Risk Analysis of Aseptic Meningitis after Measles-Mumps-Rubella Vaccination in Korean Children by Using a Case-Crossover Design

Moran Ki1, Taesung Park2, Sung Gon Yi2, Jin Kyoung Oh3, and BoYoul Choi3

1 Department of Preventive Medicine, Eulji University School of Medicine, Daejon, Korea.  
2 Department of Statistics, Seoul National University, Seoul, Korea.  
3 Department of Preventive Medicine, Hanyang University College of Medicine, Seoul, Korea.

Received for publication March 5, 2002; accepted for publication July 24, 2002.

Epidemiologic study of a vaccine's adverse events is not easy; so many countries have no reliable data. Vaccines containing the Urabe or Hoshino strain have been withdrawn from use in several countries. However, the data are not strong enough to form the basis of a recommendation not to use specific strains. The authors used a case-crossover design to estimate the relative risk of aseptic meningitis in children after receiving the measles-mumps-rubella vaccine in Korea. Study subjects were hospitalized children aged 8–36 months who had aseptic meningitis in 1998. Cases were confirmed by hospital chart reviews using previously defined criteria. Through a telephone survey, the authors obtained vaccination date and place information from parents' vaccination records. Study results showed that no significant risk was associated with the Jeryl Lynn or Rubini strain of the vaccine (relative risk = 0.6, 95% confidence interval (CI): 0.18, 1.97). For the Urabe or Hoshino strain, the relative risk was 5.5 (95% CI: 2.6, 11.8); the risk increased in the third week after vaccination (relative risk = 15.6, 95% CI: 5.9, 41.2) and was elevated until the sixth week. The case-crossover design was useful in confirming the risk of acute adverse events after receiving vaccines.

child, hospitalized; epidemiologic research design; infant; meningitis, aseptic; mumps vaccine; vaccines

Abbreviations: CI, confidence interval; MMR, measles-mumps-rubella; RR, relative risk.

Vaccination has proven to be one of the most effective methods for reducing the incidence of disease worldwide. However, higher vaccination rates result in an increase in adverse events in those vaccinated. Some developed countries are burdened with more adverse events cases from vaccination than with disease incidence cases (1). In spite of adverse events, a decrease in vaccination rates increases the chance that the vaccine-preventable disease will reemerge (2). Therefore, many countries are making more of an effort to supply safe vaccines and to maintain higher vaccination rates. Rates of mandatory vaccination in Korea are above 90 percent (3), but the gradually increasing concern about adverse events could result in lowered vaccination rates. In Korea, vaccines containing the Urabe or Hoshino strain have not been used since March 2000. However, the costs of the measles-mumps-rubella (MMR) vaccines containing the Jeryl Lynn or Rubini strain are much higher, the immunogenicity of the Jeryl Lynn strain is lower than that of the Urabe strain (4, 5), and the efficacy of the Rubini strain is much lower than that of the Jeryl Lynn or Urabe strain (4, 6, 7). Because of its known low effectiveness, the World Health Organization recommends that the Rubini strain not be used in national immunization programs (8). We have to consider the cost versus the benefits of continuing to use Jeryl Lynn- or Rubini-containing MMR vaccines in Korea.

The association between mumps vaccine containing the Urabe Am9 or Hoshino strain and aseptic meningitis gradually became clear to researchers (9–12). However, the rates of contracting aseptic meningitis after vaccination with Urabe strains vary according to the manufacturer, the index of clinical suspicion, and the intensity of surveillance. In Japan and the United Kingdom, the variation is between 1 per 900 and 1 per 11,000 vaccinations (9, 10, 13–15). In Canada, the rate was calculated to be 1 per 62,000 doses of the vaccine manufactured by SmithKline Beecham (16). In France, the estimate by capture-recapture methods was 1 per 28,400 vaccinations (17); by retrospective passive surveillance, it was 1 per 120,000 vaccinations (18). Hospitaliza-
tion data collected by Black et al. found that Jeryl Lynn strain vaccinees did not show an increased risk of aseptic meningitis (19). The risk level of aseptic meningitis following MMR vaccination with various strains was not clear because of the limitation of research methods (8). Among epidemiologic studies for adverse events related to vaccine use, cohort studies require enough time and funds for validation of the thousands of vaccinees. Use of a data linkage system requires vaccination records and hospital records that must include a matching identification code (11, 19), and this procedure is not possible in many countries. Performing case-control studies is impractical in many countries with high vaccination rates; unvaccinated children are very rare and could have a variety of reasons for not being vaccinated, which could produce bias. Randomized controlled clinical trials with a vaccine known to be safe and effective are also impractical because not vaccinating persons in the control group is unethical. Surveillance methods are useful after new vaccine introductions (9) or mass vaccinations (12), but these situations are not common. Eventually, we have to find an appropriate study method to assess a vaccine’s adverse events.

