Age-related risk of adverse events following yellow fever vaccination in Australia

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Abstract
Reports of six deaths internationally, including one from Australia, plus other cases of severe systemic adverse events following yellow fever (YF) vaccination have raised concern about the safety of YF vaccine, particularly among older vaccinees. We investigated the age-related reporting rates of adverse events following YF vaccination reported to the Australian Adverse Drug Reactions Advisory Committee for the period 1993 to 2002. The reporting rate of systemic adverse events leading to hospitalisation or death was significantly higher among vaccinees aged ≥65 years (reporting rate ratio (RRR) 8.95, 95% confidence interval (CI) 1.49–53.5) or ≥45 years (RRR 5.30, 95% CI 1.33–21.2) compared with younger YF vaccinees. The higher reporting rates among older vaccinees are similar to those identified in the United States of America. The data highlight the importance of assessing the destination-specific risk, especially for older travellers to yellow fever endemic areas, and careful monitoring of those who are vaccinated. Commun Dis Intell 2004;28:244–248.

Keywords: vaccination, yellow fever

Introduction
Until recently, the live attenuated 17D strain of yellow fever (YF) vaccine had a 50 year history as a safe and effective vaccine.1,2 Mild adverse events, including mild headaches and fevers, occur in 2–5 per cent of vaccinees. Life-threatening systemic adverse events following YF vaccination are rare. Data from the United States of America (USA) suggest that viscerotropic disease (multiple organ involvement) occurs in 1 in 400,000 YF vaccinees, while in Brazil the estimate is 1 in 1.1 million vaccinees. Severe neurological disease is estimated to occur in <1 in 8 million YF vaccinees.3

In 1998, two reports to the US Vaccine Adverse Events Reporting System (VAERS) of multiple organ failure in elderly YF vaccinees led to a study to assess the age-related reporting rates to VAERS of serious systemic illnesses temporally associated with YF vaccination that led to hospitalisation or death.5 The investigators identified three deaths among elderly YF vaccinees and estimated that the reporting rate of systemic illnesses leading to hospitalisation or death was 16 times higher among vaccinees aged ≥65 years compared with those aged 25–44 years.5

More recently, in 2001, a further three deaths among YF vaccinees in the USA, Brazil and Australia,6–8 were reported in The Lancet. Common findings were viscerotropic disease, characterised by multiple organ failure and isolation of the vaccine strain of YF virus. That publication was followed by three additional case reports from Europe which described similar serious systemic adverse events among YF vaccinees.9–11 The majority of deaths and serious adverse events following immunisation were in adults aged 45 years or older. The US Centers for Disease Control and Prevention (CDC) commenced active surveillance of serious adverse events following YF vaccination in mid-2001.3,4

The study reported here was undertaken following enquiries from the US CDC, the World Health Organization and the United Kingdom about age-related rates of serious systemic adverse events among YF vaccinees in Australia. The aim of the study was to estimate the age-specific reporting rates of systemic adverse events leading to hospitalisation or death among Australian YF vaccinees and compare these rates to those published for the USA. We also estimated the expected frequency of YF vaccine-associated viscerotropic disease (YFV-AVD) in Australia, based on the observed passive reporting rates of this in the USA and YF vaccine usage in Australia.
Methods

Data sources

Cases of adverse events following YF vaccination were identified from the Adverse Drug Reactions Advisory Committee (ADRAC) database. This is a national database which contains spontaneous reports, from 1972 onwards, of adverse events following the administration of drugs or vaccines. The number of doses of YF vaccine administered by age group was estimated from sales data supplied by the sole supplier of YF vaccine in Australia and from the age distribution of YF vaccine recipients recorded in the immunisation register of a national network of travel vaccination clinics.

Cases

All reports in the ADRAC database for the period 1993 to 2002 were reviewed where:

- YF vaccine was recorded as ‘suspected’ of being involved in the reported adverse event (with or without other vaccines or drugs);
- the report was assigned a causality rating of ‘certain’, ‘probable’ or ‘possible’; and
- the age of the person was recorded and was ≥15 years.

