Postlicensure Safety Surveillance for Varicella Vaccine

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Context Since its licensure in 1995, the extensive use of varicella vaccine and close surveillance of the associated anecdotal reports of suspected adverse effects provide the opportunity to detect potential risks not observed before licensure because of the relatively small sample size and other limitations of clinical trials.

Objectives To detect potential hazards, including rare events, associated with varicella vaccine, and to assess case reports for clinical and epidemiological implications.

Design and Setting Postlicensure case-series study of suspected vaccine adverse events reported to the US Vaccine Adverse Event Reporting System (VAERS) from March 17, 1995, through July 25, 1998.

Main Outcome Measures Numbers of reported adverse events, proportions, and reporting rates (reports per 100000 doses distributed).

Results VAERS received 6574 case reports of adverse events in recipients of varicella vaccine, a rate of 67.9 reports per 100000 doses sold. Approximately 4% of reports described serious adverse events, including 14 deaths. The most frequently reported adverse events were rashes, possible vaccine failures, and injection site reactions. Misinterpretation of varicella serology after vaccination appeared to account for 17% of reports of possible vaccine failures. Among 251 patients with herpes zoster, 14 had the vaccine strain of varicella zoster virus (VZV), while 12 had the wild-type virus. None of 30 anaphylaxis cases was fatal. An immunodeficient patient with pneumonia had the vaccine strain of VZV in a lung biopsy. Pregnant women occasionally received varicella vaccine through confusion with varicella zoster immunoglobulin. Although the role of varicella vaccine remained unproven in most serious adverse event reports, there were a few positive rechallenge reports and consistency of many cases with syndromes recognized as complications of natural varicella.

Conclusion Most of the reported adverse events associated with varicella vaccine are minor, and serious risks appear to be rare. We could not confirm a vaccine etiology for most of the reported serious events; several will require further study to clarify whether varicella vaccine plays a role. Education is needed to ensure appropriate use of varicella serologic assays and to eliminate confusion between varicella vaccine and varicella zoster immunoglobulin.
the context of previous studies and other information, including Merck’s postmarketing study of acute safety,24,25 and the pregnancy registry for varicella vaccine (telephone: 800-986-8999), which seeks information about pregnancies with conception during the 3 months following receipt of varicella vaccine or with varicella vaccine administration during any trimester.26

METHODS

These analyses encompass reports received by the Vaccine Adverse Event Reporting System (VAERS) from March 17, 1995, through July 25, 1998. Jointly operated by the FDA and the CDC, VAERS consolidates voluntarily submitted reports of suspected vaccine adverse effects from manufacturers, health care workers, and patients for postlicensure vaccine safety surveillance.20,27-29 Although the National Childhood Vaccine Injury Act of 1986 (Pub L No 99-660) obliges physicians to submit certain reports, VAERS data are typical of passive drug safety surveillance programs, with case counts that represent unknown but probably highly variable fractions of actual event numbers. Nonetheless, with its national scope and open-ended format, VAERS can reveal potential vaccine safety problems with new vaccines.30 Increased numbers for previously reported events,31 and potential associations between vaccines and entirely unanticipated events32 that might not have occurred in the relatively small prelicensure clinical trials. (The National Technical Information Service distributes VAERS data [http://www.ntis.gov], and the FDA provides additional information [http://www.fda.gov/cber/vaers/vaers.htm].)

The VAERS report form solicits information regarding the vaccinee (name, date of birth, current age, sex, and address), the adverse event or events (date of onset, therapy, and clinical course), and vaccine or vaccines administered (date, lot identifier, and dose sequence). VAERS adapted standardized coding terms to index each patient’s reported event.33 In selecting syndromes and other subsets for description here, we weighed medical severity, frequency, and potential preventability. Serious cases mainly encompass fatal or life-threatening events, hospitalizations, and permanent disabilities.

Reporting rates are numbers of reports divided by estimated varicella vaccine doses sold.23 They cannot be interpreted as incidence rates because of potentially substantial underreporting and overreporting. In positive rechallenge cases, an adverse event recurred after a second dose of varicella vaccine. Occasional reports include information from a research laboratory’s polymerase chain reaction (PCR) studies of viral DNA, which can confirm the presence of varicella zoster virus (VZV) in an isolate. Restriction fragment length polymorphisms can then often distinguish the Japanese-origin Oka vaccine strain from wild-type VZV circulating in the United States.34 Vaccine failure refers to primary (breakthrough) wild-type VZV infection long enough after vaccination for most subjects to develop protective immunity. Because few patients had confirmatory PCR studies, we classified reports of generalized varicella at least 6 weeks after vaccination as possible vaccine failures.

RESULTS

Overview

VAERS received 6574 varicella vaccine reports between March 1995 and July 1998 (FIGURE), an overall rate of 67.5 reports per 100 000 doses distributed, with largest numbers of reports soon after licensure. There were 0.1 deaths, 2.8 other serious adverse events, and 64.5 nonserious adverse events per 100 000 doses. Number of reports by age, sex, and severity are presented in TABLE 1.

TABLE 1 presents selected adverse events. Approximately 4% of cases (2.9/100 000) were serious, including 14 deaths (BOX 1). Among all reports, 82% of patients received only varicella vaccine, 12% also received measles, mumps, and rubella vaccine (MMR), and other vaccine combinations (without MMR) accounted for the balance. For children, the sex ratio was close to 1, but females predominated among reports for teenagers and adults.
came from every state, and 9 reports originated abroad.

