Yellow Fever Virus Vaccine–associated Deaths in Young Women

Stephen J. Seligman

Yellow fever virus–associated viscerotropic disease is a rare sequela of live-attenuated virus vaccine. Elderly persons and persons who have had thymectomies have increased susceptibility. A review of published and other data suggested a higher than expected number of deaths from yellow fever vaccine–associated viscerotropic disease among women 19–34 years of age without known immunodeficiency.

Yellow fever virus (YFV) vaccine had been considered the safest of the live-virus vaccines. Rare neurologic adverse events, called yellow fever vaccine–associated neurotropic disease (YEL-AND), have long been recognized but are seldom fatal. However, in 2001, the vaccine was found to cause a serious, frequently fatal, multisystemic illness, called yellow fever vaccine–associated viscerotropic disease (YEL-AVD), which resembles the illness it was designed to prevent (1–3). According to reports from the Vaccine Adverse Event Reporting System (VAERS) (www.vaers.hhs.gov), the frequency of YEL-AVD in US vaccinees was 0.4 per 100,000 doses of vaccine administered (4).

Elderly persons (4) and patients who have undergone thymectomies secondary to thymoma (5) are recognized as groups at risk for YEL-AVD. However, several case reports of YEL-AVD in young women raise concern that women of childbearing age might also be at increased risk.

**The Study**

To investigate the possibility of age- and sex-specific risk groups, a comprehensive YEL-AVD dataset (Table 36-30 in 11), was analyzed (Figure). This dataset has the advantage of having been compiled with information that is not otherwise publicly available: data from the Centers for Disease Control and Prevention (Atlanta, GA, USA), patient charts, and vaccine manufacturers (T.P. Monath, pers. comm.).

Two concentrations of cases were evident: cases in men ≥60 years of age who survived and in women 19–34 years of age who died. Although selection bias may have influenced the cases reported, the sex-specific survival rates for these 2 age groups statistically differed: 21% (3/14) versus 0% (0/6) (p = 0.002 by Fisher exact test). In addition to the surprisingly low case-fatality rate for elderly men, only 2 of the 4 patients who had undergone thymectomy and had YEL-AVD died.

Searches for additional YEL-AVD cases among women of childbearing age (15–44 years) and of comparably aged men included review of published cases through PubMed (www.ncbi.nlm.nih.gov/sites/entrez) and reports from the ProMED Web site (http://apex.oracle.com/pls/otn/f?p=2400:1000:). In follow-up of a ProMED listing, 1 case was supplied by Bio-Manguinhos (Rio de Janeiro, Brazil), a producer of YFV vaccine. VAERS also was searched. Information was sought from authors of case reports. Cases listed in VAERS were excluded if another explanation for the adverse event was evident in the case description or if they contained insufficient information to classify the event as YEL-AVD.

A total of 9 fatal cases of YEL-AVD in young adults, all women, were found (Table). Six cases were included in the report by Monath et al. (11), and 3 cases were found through the author’s search. The eldest of the 9 case-patients was 34 years of age. One case listed by Monath et al. occurred in 1975 and was originally thought to be yellow fever but was documented as vaccine-related ≈2 decades later (13). This patient’s age is not known, but she was reported to be a young woman (P. Vasconcelos, pers. comm.).

Three fatal cases of possible YEL-AVD among young women reported in VAERS were excluded from the Table because information was insufficient to document the diagnosis. Two other cases of suspected YEL-AVD, 1 each in an 18-year-old man and a 24-year-old woman, occurred outside the United States. Hence, these patients could have come from regions where yellow fever was endemic and thus might have had wild-type yellow fever.

Also excluded from the Table are 2 cases reported in the published literature: 1 in a 23-year-old woman with a partial C4 deficiency and discoid lupus erythematosus hospitalized with severe YEL-AND and YEL-AVD who survived (14) and 1 in a 43-year-old woman with systemic lupus erythematosus who died (10). The first was excluded because she survived, had clinical features that included YEL-AND, and had known immunodeficiency. For the second patient, a history of disseminated lupus

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Author affiliation: New York Medical College, Valhalla, New York, USA

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erythematosis, the relatively long interval (30 days) until death (in contrast to the 9–14 days in the other women), and her older age suggest that her susceptibility to the vaccine differed from those listed in the Table.

In several investigations of YEL-AVD cases, extensive sequence analyses did not indicate any substantial evidence of reversion of the vaccine to virulence (1,10). Two varieties of YFV vaccine are available: the 17DD vaccine produced in Brazil and used in South America and the 17D-204 vaccine (YF-Vax, Sanofi Pasteur, Swiftwater, PA, USA; and Stamaril, Sanofi Pasteur, Lyon, France) used elsewhere. Six cases listed in the Table occurred in 17DD vaccine recipients in South America, and 3 occurred in persons who received 17D-204 as prospective travelers.

The limited racial information available indicates that cases were not confined to persons of any particular racial group. Of 3 case-patients for whom racial information was available, 1 each was described as Caucasian (8), black (2), and of Pacific Islander ancestry (7).

