Original Article

Poisson-Model Analysis of the Risk of Vaccine-Associated Paralytic Poliomyelitis in Japan between 1971 and 2000

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SUMMARY: This study estimates the risk of vaccine-associated paralytic poliomyelitis (VAPP) in Japan between 1971 and 2000. We acquired data regarding the number of VAPP cases from the website of the Ministry of Health, Labour and Welfare, and we estimated the number of oral poliovirus vaccines (OPV) administered based on the reported immunization data. Risk was calculated as the ratio between the number of VAPP cases and the number of OPV doses administered. Both the Runs test and the Poisson model were used to analyze the occurrence of VAPP. Thirty-three cases of VAPP were recorded in Japan between 1971 and 2000; approximately one case occurred per year. There were no statistical changes in temporal trends as regards the occurrence of VAPP between 1971 and 2000. The overall risk for VAPP, including both recipient and contact VAPP, was one per 2.0 million OPV doses administered. The risk of recipient VAPP was one per 3.7 million doses, among which the first dose posed a much higher risk of one per 2.3 million than that of the subsequent dose. These data indicated that the occurrence of VAPP is rare, but the risk has remained constant for as long as OPV has been used in Japan.

INTRODUCTION

Since the Global Polio Eradication Initiative was launched in 1988, extraordinary progress has been made toward the eradication of global poliomyelitis. The disease burden has been reduced by more than 99%, and the number of countries with endemic transmission has been reduced by more than 96% (1). By the end of 2006, only four countries still harbored indigenous wild polioviruses worldwide, including Afghanistan, India, Pakistan, and Nigeria (2). As an important eradication strategy, routine immunization with oral poliovirus vaccine (OPV) has been adopted by most countries. However, use of this live-virus vaccine is also associated with a serious consequence, namely, vaccine-associated paralytic poliomyelitis (VAPP). In 2002, the World Health Organization (WHO) estimated that between 250 and 500 cases of VAPP occur annually due to the use of OPV in routine childhood immunization programs around the world (3).

In Japan, OPV use started in 1961 and it became a routine immunization in 1964. During the 1960s, the widespread use of OPV led to a dramatic decrease in poliomyelitis (4). Since 1981, no poliomyelitis cases due to wild poliovirus have been reported in Japan (5). In November 2000, the WHO certified the entire WHO Western Pacific Region, including Japan, as polio-free (6). However, VAPP due to OPV use has continued to occur in Japan.

Several reports have mentioned the occurrence of VAPP in Japan, and reported occurrences of VAPP have been estimated based on doses of OPV distributed (4,7-9). In the present study, the occurrence of VAPP in Japan was estimated based on the doses of OPV administered between 1971 and 2000, and the levels of overall VAPP risk, recipient VAPP risk, and contact VAPP risk.

METHODS

Sources of data: Epidemiological data for VAPP occurrences between 1971 and 2000 were acquired by a review of data and notification records from the website of the Ministry of Health, Labour and Welfare of Japan (MHW) (10).

In Japan, the national childhood immunization program recommends that the OPV be administered twice to children from age 3 to 90 months; typically, the vaccine is administered between the ages of 3 to 18 months, twice annually (i.e., in spring and fall). The numbers of OPV doses administered are reported to the MHW after each immunization session by the local health authorities, and the MHW in turn reports the annual nationwide statistics (11). Using the annual immunization data (12,13), we estimated the amount of OPV administered between 1971 and 2000. Since the annual number of immunizations given between 1971 and 1986 was not available, we calculated the number based on the reported vaccination coverage (13) and the size of the target population (14).

Case definition: VAPP is defined as “acute flaccid paralysis 4-30 days following the receipt of OPV or within 4-75 days after contact with a recipient of OPV (secondary infections), with neurological deficits remaining 60 days after onset, or death” (15). In Japan, a more strict definition that required the isolation of vaccine-related poliovirus from any stool sample has been adopted, and we utilized that latter definition. Here, we refer to VAPP cases that occur in vaccinees as “recipient VAPP”, and to those cases associated with secondary infections as “contact VAPP”.

Estimation of VAPP risk: Risk was calculated as the ratio between the number of VAPP cases and the number of OPV doses administered between 1971 and 2000. The overall VAPP risk, recipient VAPP risk, and contact VAPP risk were all calculated using the total number of OPVs administered as the denominator. For the calculation of the recipient VAPP risk following the first and second OPV doses, the number of the first and second OPV doses administered during the study period, respectively, were used as the denominators. The rela-
tive risk (RR) between recipient VAPP risk following the first OPV dose and the risk following the second was calculated.

**Statistical analysis:** We used the Runs test to test the temporal trend of VAPP occurrence. We also employed the Poisson assumption to derive estimates of the occurrence of VAPP during the study period.