**Most Frequent and Other Selected Events**

**Rash and Possible Vaccine Failure.** Rash, usually vesicular, accounted for more than half of all reports (3640 cases, 37.4/100,000 doses) (Table 2). Polymerase chain reaction studies found VZV in 70 adequate rash specimens. Wild-type virus appeared in 43 patients (61%), who had symptoms at a median of 1 week postimmunization, while the Oka strain was identified in 22 patients (31%) whose symptoms began a median of 4 weeks after vaccination. The VZV type could not be distinguished in 5 cases. Of the 1260 reports of possible vaccine failure (12.9/100,000), 51% described rash; 9 patients had complications, particularly secondary bacterial infections of vesicles. Negative serologic tests, rather than varicella infections, seemed to prompt 17% of the reported possible vaccine failures.

**Injection Site Reactions.** Among 575 patients with reported injection site reactions (5.9/100,000), the majority of reactions followed varicella vaccine administration by less than a week, and 77% of patients received no other vaccine. Eight reports described positive rechallenge. Four patients developed a shingles-like rash in the immediate vicinity of the injection site from 2 to 16 weeks after vaccination. Most of 10 serious cases involved the injection site only incidentally or as a possible portal of initial infection.

**Herpes Zoster.** The characteristic rash of herpes zoster (HZ) (asymmetrical, dermatomal, and vesicular) facilitates specific diagnosis, but the reactivated virus may be of wild-type or Oka strain. Polymerase chain reaction studies found VZV in 37.4/100,000 doses) (Table 2). Polymerase chain reaction studies found VZV in 37.4/100,000 doses.

### Table 1. Varicella Vaccine Reports by Age, Sex, and Severity*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Deaths</th>
<th>Other Serious Adverse Events</th>
<th>Nonserious Adverse Events</th>
<th>Sex</th>
<th>Total†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 mo</td>
<td>0</td>
<td>6</td>
<td>37</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>12-23 mo</td>
<td>6</td>
<td>119</td>
<td>1250</td>
<td>662</td>
<td>693</td>
</tr>
<tr>
<td>2-4 y</td>
<td>3</td>
<td>51</td>
<td>1486</td>
<td>675</td>
<td>830</td>
</tr>
<tr>
<td>5-9 y</td>
<td>1</td>
<td>25</td>
<td>1016</td>
<td>520</td>
<td>508</td>
</tr>
<tr>
<td>10-17 y</td>
<td>1</td>
<td>9</td>
<td>310</td>
<td>177</td>
<td>138</td>
</tr>
<tr>
<td>&gt;17 y</td>
<td>3</td>
<td>46</td>
<td>1365</td>
<td>1094</td>
<td>306</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>15</td>
<td>825</td>
<td>261</td>
<td>152</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>271</td>
<td>6289</td>
<td>3408</td>
<td>2647</td>
</tr>
</tbody>
</table>

*By Food and Drug Administration regulations, reports of serious adverse events describe deaths, life-threatening events, hospitalizations, persistent or significant disabilities, congenital anomalies, and other events of medical importance. Reporting rates, ie, reports per 100,000 doses distributed, cannot be calculated by sex or age group without corresponding stratified denominators.

†Totals include 519 patients without reported sex, most of whom (82%) also lacked age data.

