failure at a time when VZV was still
circulating. Our results seem to conflict
with those in an earlier study,\textsuperscript{13} in which
breakthrough varicella seemed to be
increasing in the years after vaccina-
tion. Because our population is based
on nearly 100\% capture of data, it is
possible that this difference may be
due to increased reporting and aware-
ness of varicella over time in the earlier
study.

The apparent increase in vaccine effec-
tiveness over time may seem counter-
intuitive. It is likely the result of vaccine
failure occurring early while break-
through episodes became rare over
time due to high vaccine effectiveness
both directly and through herd im-

unity, with little sign of any waning of
vaccine effectiveness. Because our
cohort was all of the same age, and all
vaccinated at the same time, we are
unable to disentangle these effects
with our analyses.

In this study, no breakthrough varicella
was reported after the receipt of a sec-
ond dose of varicella vaccine. Of note, due
to a catch-up program at KPN, 38\% of the
study cohort received a second dose. Few
previous studies have examined the ef-
fectiveness of the second dose. One
prospective study\textsuperscript{11} and 2 observational
studies\textsuperscript{16,17} showed that the second dose
was highly effective, and our findings are
consistent with the results of those
studies. The further decrease in break-
through rates, observed in 2008 and
2009, may have been the result of the
implementation of the second dose in
2008. Prevention of residual cases of
varicella increases protection for infants
too young to receive the vaccine and
immunocompromised children who can-
not receive a live vaccine, and decreases
days lost to school or work.\textsuperscript{17,38} In the
United States, the second dose of var-
icella is typically given at ages 4 to 6
years, but it could potentially be of
more benefit, if varicella is circulating,
if given early after the first dose.

Overall, this study suggests that the
incidence rate of HZ among vaccinated
children may be lower than after
naturally acquired varicella in un-
vaccinated children of the same age.\textsuperscript{19}
HZ rates have tended to increase over
the last several decades in the United
States, beginning before the intro-
duction of varicella vaccination, as well
as in other countries not routinely us-
ing varicella vaccine.\textsuperscript{39,40} Thus, the his-
torical rates of HZ we used from the
1960s to 1970s may underestimate
current unvaccinated HZ rates. In ad-

dition, although the historical cases of
HZ were all from wild-type virus, our
study HZ cases were likely a mixture of
wild-type and vaccine strain virus. In
areas of high vaccine coverage, wild-
type VZV may be much lower than
during the early phase of our study. If
these assumptions are correct, the
protective effect of varicella vaccina-
tion on HZ in children could be of
a greater magnitude than suggested
from the study data.

Our study has some limitations. Al-
though parental reports of varicella
have been shown to be reliable for
young children,\textsuperscript{5,6,9} reporting of vari-
cella in adolescents may be less reli-
able. In the vaccine era, even physician
diagnosis of varicella may be less ac-
curate. Thus, varicella may have been
underreported or overreported in
this study. Because most cases were
reported only at the time of the 6-
month interview, parents may not
recall the severity of the rash, which
could have resulted in misclassification
of rash severity. Finally, comparisons
of current rates of varicella and
zoster versus published historical
rates may be somewhat problematic
for several reasons, including pos-
sible changes over time in disease
incidence and case ascertainment,
and potential differences in underlying
populations.

CONCLUSIONS

This study demonstrated that varicella
vaccine was effective at preventing
chicken pox, and no evidence of waning
protection was noted over a 14-year
period. One dose of vaccine resulted in
excellent protection against moderate
to severe disease, and no cases of
varicella occurred after a second dose.
Most varicella cases occurred shortly
after the cohort was vaccinated, dur-
ing a time when VZV was still widely
circulating. The risk of HZ was not in-
creased in vaccinated children, and the
risk seemed to be lower in vacci-
nated children than in the prevaccine
era.

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REFERENCES


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