Cases were classified as having a ‘systemic’ adverse event or ‘other’ adverse event based on the timing of the onset of the reaction following immunisation, and the symptoms and signs listed in the database (Box). Classification was done independently by two of the authors (GL, MB) who were blinded to the age of person reported. Discrepancies were resolved by consensus before ages were revealed. The definitions of ‘systemic’ and ‘other’ adverse events were based on those used by USA researchers. There was insufficient information recorded in the ADRAC database about the duration of symptoms to include duration as a component of the case definitions, so they were more sensitive than those used in the USA study. Cases of ‘systemic’ adverse events were defined as ‘serious’ if hospitalisation or death was recorded either in the database or on the original report card. The original report card was reviewed if information about hospitalisation or death was missing from the database.

Denominator data

Only one company sells YF vaccine in Australia (Aventis-Pasteur). They provided the annual number of doses sold to the civilian sector for the four years 1999 to 2002. Prior to 1998, most YF vaccine sold in Australia was in five-dose vials. To estimate the number of individual doses administered during 1993 to 2002, it was assumed that there had been minimal wastage of single doses in the 1999 to 2002 period and that the rate of increase in doses administered over the six years 1993 to 1998 was similar to that for the period 1999 to 2002.

YF vaccine providers in Australia require a specific license, which is reviewed regularly. The majority of providers work in travel vaccination centres. The number of doses of YF vaccine administered to the age groups <15 years, 15–24 years, 25–44 years, 45–64 years and ≥65 years was obtained from the immunisation registry of a national network of clinics for the period 1999 to 2002. This was a large sample comprising 15 per cent of the total YF vaccine sales for 1999 to 2002 and is likely to be representative of YF vaccinees. The total number of doses administered to each age group for the 10-year period analysed (1993 to 2002) was estimated from the total sales estimates and the age-distribution data.

Data analysis

Age-specific adverse events reporting rates per 100,000 doses of YF vaccine were estimated. The reporting rate ratios (RRR) of ‘serious systemic’ adverse events were calculated using either the 25–44 year or the 15–44 year age group as the

Box. Categories of vaccine adverse events*

<table>
<thead>
<tr>
<th>Systemic adverse events – onset within two weeks of vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neurological:* new onset seizures, encephalitis, myelitis, altered mental status, focal cranial or peripheral neurological deficits, paraesthesia, vertigo, +/- headache.</td>
</tr>
<tr>
<td>• Multi-systemic:* myalgia, arthralgia, impaired hepatic function, respiratory distress, nausea, vomiting, impaired renal function, +/- fever.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other adverse events – onset within two weeks of vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mild non-specific:* headache or dizziness without other symptoms or signs.</td>
</tr>
<tr>
<td>• Hypersensitively:* rash, urticaria, +/- fever; anaphylaxis, angioedema.</td>
</tr>
<tr>
<td>• Local reaction:* localised pain, swelling, erythema or warmth at the injection site.</td>
</tr>
</tbody>
</table>

* Cases that were reported with more than one category of reaction were only counted once, in the most serious reaction category.
† Examples of symptoms and signs.
referred group. Epi Info software\textsuperscript{13} was used to calculate RRR values and 95 per cent confidence intervals (CI). The reporting rates per 100,000 vaccine doses and the RRR values estimated for Australia for 1993 to 2002 were compared with those published for the USA for the period 1990 to 1998.\textsuperscript{5} Due to the lower number of cases identified in Australia, the published USA data were combined into broader age groups (15–44 years, ≥65 years) and rates, RRR values and 95 per cent confidence intervals were recalculated for comparison with Australian data.

Results

Vaccine distribution

It was estimated that 210,656 doses of YF vaccine were administered to the civilian population in Australia in the 10 years 1993 to 2002. Approximately 4.3 per cent of YF vaccinees recorded on the travel clinic network immunisation register were aged ≥65 years, while 57.2 per cent were aged between 25 and 44 years (Table 1).

Adverse events reports

For the period 1993 to 2002, we identified 42 reports of adverse events following YF vaccination in the ADRAC database that met the criteria for review. Of these, 26 (62%) met the study definition of a 'systemic' adverse event with nine (21%) defined as 'serious systemic' adverse events (Table 1). One of these nine had died of YFV-AVD.\textsuperscript{8} No cases of severe neurological disease were identified. YF vaccine was the only suspected vaccine or drug for 15 (36%) of the 42 reports. The most common vaccines administered at the same time as YF vaccine were typhoid (n=13), hepatitis A (n=12) and oral polio (n=10).