### Table 2. Selected Adverse Events Reported to VAERS for Varicella Vaccine, March 1995–July 25, 1998*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Serious, No. (%)</th>
<th>Other, No. (%)</th>
<th>Age &lt;18 y, No. (%)†</th>
<th>Varicella Vaccine Alone, No. (%)‡</th>
<th>Reporting Rate§</th>
<th>Total‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>80 (2)</td>
<td>3650 (98)</td>
<td>2698 (81)</td>
<td>3005 (83)</td>
<td>37.4</td>
<td>3640</td>
</tr>
<tr>
<td>Possible vaccine failure</td>
<td>9 (1)</td>
<td>1251 (99)</td>
<td>1019 (84)</td>
<td>1097 (87)</td>
<td>12.9</td>
<td>1260</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>10 (2)</td>
<td>565 (98)</td>
<td>296 (57)</td>
<td>444 (77)</td>
<td>5.9</td>
<td>575</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>13 (5)</td>
<td>238 (95)</td>
<td>194 (87)</td>
<td>203 (81)</td>
<td>2.6</td>
<td>251</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>11 (6)</td>
<td>161 (94)</td>
<td>118 (73)</td>
<td>143 (83)</td>
<td>1.8</td>
<td>172</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>8 (21)</td>
<td>30 (79)</td>
<td>25 (68)</td>
<td>32 (84)</td>
<td>0.4</td>
<td>38</td>
</tr>
<tr>
<td>Hepatic pathology</td>
<td>14 (56)</td>
<td>11 (44)</td>
<td>11 (46)</td>
<td>18 (72)</td>
<td>0.3</td>
<td>25</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11 (58)</td>
<td>8 (42)</td>
<td>16 (94)</td>
<td>14 (74)</td>
<td>0.2</td>
<td>19</td>
</tr>
<tr>
<td>Possible immune-mediated syndromes</td>
<td>44 (28)</td>
<td>114 (72)</td>
<td>121 (78)</td>
<td>116 (73)</td>
<td>1.6</td>
<td>158</td>
</tr>
<tr>
<td>Erythema multiforme, SJS</td>
<td>7 (15)</td>
<td>39 (85)</td>
<td>43 (83)</td>
<td>52 (70)</td>
<td>0.5</td>
<td>46</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>7 (16)</td>
<td>38 (94)</td>
<td>21 (48)</td>
<td>38 (94)</td>
<td>0.5</td>
<td>45</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19 (61)</td>
<td>12 (39)</td>
<td>25 (63)</td>
<td>19 (61)</td>
<td>0.3</td>
<td>31</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>9 (30)</td>
<td>21 (70)</td>
<td>30 (100)</td>
<td>20 (67)</td>
<td>0.3</td>
<td>30</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>6 (40)</td>
<td>9 (60)</td>
<td>12 (79)</td>
<td>13 (87)</td>
<td>0.2</td>
<td>15</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>2 (100)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>1 (50)</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Neurological syndromes</td>
<td>128 (85)</td>
<td>243 (65)</td>
<td>293 (83)</td>
<td>208 (56)</td>
<td>3.8</td>
<td>371</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>57 (90)</td>
<td>136 (70)</td>
<td>126 (71)</td>
<td>138 (72)</td>
<td>2.0</td>
<td>193</td>
</tr>
<tr>
<td>Convulsion</td>
<td>57 (25)</td>
<td>106 (65)</td>
<td>158 (98)</td>
<td>54 (33)</td>
<td>1.7</td>
<td>163</td>
</tr>
<tr>
<td>Ataxia</td>
<td>21 (49)</td>
<td>22 (51)</td>
<td>39 (95)</td>
<td>31 (72)</td>
<td>0.4</td>
<td>43</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>25 (78)</td>
<td>7 (22)</td>
<td>24 (80)</td>
<td>20 (63)</td>
<td>0.3</td>
<td>32</td>
</tr>
<tr>
<td>Meningitis</td>
<td>11 (100)</td>
<td>0 (0)</td>
<td>9 (82)</td>
<td>8 (73)</td>
<td>0.1</td>
<td>11</td>
</tr>
</tbody>
</table>

*VAERS indicates Vaccine Adverse Event Reporting System; SJS, Stevens-Johnson syndrome. See footnote to Table 1 for definition of serious adverse events. Serious cases included 14 deaths. Event categories are not mutually exclusive. Percentages indicate fractions of all reports in each adverse event group that have each characteristic. Percentages may not sum to 100 because of rounding.

†Percentages for age <18 y exclude reports missing age.

‡Varicella vaccine alone indicates that no other vaccines were coadministered.

§Reporting rate is reports per 100,000 doses.

Heptatic pathology omits 2 reports of neonatal hyperbilirubinemia after fetal exposure to varicella vaccine.
Box 1. Varicella Vaccine Fatality Reports

Patient A. Shortly before her eighth birthday, a girl with history of chronic severe asthma received a tuberculin skin test and multiple vaccines (DT, MMR, OPV, and VV), which were followed by hives. Her brother had chicken pox 3 years earlier. The patient’s medications included inhaled corticosteroids. She was hospitalized for asthma during the month after the vaccinations and again 19 months later, when she required intubation. She died with coagulopathy and Staphylococcus aureus sepsis. No rash had been recognized antemortem, but at autopsy 2 of several scattered papules showed “intraepidermal vesicles with viral inclusions and multinucleated cells.” The autopsy disclosed fulminant hepatitis, esophagitis, and epiglottitis, with disseminated intravascular coagulation and positive varicella virus cultures from pharynx, lung, blood, and urine. Her liver was diffusely necrotic, and the few surviving hepatocytes showed viral cytopathic changes. The pathologist interpreted thymic depletion (weight 13.9 g vs 31.0 g expected at her age) and marked depletion of splenic white pulp as effects of corticosteroid therapy. Polymerase chain reaction studies identified wild-type VZV.

Patient B. A 16-month-old girl with history of upper respiratory tract infections was receiving an antibiotic for otitis media when she was immunized with HibV and VV. Three days later, she began to vomit, developed progressive lethargy, and died the next day. At autopsy, she had meningitis, hepatitis, and otitis media. Chronic inflammatory cell infiltrates and multiple foci of isolated necrosis were found in the liver, but no viral inclusions were found. Viral culture of liver tissue was negative. Polymerase chain reaction identified wild-type VZV in brain tissue.

Patient C. A healthy 18-month-old boy had no history of allergy or any prior postvaccinal adverse event when he received multiple vaccinations (DTaP, OPV, VV) 2 to 3 weeks after a viral syndrome. He was admitted to the intensive care unit 4 days later with a low platelet count. He began to bleed from the mouth, had an abnormal computed axial tomography scan of the head, and died 2 days later from cerebral hemorrhage after an emergency left frontal lobectomy. His autopsy showed profound thrombocytopenia with changes compatible with idiopathic thrombocytopenic purpura, including hypercellular bone marrow with abundant megakaryocytes. Polymerase chain reaction studies detected neither wild-type nor Oka-strain VZV. Because of the short interval from vaccinations until recognition of thrombocytopenia, the prevaccination viral syndrome is thought to be a more plausible trigger for idiopathic thrombocytopenic purpura than the varicella or poliomyelitis vaccine strains.