### Table. Characteristics of fatal yellow fever vaccine–associated viscerotropic disease in women of childbearing age who had no known immunologic defects*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Country</th>
<th>Year</th>
<th>Vaccine</th>
<th>Days after vaccination</th>
<th>Possible predisposing factors</th>
<th>Virus detection</th>
<th>Neutralizing antibody test results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Brazil</td>
<td>2001</td>
<td>17DD†</td>
<td>2</td>
<td>None known</td>
<td>RT-PCR liver and spleen</td>
<td></td>
<td>(12)</td>
</tr>
<tr>
<td>22</td>
<td>United States</td>
<td>2002</td>
<td>17D-204 YF-Vax‡</td>
<td>2</td>
<td>None known</td>
<td>YF viral antigen in multiple organs, i.e., liver, lungs, brain, heart, spleen, kidney, lymph nodes</td>
<td></td>
<td>(7)</td>
</tr>
<tr>
<td>22</td>
<td>United States</td>
<td>2005</td>
<td>17D-204 YF-Vax‡</td>
<td>2</td>
<td>None known</td>
<td>See text for postmortem description of thymus</td>
<td>Plasma virus 1.1 × 10⁵ PFU/mL</td>
<td>2,560, day 10</td>
</tr>
<tr>
<td>22</td>
<td>Brazil</td>
<td>2000</td>
<td>17DD†</td>
<td>4</td>
<td>None known</td>
<td>Hepatitis A and nephritis as a child</td>
<td>+ Culture IgM +</td>
<td>(2)</td>
</tr>
<tr>
<td>23</td>
<td>Peru</td>
<td>2007</td>
<td>17DD†</td>
<td>1</td>
<td>None known</td>
<td>Acne rosacea</td>
<td>Viral RNA lung 7.6 × 10⁶ and serum 3.9 × 10⁶ PFU equivalents/mL</td>
<td>160 (by PRNT), day 9</td>
</tr>
<tr>
<td>Young adult §</td>
<td>Brazil</td>
<td>1975</td>
<td>17DD†</td>
<td>5</td>
<td>None known</td>
<td>+ Culture</td>
<td></td>
<td>Table 36-30 in (11), (13)</td>
</tr>
<tr>
<td>24</td>
<td>Peru</td>
<td>2007</td>
<td>17DD†</td>
<td>&lt;1</td>
<td>None known</td>
<td>Egg allergy</td>
<td>Viral RNA liver 1.1 × 10⁷ and brain 4.2 × 10⁶ PFU equivalents/mL</td>
<td>10,240 (by PRNT), day 11</td>
</tr>
<tr>
<td>26</td>
<td>Spain</td>
<td>2004</td>
<td>17D-204¶</td>
<td>4</td>
<td>None known</td>
<td>+ Culture liver, kidney, plasma; real-time PCR liver 6.2 × 10⁶ genome equivalents/g</td>
<td>Culture</td>
<td>512 (by microneutralization assay), day 8</td>
</tr>
</tbody>
</table>

*+, positive test result; RT-PCR, reverse transcription PCR; YF, yellow fever; Ig, immunoglobulin; PRNT, plaque-reduction neutralization test. Blank cells indicate information is not in the reference cited.
†Bio-Manguinhos, Rio de Janeiro, Brazil.
‡Sanofi Pasteur, Swiftwater, PA, USA.
§The age of this patient is not known, but she was a young woman (P. Vasconcelos, pers. comm.).
¶Stamaril, Sanofi Pasteur, Lyon, France.
#R. Menezes-Martins, pers. comm.
Despite the known association of thymectomy with YEL-AVD, the only observation on possible thymic disease in the reports of the 9 cases is the statement that, at autopsy of a 22-year-old woman from the United States, the thymus was replaced by fat (Table 36-3 in [1]). However, the accuracy of the finding should be considered in the context that, at surgery, experienced cardiothoracic surgeons may have difficulty in distinguishing thymus from adipose tissue (R.L. Berger, pers. comm.) and that the thymus was not examined histologically (R.V. Ridenour, III, pers. comm.). Because the thymus may be difficult to separate from surrounding adipose tissue and is infrequently a source of disease, pathologists, at least in the United States, do not routinely examine it histologically at autopsy (I. Argani, pers. comm.). Thymic deficiencies such as Sutton thymic dysplasia (fatal viral infection in young women with a dysplastic thymus) ([5]) have yet to be excluded.

Conclusions

Although accurate denominators are not available for calculating age- and sex-specific incidence of YEL-AVD, the number of fatal YEL-AVD cases among women of childbearing age appears to be higher than expected. Further investigation should include ascertainment of family history; exploration of contraceptive medications; determination of childbearing age appears to be higher than expected. Further investigation should include ascertainment of family history; exploration of contraceptive medications; further evaluation of possible complement defects; and evaluation of any associations with autoimmune disease.

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Dr Seligman is a research professor in the Department of Microbiology and Immunology, New York Medical College. His current research interests include flaviviruses with emphasis on the safety of flavivirus vaccines.

References


Address for correspondence: Stephen J. Seligman, Department of Microbiology and Immunology, New York Medical College, Valhalla, NY 10595, USA; email: stephen_seligman@nymc.edu

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