**RESULTS**

Thirty-three cases of VAPP were recorded in Japan between 1971 and 2000. Of the 33 cases of VAPP, 18 (55%) were recipient VAPP cases, and 15 cases (45%) were contact VAPP cases. Among the recipient VAPP cases, 15 (83%) were associated with the first dose and 3 (17%) with the second dose. Twenty-six (79%) VAPP cases were male and 2 (6%) were female. Cases of VAPP were reported in 15 prefectures. The highest number was reported in Hokkaido, with 7 cases (21%), followed by Fukuoka, with 6 cases (18%). Table 1 shows the distribution of poliovirus serotypes isolated for the cases of recipient and contact VAPP. Of the 33 cases of VAPP, type 1 virus was identified in 2 cases (6%), type 2 virus in 17 cases (52%), type 3 virus in 7 cases (21%), and more than one serotype in 7 cases (21%).

According to the results of the Runs test, there were no substantial temporal changes in the occurrence of VAPP between 1971 and 2000 ($P = 0.35$). The highest number of VAPP cases was 5, reported in 1973. We also constructed a Poisson model to estimate the frequency of years by the number of VAPP cases occurring between 1971 and 2000. The results showed a good fit between the model and the observed data (Fig. 1). The probability of VAPP occurrences per year (≥1 case) in Japan was estimated to be 66.7%, based on the Poisson model.

The total number of OPVs administered was 66.4 million doses between 1971 and 2000, and the total number of VAPP occurrences during this period was 33. Thus, the overall risk for VAPP was one case per 2.0 million doses administered. The risks of recipient VAPP and contact VAPP were one case per 3.7 million doses administered and one case per 4.4 million doses administered, respectively. The risk of recipient

**DISCUSSION**

Previous studies (4,7-9) have presented the occurrence of VAPP in Japan, as shown in Table 3. The estimates in these studies were all based on OPV doses distributed, similar to the studies of VAPP risk in the United States (16,17). The number of doses of OPV administered was very close to the net doses distributed in the United States, because only single-dose vials of OPV were used, while unused doses of vaccine were returned to the manufacturer for reimbursement (18). However, in Japan, 20-dose vials of OPV are used (8), and therefore wasted OPV doses could be overlooked. Consequently, the number of OPV doses distributed is larger than the number of OPV doses administered in Japan. Thus, previous studies might have underestimated the risk of VAPP in Japan. Given this line of reasoning, our estimates were based on the number of OPV doses administered. As a result, our estimates are considered to be closer to the “true risk” of VAPP in Japan.

In this study, we estimated overall risk as well as recipient and contact risks for VAPP in Japan. To the best of our knowledge, this is the first study to report the risk of recipient

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**Table 1.** Distribution of serotypes isolated from cases of recipient and contact VAPP in Japan between 1971 and 2000

<table>
<thead>
<tr>
<th>Type</th>
<th>No. with type 1</th>
<th>No. with type 2</th>
<th>No. with type 3</th>
<th>No. with mixtures of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient VAPP ($n = 18$)</td>
<td>1</td>
<td>7</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Contact VAPP ($n = 15$)</td>
<td>1</td>
<td>10</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total ($n = 33$)</td>
<td>2</td>
<td>17</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

**Table 2.** Risk of VAPP in Japan between 1971 and 2000

<table>
<thead>
<tr>
<th>Type of case</th>
<th>Overall dose (95% CI)</th>
<th>First dose (95% CI)</th>
<th>Second dose (95% CI)</th>
<th>Relative risk$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient VAPP$^a$</td>
<td>$1.37 \times 10^6$ (1/6.2 - 1/2.3)</td>
<td>$1.23 \times 10^6$ (1/4.1 - 1/1.4)</td>
<td>$1/10.9 \times 10^6$ (1/54.5 - 1/3.4)</td>
<td>4.7</td>
</tr>
<tr>
<td>Contact VAPP$^a$</td>
<td>$1.44 \times 10^6$ (1/7.9 - 1/2.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$1.20 \times 10^6$ (1/2.9 - 1/1.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$: The ratio between one VAPP case and the number of million OPV doses administered.
$^b$: First dose risk/second dose risk.
$^c$: Includes normal as well as immunologically abnormal cases.
$^d$: Includes cases which immunization history were unclear.
VAPP in Japan following administration of the first dose of OPV. It has been suggested that the first-dose recipient risk estimates might be more accurate for international comparisons (18,19). The risk of recipient VAPP following the first OPV dose in Japan, which was estimated to be one case per 2.3 million doses administered, was slightly higher than those in India (one case per 2.8 million doses administered) (19) and Brazil (one case per 2.39 million doses administered) (20), but lower than those in the United States (one case per 0.75 million doses distributed) (17), England and Wales (one case per 0.7 million doses distributed) (21), and Latin America (one case per 1.1-1.2 million doses administered) (18). In the case of the latter difference (i.e., the lower rate in Japan), a possible explanation could be differences between the definitions of VAPP in each country. In the studies in the United States (16), England and Wales (21), and Latin America (18), an isolation of vaccine-related virus is not required for a confirmation of VAPP. As a result, some confirmed cases of VAPP might in fact represent paralytic disease with non-polio enteroviruses (NEPV) (22); however, in the present study, NEPV-related paralytic cases were excluded, because isolation of vaccine-related virus from stool samples is required for confirmation of VAPP. As regards the former discrepancy (i.e., the higher rate in Japan), a possible explanation might be the use of different denominators. The birth cohort for the study period was used as the denominator to calculate the risks of recipient VAPP following the first OPV dose in India (19) and Brazil (20); however, in our study, a more accurate number was used as the denominator, i.e., the number of first-OPV doses administered during the study period.