Patient D. A 15-year-old boy’s history included microcephaly, cerebral palsy, quadriplegia, mental retardation, multiple episodes of aspiration pneumonia, permanent tracheostomy, and thrombocytopenia thought to be secondary to an anticonvulsant drug. One month after vaccination against varicella, he developed adult respiratory distress syndrome with severe varicella pneumonia, disseminated varicella sepsis, and renal failure. He died 10 days later; no autopsy or PCR studies were performed.

Patient E. A 12-month-old boy received VV at a well-baby visit. He had no significant history beyond colds and ear infections, but his father and grandfather had apparently viral enteritis. The patient vomited once and became irritable 3 days after vaccination. He received acetaminophen the next day for irritability and fever (102°F [38.9°C]). A rash developed 1 week after vaccination, which a physician diagnosed as roseola, describing it as erythematous, maculopapular, and extending from torso to groin. An apparently minor recent head trauma from a fall was also noted. Five days later the patient seemed well, but he became irritable and received acetaminophen. Some 6 hours later, his mother heard a “shriek” cry and found the patient supine and convulsing. Emergency personnel found the patient apneic and pulseless. At autopsy, he had no histologic signs of VZV. “Morphologic findings to suggest varicella as an etiology are not seen. The findings are interpreted to be most suggestive of early changes of viral meningoencephalitis. . . .”
cerebrospinal fluid (CSF) in one and magnetic resonance imaging in the other. A patient with vomiting (another potential sign of Reye syndrome) and lethargy died with meningitis and chronic hepatic inflammation; brain tissue yielded wild-type VZV (Box 1, Patient B). Two patients had vomiting without encephalopathy. One had hepatitis A, and the other probably had Gilbert syndrome.

**Pneumonia.** Nineteen patients with pneumonia included 5 with predisposing immunodeficiencies from acquired immunodeficiency syndrome (AIDS), corticosteroids, or other conditions. In addition, 2 mothers developed severe varicella pneumonia during pregnancy. One received “shots” that may have included varicella vaccine at 5 months’ gestation after her children developed chickenpox. The vaccinated child of the other mother developed a mild rash 2 weeks after vaccination, with the mother’s varicella and pneumonia ensuing after another 2 weeks. Neither mother had PCR confirmation of VZV strain. A severely immunodeficient 13-month-old human immunodeficiency virus (HIV)–positive boy with pneumonia did have direct evidence of vaccine involvement. Approximately 10 weeks after vaccination, while he was hospitalized for gram-negative pneumonia, serology and a bronchoalveolar lavage specimen had positive results for VZV, and PCR studies from the lavage and a lung biopsy both identified the Oka strain.

**Possible Immune-Mediated Syndromes**

**Erythema Multiforme and Stevens-Johnson Syndrome.** Erythema multiforme (EM) or its more severe form, Stevens-Johnson syndrome (SJS), or both developed in 46 patients. Among 42 cases reported as EM, 16 patients described symptom onset within 1 week after vaccination, and disease developed in 23 patients 1 to 5 weeks postvaccination; 3 reports lacked dates. One individual progressed to SJS; and 4 other patients (not reported as having EM) developed SJS. Three of the 5 SJS cases began within 1 week after vaccination. Except for 3 adults with EM, all patients with EM or SJS were younger than 9 years.

**Arthropathy.** Adults accounted for about half of the 45 reports of arthropathy. Thirteen patients developed arthritis, and 32 reported only arthralgias. Specified joints in arthritis reports included knee, ankle, metacarpal, metatarsal, or hip, but 3 patients described neck stiffness or pain. Although arthritis usually affected multiple joints, 3 patients had monoarticular presentations, and 2 had negative bacterial cultures. Arthritis developed in 8 patients within 2 days after vaccination, including 4 patients with EM-associated symptoms. Five patients had first symptoms of probable reactive arthritis 1 to 4 weeks after vaccination.

**Thrombocytopenia.** Fifteen children in the second year of life accounted for almost half of 31 thrombocytopenia reports. Two patients died. One received varicella vaccine shortly after a viral illness and then developed fulminant idiopathic thrombocytopenic purpura (Box 1, Patient C). The other patient had a history of drug-related thrombocytopenia (Box 1, Patient D). Symptoms in most cases (24/31) began 4 to 28 days after vaccination. Five patients had borderline platelet count decrements (120-147 × 10^9/L), but 22 had counts of 52 × 10^9/L or less, including 10 below 10 × 10^9/L. A 14-year-old boy with probable positive rechallenge noted petechiae on his extremities about 1 week after receiving varicella vaccine and tetanus-diphtheria toxoid. Ten days after his second dose of varicella vaccine, his platelet count fell to 11,000.

**Anaphylaxis.** All 30 patients with anaphylaxis survived (9 reports specified anaphylaxis, and we classified another 21 as probable cases, based on compatible clinical features, including respiratory and skin symptoms within 4 hours after vaccination). In half of 22 detailed reports, symptoms developed within 15 minutes after vaccination. Five of the 30 patients had significant past medical histories of surgery for congenital cardiac anomalies or spina bifida, and several others had asthma. Four patients had food sensitivities, including 1 with a history of egg allergy and a similar reaction to MMR. Three patients had medication allergies to antibiotics (2 patients) or to atropine and an unspecified ophthalmic solution (1 patient).