Age-specific adverse event reporting rates

There was an increasing trend in the reporting rates per 100,000 doses of YF vaccine for both 'systemic' adverse events and 'serious systemic' adverse events among vaccinees aged 45–64 years and ≥65 years compared with the 25–44 year reference group (Table 1). However, only the reporting rate of 'serious systemic' adverse events among people aged ≥65 years was significantly higher than that of the 25–44 year age group (RRR 8.95, 95% CI 1.49–53). Comparison of reporting rates for broader age groups revealed a significantly higher reporting rate of 'serious systemic' adverse event among vaccinees aged ≥45 years compared with those aged 15–44 years (RRR 5.30, 95% CI 1.33–21). The age-related RRR values showed similar patterns to that seen in the USA (Table 2).

Expected frequency of YFV-AVD

Based on the current Australian YF vaccine distribution data of approximately 24,000 doses per annum, and the reported rates of YFV-AVD in the USA of one in 400,000 doses, the expected frequency of YFV-AVD in Australia is one case in 16 years. The case reported in 2001 who died\textsuperscript{8} is the only one recorded in the ADRAC database, which commenced in 1972.

Discussion

This study was prompted by international concern about the risk of serious adverse events caused by YF vaccine, particularly among the older vaccinees. It was found that, like the USA, there was a significantly higher reporting rate of serious systemic adverse events (leading to hospitalisation or death) temporally associated with YF vaccination among Australians aged ≥65 years and ≥45 years, compared with younger YF vaccinees.

The study had some limitations. Cases were identified through passive surveillance and are subject to the biases inherent in systems that rely on spontaneous reporting,\textsuperscript{12} including the possibility of age-related reporting biases. The case definitions derived from the ADRAC data were more sensitive than those used in the USA study\textsuperscript{5} because the duration of symptoms could not be used as part of the case definition. This contributed to the estimation of higher reporting rates compared with the USA, although this is unlikely to have impacted on the trends in age-related reporting rate ratios. The denominator data were estimates only and assumed that older YF vaccinees were as likely as younger YF vaccinees to attend travel vaccination clinics. Clinic data support this, showing that older travellers are more likely to attend for yellow fever vaccination than they are for other travel-related health matters such as typhoid vaccination or antimalarial prophylaxis. It was also found that the proportion of older YF vaccinees recorded on the travel clinic immunisation register differed according to the city of residence and reflected the population structure of the local region (e.g. there was a smaller proportion of older vaccinees at the Sydney clinic, and a higher proportion at the Adelaide clinic). If older YF vaccinees were less likely to attend travel vaccination clinics, the number of doses received by this age group would be higher than was estimated and would have resulted in lower age-related adverse event reporting than estimated.

As found in the USA study, YF vaccinees reported to ADRAC had often received other vaccines at the same time and these vaccines may have caused the reported reactions. To assess this, USA researchers estimated the age-specific reporting rates of serious
Table 1. Reporting rates per 100,000 vaccine doses and reporting rate ratios for adverse events following yellow fever vaccination, Australia, 1993 to 2002

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of doses</th>
<th>% of doses</th>
<th>Systemic adverse events*</th>
<th>Serious systemic adverse events*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>RRRI (95% CI)</td>
<td>n %† RRRI (95% CI)</td>
</tr>
<tr>
<td>15–24</td>
<td>32,423</td>
<td>15.4</td>
<td>0 0.00 0.00</td>
<td>0 0.00 0.00</td>
</tr>
<tr>
<td>25–44</td>
<td>120,552</td>
<td>57.2</td>
<td>14 11.61 1.00†</td>
<td>3 2.49 1.00†</td>
</tr>
<tr>
<td>45–64</td>
<td>48,697</td>
<td>23.1</td>
<td>9 18.48 1.59 (0.69–3.68)</td>
<td>4 8.21 3.30 (0.62–9.90)</td>
</tr>
<tr>
<td>≥65</td>
<td>8,984</td>
<td>4.3</td>
<td>3 33.39 2.88 (0.83–10.0)</td>
<td>2 22.26 8.95 (1.49–53.5)</td>
</tr>
<tr>
<td>15–44</td>
<td>152,975</td>
<td>72.6</td>
<td>14 9.15 1.00I†</td>
<td>3 1.96 1.00I†</td>
</tr>
<tr>
<td>≥45</td>
<td>57,681</td>
<td>27.4</td>
<td>12 20.80 2.27 (1.05–4.91)</td>
<td>6 10.40 5.30 (1.33–21.2)</td>
</tr>
<tr>
<td>Total</td>
<td>210,656</td>
<td>100.0</td>
<td>26 12.34</td>
<td>9 4.27</td>
</tr>
</tbody>
</table>

* See Box for definitions of adverse event categories; ‘serious’ adverse events were those leading to hospitalisation or death.
† Rate per 100,000 doses of vaccine.
‡ Confidence interval.
§ Reference age group for comparison.