The following aspects of our findings are compatible with the results of other countries’ studies. First, the risk of recipient VAPP following the first OPV dose is higher than the risk following the second OPV dose. Second, type 2 and type 3 strains are more frequently isolated in VAPP (20,23). This provides additional empirical evidence in support of the previous finding that the type 1 strain is more stable in terms of safety, effectiveness, and cost. However, in Japan, with high OPV immunization coverage and a sensitive notifiable diseases surveillance system, such gender differences are implausible; further studies are nonetheless needed. Second, the data also suggested that there were geographic differences in the occurrence of VAPP. Several prefectures showed a high occurrence of VAPP in Japan; all vaccines were from the same source (there has been only one OPV manufacturer in Japan and practically every child has received its product), and the same OPV immunization schedule was carried out. Again, this issue will need to be examined in future studies. A similar phenomenon has been reported in Brazil (25). Moreover, of the 33 cases of VAPP, 4 (12%) adult cases of contact VAPP were found. There have also been a couple of reports of adult VAPP and the transmission of vaccine poliovirus from children to adults in Japan since 2000 (26,27). The repeated occurrence of adult VAPP during a polio-free phase revealed the existence and accumulation of a susceptible population in Japan.

One strength of the present study was the use of the Poisson model to analyze the occurrence of VAPP in Japan. The Poisson distribution has been used to model a wide range of natural phenomena. In our study, we considered the VAPP occurrences as random events during the study period in Japan. As the VAPP risk is rare, the number of VAPP occurrences in a year will, based on the null hypothesis of constant risk, follow a Poisson distribution with one parameter, \( \lambda \), which represents the mean VAPP occurrences per year in Japan (28). We also found that the observed values were in good agreement with the expected values, as shown in Fig. 1. An advantage of using the Poisson model is that we could calculate the probability of the occurrence of VAPP through the equation of Poisson distribution.

The main limitation of our study was the use of only the reported VAPP cases. There might have been unreported cases of VAPP, and those would have led to an underestimation in the results. Moreover, we assumed that the annual doses of OPV administered were constant for the Runs test and the Poisson model analyses, although there were variances by year. However, this fluctuation is unlikely to have influenced our results because VAPP was very rare.

VAPP is rare, but the risk of VAPP has remained constant in Japan as long as the OPV has been used for routine immunization against poliomyelitis. To eliminate the risk of VAPP, an alternative option would be to switch from regular immunization programs, i.e., the use of OPV, to the use of an inactivated poliovirus vaccine (16). As the circulation of wild poliovirus was eliminated in Japan, it will be necessary to reevaluate the current polio vaccine policy (using OPV) by comparing it with other options (e.g., using inactivated poliovirus vaccine) in terms of safety, effectiveness, and cost.

### Table 3. Reported occurrences of VAPP in Japan

<table>
<thead>
<tr>
<th>Source</th>
<th>Study period</th>
<th>No. of VAPP</th>
<th>Overall VAPP</th>
<th>Recipient VAPP</th>
<th>Contact VAPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoneyama (4)</td>
<td>1971-2000</td>
<td>33</td>
<td>1/4.0 x 10^6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Shimizu et al. (7)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1/4.4 x 10^6</td>
<td>1/5.8 x 10^6</td>
</tr>
<tr>
<td>Kimura et al. (8)</td>
<td>1970-2000</td>
<td>20¹²</td>
<td>NA</td>
<td>1/3.0 x 10^6</td>
<td>NA</td>
</tr>
<tr>
<td>Okabe (9)</td>
<td>1981-1998</td>
<td>14</td>
<td>NA</td>
<td>1/4.0 x 10^6</td>
<td>1/5.3 x 10^6</td>
</tr>
</tbody>
</table>

¹/²: The ratio between one VAPP case and the number of OPV doses distributed.
³: Recipient VAPP only.
⁴: No available data.
ACKNOWLEDGMENTS

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REFERENCES