**Vasculitis.** Among 15 vasculitis reports, 3 children aged 1 to 3 years appeared to have Kawasaki syndrome, and 10 patients developed Henoch-Schönlein purpura within 7 weeks of vaccination. Eight of these 10 patients were younger than 8 years; one also had EM, and 4 had associated joint pain, swelling, or both.

**Aplastic Anemia.** Two boys, 1 and 6 years old, developed aplastic anemia 2 months after administration of varicella vaccine alone or with MMR. Both children required bone marrow transplantation. Four patients had milder degrees of cytopenia in conjunction with arthritis (3 cases) or SJS (1 case).

**Neurological Adverse Events**

**Neuropathies.** Reports for 193 patients include a wide variety of central and/or peripheral neuropathic signs or symptoms at a median of 4 days after vaccination, with 90% of symptoms reported as beginning within 5 weeks. In 50 of 193 cases, the primary pathology may have been associated encephalopathy, ataxia, meningoitis, or seizures.

Fifteen patients developed Bell palsy, including 6 teenagers or adults, at intervals from less than 24 hours to almost 1 month after vaccination.

Another 15 patients, aged 1 to 38 years, developed demyelinating syndromes 6 to 128 days after vaccination: transverse myelitis (5 patients), optic neuritis (4 patients), acute demyelinating or disseminated encephalomyelitis (3 patients), Guillain-Barré syndrome (3 patients), and multiple sclerosis (1 patient). One patient had optic neuritis and transverse myelitis together. An unusual 16th report described a mother who developed transverse myelitis 1 month after her infant daughter’s immunization (no live vaccine product); transverse myelitis recurred 1 year later, 3 days after the daughter’s vaccination against varicella.

Among the remaining neuropathy reports, main adverse events included hypekinesia (33 cases), paresthesia (22 cases), and hypotonia (19 cases). A pa-
tient with positive rechallenge had par-
esthesias after his first dose of varicella 
vaccine, followed by resolution prior to 
exacerbation 2 weeks after his second 
dose.

**Convulsions.** Most of 163 reported 
seizures involved children aged 12 to 23 
months. Febrile seizures accounted for 
about one half of reports and usually oc-
curred after multiple immunizations. A 
larger proportion of reported seizures af-
ter administration of MMR with vari-
cella vaccine occurred in the second 
week postvaccination than did re-
ported seizures without preceding MMR 
(31/79 [39%] vs 9/82 [11%]).

In 25 reports, patients with no prior 
seizure history received only varicella 
vaccine and had no evident pathology to 
account for convulsions. Children 
younger than 5 years accounted for 12 
of 13 febrile seizures in this subset, and 
10 of these 13 had convulsions within 
4 days after vaccination.

**Ataxia.** Forty-three reports of ataxia 
included 22 patients younger than 2 
years. In 39 patients with interval infor-
mation, symptoms began 7 to 42 days 
after vaccination in 21 patients; symp-
toms developed during the first week in 
12 cases and more than 6 weeks after 
vaccination in 6 patients. Many cases 
appeared consistent with transient cer-
ebellar ataxia, although 7 included 
encephalopathic features. Unrelated eti-
ologies emerged in 2 patients: a pos-
sible brain tumor in one, and a congen-
tial metabolic defect in the other.

**Encephalopathy.** Among 32 reports 
of encephalopathy (including encephali-
tis), 8 patients had evidence for etiolo-
gies independent of varicella vaccine, 
such as brain tumors in 3 patients. The 
primary pathology in 6 reports seemed 
to be aseptic meningitis. Three patients 
were diagnosed as having acute demy-
elinating or disseminated encephalomy-
elitis. The remaining 15 had a variety of 
symptoms, usually 1 to 4 weeks after 
vaccination. In one of the better docu-
ment cases, a 15-month-old girl de-
veloped hemiparesis 18 days after re-
cieving diphtheria and tetanus toxoids 
with acellular pertussis vaccine, *Hae-
mophilus influenzae* type b conjugate vac-
cine, and varicella vaccine. Her CSF was 
normal, with no VZV found in PCR 
studies. Magnetic resonance imaging 
showed edema of the left basal ganglia.

**Meningitis.** None of 11 meningitis 
reports, including 2 deaths (Box 1, 
Patients B and E), had PCR evidence of 
Oka-strain VZV in CSF or other speci-
mens. Two patients had bacterial infec-
tions (*Neisseria meningitidis* and *Bor-
relia burgdorferi*). Brain tissue yielded 
wild-type VZV in a 16-month-old girl 
with vomiting, lethargy, and hepatitis 
(Box 1, Patient B). Another patient devel-
oped a high fever almost 24 hours after 
vaccination and progressed to aseptic 
meningitis. In a third case, a 33-month-
old girl developed right facial HZ and viral 
meningitis. She had received varicella 
vaccine at age 1 year when her sibling had 
fresh chickenpox vesicles. Polymerase 
chain reaction studies identified wild-
type VZV from HZ lesions in the trigemi-
nal distribution and no VZV in the CSF. 
The remaining 2 adults and 3 children 
al so developed meningitis approximately 
2 to 3 weeks after vaccination. One 
woman developed a broadly distributed 
vesicular rash with 75 to 100 lesions 13 
days after receiving varicella vaccine, fol-
lowed after another 9 days by aseptic 
meningitis. Neither her CSF (by viral cul-
ture) nor rash (by PCR) had evidence of 
VZV, but her 2 children developed vari-
cella 2 and 4 weeks after the appearance 
of their mother’s postvaccinal rash.