Table 2. Reporting rates per 100,000 doses and reporting rate ratios for adverse events following yellow fever vaccination, United States of America, 1990 to 1998

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of doses</th>
<th>% of doses</th>
<th>Systemic adverse events*</th>
<th>Serious systemic adverse events*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>RRRI (95% CI)</td>
<td>n %† RRRI (95% CI)</td>
</tr>
<tr>
<td>15–24</td>
<td>189,991</td>
<td>13.2</td>
<td>3 1.58 1.01 (0.28–3.6)</td>
<td>2 1.05 3.70 (0.52–26)</td>
</tr>
<tr>
<td>25–44</td>
<td>702,783</td>
<td>48.7</td>
<td>11 1.57 1.00I†</td>
<td>2 0.28 1.00*</td>
</tr>
<tr>
<td>45–64</td>
<td>442,605</td>
<td>30.7</td>
<td>12 2.71 1.73 (0.76–3.9)</td>
<td>5 1.13 3.97 (0.77–20)</td>
</tr>
<tr>
<td>≥65I</td>
<td>108,307</td>
<td>7.5</td>
<td>9 8.31 5.31 (2.2–12.8)</td>
<td>5 4.62 16.2 (3.2–84)</td>
</tr>
<tr>
<td>15–44II</td>
<td>892,774</td>
<td>61.8</td>
<td>14 1.57 1.00*</td>
<td>4 0.45 1.00*</td>
</tr>
<tr>
<td>≥45II</td>
<td>550,912</td>
<td>38.2</td>
<td>21 3.81 2.43 (1.2–4.8)</td>
<td>10 1.82 4.04 (1.3–12.9)</td>
</tr>
<tr>
<td>Total</td>
<td>1,443,686</td>
<td>100.0</td>
<td>35 2.42</td>
<td>14 0.97</td>
</tr>
</tbody>
</table>

* See Box for definitions of adverse event categories; ‘serious’ adverse events were those leading to hospitalisation or death.
† Rate per 100,000 doses of vaccine.
‡ Confidence interval.
§ Reference age group for comparison.
II Reporting rates and reporting rate ratio values for these age groups were calculated from published data.

systemic adverse events following hepatitis A vaccination and found no significant differences across age groups. We also estimated the age-specific RRR values for systemic and serious systemic adverse events following hepatitis A vaccination, using both the Australian age-specific YF vaccine distribution data and the USA hepatitis A distribution data as denominators, and found no increase in reporting rates among older hepatitis A vaccinees (data not shown).

Australia has not followed the USA in implementing active surveillance of serious adverse events following YF vaccination. It was felt that serious and life-threatening reactions are likely to be reported by clinicians and so would be detected by the current passive surveillance system. However, the Therapeutic Goods Administration (the Australian regulatory authority) did request that the vaccine manufacturer amend the product insert. This now describes increased risks with YF vaccine in individuals aged ≥65 years and includes precautions for older individuals concerning pre-vaccination evaluation of health status and post-vaccination monitoring. A statement identifying the need to balance the risk of rare reactions in elderly travellers against the risk of YF infection is also included. This information is also available in the recently published 8th edition of the Australian Immunisation Handbook.
YF is a serious and potentially fatal disease while the YF vaccine is highly efficacious and rarely causes serious adverse events.1–3,14 The data from this study highlight the importance of assessing the destination-specific risk, especially for older travellers to YF endemic areas, and the need for appropriate monitoring of those who are vaccinated for possible serious adverse events.

Acknowledgements

We thank Dr Ian Boyd for providing ADRAC data for analysis and Paul Cohen of Aventis Pasteur for information about yellow fever vaccine sales in Australia. The National Centre for Immunisation Research and Surveillance is supported by the Australian Government Department of Health and Ageing, New South Wales Health and The Children’s Hospital at Westmead.

References