**Inadvertent Exposures**

Reports of unintentional exposures to 
varicella vaccine include 145 possible 
secondary transmissions from vaccin-
ees, usually without PCR confirmation 
of vaccine strain VZV; 43 administra-
tions to infants younger than 12 months 
(Table 1); 19 vaccinations of pregnant 
women given varicella vaccine by mis-
take (instead of varicella zoster im-
mune globulin) after chickenpox expo-
sures; 6 ocular contacts (from splashing 
during administration), usually fol-
lowed by irritation and redness, with no 
case of HZ ophthalmicus; 5 unint-
tended double doses (at the same visit 
or months apart), associated with injec-
tion site reactions, irritability, and anxi-
ety; and 2 cutaneous exposures leading 
to localized vesicles.

VAERS received reports of 87 women 
who received varicella vaccine prior to 
or during pregnancy. None depicts 
characteristic features of congenital 
varicella infection in the exposed off-
spring. Several reports describe gesta-
tional varicella vaccine exposure fol-
lowed by malformations (eg, Down 
syndrome and tetralogy of Fallot).

**COMMENT**

Growing use of varicella vaccine in the 
United States promises substantial con-
trol of chickenpox and its serious com-
lications. Consistent with experiences 
in clinical trials, our review of 6574 spo-
naneous reports of suspected adverse ef-
fects from varicella vaccine during the 
first 3 years after licensure found that the 
vast majority of reported cases were not 
serious. Symptoms like fever, rash, and 
junction site reactions can be expected 
from this live virus vaccine, while the 
vaccine’s role in most of the infrequent 
reports of serious adverse events re-
 mains unconfirmed.

VAERS data, subject to the inherent 
limitations of passive safety surveillance, 
merit cautious interpretation. Most re-
ports cannot prove whether vaccination 
caus ed the subsequent symptoms. Not 
all adverse events that occur after vacci-
nation are reported, and many reports de-
scribe events that may have been caused 
by confounding factors, including medi-
cations and diseases. Chickenpox remains 
prevalent, and the wild-type virus ac-
counts for many reported events, includ-
ing some serious cases. Follow-up dis-
closed tumors or other causes unrelated 
to vaccines in other cases of serious ad-
verse events. Larger numbers of reports 
soon after licensure probably reflect the 
“Weber effect” of greater adverse event 
reporting for new drugs. The quality of 
reported information varies widely, and 
simultaneous administration with other 
vaccines (especially MMR) confounds 
attrition. In addition, crude sales data 
preclude calculation of age-specific reporting 
rates. However, surveillance data can stimulate hypotheses for systematic 
evaluation through controlled studies.
Serious Events
This study extends safety data from clinical trials and postlicensure studies. Serious adverse events had not been seen before licensure, and a systematic search afterward in hospitalization and other records of almost 90,000 vaccinated members in a health maintenance organization found no case of an acute, serious adverse event.24,25 In clear contrast, VAERS received multiple reports of anaphylaxis. All of these patients survived without complications. The offending allergen may be a gelatin stabilizer in varicella vaccines, MMR, and other products.38-40

The majority of patients for whom serious adverse events were reported, including pneumonia, encephalitis, ataxia, thrombocytopenia, SJS, arthritis, vasculitis, and hepatitis, lacked varicella strain testing. Wild-type VZV and other mechanisms could also cause these syndromes, and alternative etiologies were confirmed for some patients through follow-up. Nonetheless, these and other diseases described in multiple serious reports are plausible as potential effects of varicella vaccine. Some are commonly recognized complications of natural chickenpox, particularly ataxia, cellulitis, and encephalitis.41 Others have also been described with wild-type VZV infections, including arthropathy, EM and SJS, aplastic anemia, pneumonia (usually in adults),7 thrombocytopenia,7,23 Henoch-Schönlein purpura or vasculitis of the central nervous system,38-50 and central and peripheral neuropathies.31-36 Positive rechallenge reports (eg, for idiopathic thrombocytopenic purpura and paresthesias) bolster suspicion of relationships with varicella vaccine. Continued safety surveillance and epidemiologic evaluations may clarify whether these and other rarely reported adverse events can be attributed to varicella vaccine. Since many adverse events may be caused by wild-type VZV, physicians should obtain appropriate specimens for laboratory evaluation, including strain identification. While commercial laboratories do not yet have this capability, physicians can consult with CDC's National Varicella Reference Laboratory (Scott Schmid, PhD, telephone: 404-639-0066, e-mail: ds@cdc.gov).

Reported seizures after administration of varicella vaccine and MMR clustered in the second week after vaccination to a much greater extent than did reported seizures after receipt of varicella vaccine alone. These patterns support a role of MMR in postvaccination febrile seizures, but further research is needed.

Where autopsy and other follow-up data were available, investigations of reported deaths often disclosed clear causes unrelated to vaccination, including malignancies, wild-type VZV, respiratory syncytial virus, and echovirus. An immunocompromised patient died with clinical diagnoses of varicella sepsis and pneumonia but without laboratory studies to confirm VZV or distinguish the strain. Another patient, severely asthmatic, died with wild-type VZV documented 21 months after vaccination. She may have had a primary varicella infection prior to vaccination, with subsequent disseminated HZ under the influence of corticosteroid therapy. Alternatively, corticosteroids, other asthma medications, or both might have attenuated her response to vaccination or later depressed her immune defenses.

Frequently Reported Events
The most commonly reported adverse events included rash, possible vaccine failures, and injection site reactions. Many cases likely represent unrelated infectious diseases. Wild-type VZV accounts for much of the postvaccinal varicella-like rash. If caused by VZV, rash within 7 days after vaccination is almost certain to be wild-type virus, while cases occurring 1 to 6 weeks after vaccination may be either Oka-strain or wild-type virus; almost all disseminated varicella rash beyond 6 weeks after vaccination is caused by wild-type virus and represents partial or complete vaccine failure. Most suspected secondary transmissions occurred between 7 and 42 days after vaccination and would require laboratory studies to distinguish between Oka-strain and wild-type VZV.

Herpes Zoster
Vaccine-strain HZ may occur among vaccinated immunocompromised patients at a lower rate than in similar patients after natural varicella.37 Our data verify that Oka-strain HZ can also occur in immunocompetent vaccinees. However, half of the reported HZ cases with adequate laboratory specimens had wild-type virus, which is evidence of natural VZV infection before immunization. The short intervals after vaccination until HZ occurrence in several patients seem consistent with the intriguing hypothesis that varicella vaccine might, in rare cases, provoke reactivation of latent wild-type VZV.38

Immune Competence
Involvement of the Oka strain in an immunocompromised patient with pneumonia was confirmed with PCR studies. Immune deficits (eg, congenital or resulting from AIDS or drug-induced immunosuppression) may contraindicate live virus vaccination. In addition, a postlicensure field study found lower vaccine effectiveness among children with asthma.33 Further studies should examine immune responses to vaccination in asthmatics receiving various treatment regimens. For patients who require varicella vaccine prior to planned immunosuppression, risks may be minimized by first allowing some weeks for the acute vaccine-induced VZV infection to resolve. (However, this precaution may not be necessary with relatively low-dose therapy.)1) Vaccinees with potentially impaired defenses should be closely monitored for the possible need to treat complications with acyclovir.

Secondary Transmission
VAERS reports confirm that secondary transmission of the vaccine virus can occur, probably rarely. The risk of person-to-person passage of Oka-strain VZV is quite small39,59,60 and probably limited to patients with a rash.3 Only 3 cases of secondary transmission have been confirmed in immunocompetent persons.3 Public health authorities recommend that family members and other close contacts of immunocompromised persons...
should receive varicella vaccine, in view of the threat otherwise faced by these patients from natural chickenpox and its complications. If a vaccinee develops a rash, isolation from the immunocompromised person can reduce the transmission risk, but even with contact, vaccine-strain disease is unlikely and usually mild.

### Vaccine Failure

No vaccine has perfect efficacy, but varicella vaccine nearly always protects against severe varicella. Three postlicensure studies have demonstrated vaccine effectiveness in the range of 85% to 90% for prevention of all disease and 100% for prevention of severe disease. Currently, approximately 1 of 10 vaccinated children may develop mild breakthrough disease following exposure to chickenpox. As exposures to natural varicella decline with increasing vaccine coverage, numbers of breakthrough cases should also fall.

More than 200 reports of possible vaccine failure apparently stemmed from misinterpretation of negative postvaccination serologic results as failures to seroconvert. Commercial assays are not sufficiently sensitive to detect all protective antibody responses following vaccination. Physicians and pertinent laboratory personnel should recognize this limitation in available tests.

### Pregnancy Exposures

Merck and the CDC jointly monitor potential fetal risks from gestational exposures through a pregnancy registry, which, like VAERS, has received no report of congenital varicella syndrome. However, reported pregnancy exposures highlight the need for physicians to ask women of childbearing age, before administering varicella vaccine, about the possibilities of current pregnancy or planned or potential conception in the next month. Gestational exposures to varicella vaccine through confusion with varicella zoster immune globulin delay protection against VZV and expose the developing embryo to a potentially teratogenic virus. Continued reporting of this error despite initial publicity indicates a need for additional educational interventions.

### CONCLUSION

Chickenpox can be serious and even deadly, but varicella vaccine can now prevent serious varicella infections with a high degree of reliability. Safety surveillance through VAERS confirms that most of the vaccine’s adverse effects are minor. Although reports to VAERS provide either tentative or clear evidence for a variety of serious vaccine risks, all appear to be rare, and the majority, while plausible, lack confirmation of causation by Oka-strain VZV. The manufacturer, in consultation with the FDA, has revised safety labeling for varicella vaccine (TABLE 3) based on continuous assessment of postmarketing spontaneous reports. Additional studies and ongoing investigations within the CDC’s Vaccine Safety Datalink (VSD) Project will evaluate several of the hypothesized vaccine risks, including ataxia, aplastic anemia, encephalopathy, seizures, and thrombocytopenia. Our analysis also suggests that further educational measures might help assure appropriate use and interpretation of varicella serologic assays and eliminate inadvertent substitutions of varicella vaccine for varicella zoster immune globulin, particularly in pregnancy. With continuing improvements in varicella vaccine coverage, evidence for control of varicella will emerge as declines in disease incidence, varicella-related hospitalizations, and mortality.

A summary of safety reports received since preparation of this article is presented in Box 2.

### Box 2. New Safety Reports

Vaccine safety surveillance is an ongoing process. VAERS received over 3000 additional varicella vaccine case reports in the 18 months after July 1998, with most patterns remaining stable as reports continue to accrue. However, 3 reports from this period subsequent to our primary analysis have positive rechallenge or other special information value.

**Patient A.** A 13-month-old boy with severe combined immunodeficiency developed hepatitis and respiratory distress 2 weeks after receiving varicella vaccine. Liver biopsy showed VZV infection, and PCR testing of the biopsy supernatant and of a rash specimen 6 weeks after vaccination both identified Oka-strain VZV. This case verifies vaccine virus involvement in hepatic pathology. In addition, as in the HIV-positive patient who developed pneumonia, it demonstrates persistence of vaccine virus activity for at least 6 weeks in an immunocompromised host.

**Patient B.** A 16-year-old boy without previous convulsions had an absence seizure 3 days after varicella vaccine. One month later, 2 generalized tonic-clonic seizures followed his second vaccine dose at the same interval. This patient’s positive rechallenge for seizure activity increases suspicion that varicella vaccine may be more than a coincidental factor in observations of postvaccinal convulsions.

**Patient C.** Two weeks after receiving varicella vaccine, a 4-year-old girl developed hemiparesis with evidence from magnetic resonance imaging for cerebral infarctions in the putamen and internal capsule. Her apparent cerebrovascular accident assumes particular importance after recent description of a significant statistical association between natural chickenpox and subsequent ischemic strokes in children.

### Table 3. Safety Revisions* in Varicella Vaccine Label Since Licensure

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
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<tbody>
<tr>
<td>Anaphylaxis</td>
<td></td>
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<tr>
<td>Erythema multiforme, Stevens-Johnson syndrome</td>
<td></td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
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<tr>
<td>Herpes zoster</td>
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<tr>
<td>Neurological</td>
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<tr>
<td>Ataxia</td>
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<tr>
<td>Bell palsy</td>
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<td>Encephalitis</td>
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<tr>
<td>Guillain-Barré syndrome</td>
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<tr>
<td>Paraplegias</td>
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<tr>
<td>Transverse myelitis</td>
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<tr>
<td>Pharyngitis</td>
<td></td>
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<tr>
<td>Secondary bacterial infections, cellulitis, impetigo</td>
<td></td>
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<tr>
<td>Secondary transmission</td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td></td>
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</tbody>
</table>

*Revisions due to adverse reactions . . . reported since the vaccine has been marketed.
VARICELLA VACCINE SAFETY SURVEILLANCE

References

14. *COSTAR*™: Coding Symbols for Thesaurus of Adverse Reaction Terms

also significantly more likely to achieve initial and durable responses than those with higher viral loads, after adjustment for CD4 cell count and other factors. The number of nucleoside analogue drugs received prior to combination therapy was inversely associated with achieving an undetectable viral load. Age, sex, and injection drug use history were not associated with outcomes, while black race was associated with a lower odds of achieving a durable response.

Comment. These data suggest that the initial timing of antiretroviral therapy should consider both CD4 cell count and viral load. Patients with CD4 cell count levels greater than 350/mm³ or with viral loads of 25 000 copies/mL or less had more favorable initial and durable responses than those with lower CD4 cell counts or higher viral loads. It is possible that patients with lower CD4 cell counts and higher viral loads have more a virulent phenotype of HIV, although there is no evidence of reduced in vitro susceptibility to antiretroviral drugs of viruses from such patients. Because we focused on the specific outcome of virologic response rather than survival, we do not think these data are subject to lead time bias.

Although guidelines have been developed based on the natural history of untreated HIV infection, rather than the likelihood of treatment success, our results support both the British and US guidelines, which recommend starting treatment for patients before the CD4 cell count falls to less than 350/mm³ and for a CD4 cell count less than 500/mm³ or viral load greater than 10 000 to 20 000 copies/mL, respectively. Although these observational data are not derived from a randomized trial, we think they indicate that highly active antiretroviral therapy is more likely to succeed in suppressing viremia when given before immunodeficiency has progress to a moderate or severe level.

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### Table 2. Conditional Logistic Regression Analyses for Achieving an Initial or Durable Response to Therapy

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Odds Ratio (95% CI) for Achieving Initial Response</th>
<th>Odds Ratio (95% CI) for Achieving Durable Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count &gt;350/mm³</td>
<td>1.8 (1.10-2.96)</td>
<td>1.9 (1.14-3.08)</td>
</tr>
<tr>
<td>CD4 cell count 200-350/mm³</td>
<td>0.98 (0.61-1.57)</td>
<td>1.4 (0.82-2.42)</td>
</tr>
<tr>
<td>RNA &lt;25 000 copies/mL</td>
<td>2.5 (1.59-4.04)</td>
<td>2.5 (1.45-4.35)</td>
</tr>
<tr>
<td>RNA 25 000-100 000 copies/mL</td>
<td>1.8 (1.10-2.90)</td>
<td>1.7 (0.94-3.11)</td>
</tr>
<tr>
<td>Prior nucleosides</td>
<td>0.84 (0.73-0.97)</td>
<td>0.72 (0.61-0.86)</td>
</tr>
<tr>
<td>Black race</td>
<td>0.85 (0.56-1.29)</td>
<td>0.52 (0.34-0.80)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†Age, sex, and HIV transmission categories were not significant. The reference categories used in the logistic analyses were CD4 cell count <200 and RNA >100 000 copies/mL.