The case-crossover design is a useful research tool when there is a transient risk factor with acute onset of the disease, and it requires only patient data (20). When researching a vaccine’s adverse events, this case-crossover design can be very effective because incidences of adverse events are very rare. Additionally, in many countries, only the patient’s data are available. Even more advantageous is that the risk factor measurement is easy and definite because, even though the vaccination exposure period has passed, the vaccination records can be confirmed. However, few studies have used this research design to assess the adverse events associated with vaccines. Confavreux et al. recently published a study in which they used a case-crossover design to investigate the association between vaccination and the risk of relapse with multiple sclerosis (21). Our study was carried out to estimate the risk of contracting aseptic meningitis following MMR vaccination of Korean children.

MATERIALS AND METHODS

The subjects for this study presented with incident aseptic meningitis during a 1-year period (1998) in Korea. We obtained patient records by using insurance claim data; the insurance coverage rate was 98.6 percent in the Korean population (22).

Study population

The insurance claim cases for treatment of aseptic meningitis totaled 3,950 children aged 8–36 months in 1998, 677 of whom had been admitted to general hospitals. We reviewed the charts of 501 of these patients (74 percent) and, by using our criteria, matched 441 aseptic meningitis diagnoses (88 percent). Among these appropriate patients, we confirmed MMR vaccination history with a telephone survey that resulted in 254 cases (58 percent). We found 224 MMR vaccinees (88 percent) and for 123 children (55 percent) could identify the vaccine date based on their vaccine record. For risk analysis, we included 67 children who had been vaccinated during the year previous to the onset of aseptic meningitis. Among these children, 38 were vaccinated in private clinics and 29 in public health centers (figure 1).

Almost none of the vaccination records included information about the strain used. However, in Korea, MMR vaccines have been distributed free of charge in public health centers and by payment in the private sector. In 1998, all public health centers used the MMR vaccine containing the Urabe or Hoshino strain because of their low price. Since private clinics or hospitals use any kind of vaccine without regard to cost, almost all private clinics used the MMR vaccines containing the Jeryl Lynn or Rubini strain because of concerns about the vaccine’s adverse events. Therefore, we classified our subjects into two groups; the first included the children vaccinated with the Urabe or Hoshino strain at public health centers, and the second included the children vaccinated with the Jeryl Lynn or Rubini strain at private clinics or hospitals.

Definition of aseptic meningitis

Aseptic meningitis is a syndrome characterized by acute onset of meningeal symptoms, fever, and cerebrospinal fluid pleocytosis with bacteriologically sterile cultures. The following criteria were used to define eligible cases of aseptic meningitis for the study: 1) Korean insurance claim cases based on the International Classification of Diseases, Tenth Revision (codes A87.9, G03.0, G03.9, and G02.0), and 2) cerebrospinal fluid pleocytosis (leukocytes ≥5) with bacteriologically sterile cultures (if measured) or 3) neck stiffness, and/or convulsions, or two other symptoms (headache or vomiting) in addition to a fever (≥38.0°C, if measured). Patients’ charts were reviewed and their symptoms, laboratory tests, and last diagnoses on the discharge record checked. If patients were diagnosed with aseptic meningitis and were hospitalized in a general hospital, in accordance with these criteria, those who had headache, fever, and vomiting could be included as subjects. Eight of 67 patients had relatively mild cases of disease; they had three to four symptoms including mild neck stiffness, convulsions, vomiting, headache, and fever. All cases of mild disease occurred during the control period. Among the mild cases, three were vaccinated with the Jeryl Lynn or Rubini strain, and five cases were vaccinated with the Urabe or Hoshino strain.

Onset date

We defined the date of disease onset by using the symptom onset date noted on the patient’s chart. If the symptom onset date was not mentioned on the chart, we used the date on which the patient visited the hospital as the disease onset date.

Confirmation of MMR vaccination history

We confirmed vaccination history by conducting a telephone survey. The interviewer asked whether the parents

possessed vaccination records; if so, the interviewer asked for the vaccination date and the place of vaccination. This telephone survey was carried out by a well-trained senior medical student. The parents who remembered that their child had had an MMR vaccination but did not have the vaccination record were excluded. For one child, the vaccination record did not include the vaccination date. In this instance, the date was confirmed by using the record from the public health center.

**Study design**

We used a case-crossover design, an analytic technique for assessing the brief change in risk associated with a transient exposure. According to this design, each person serves as his or her own control; confounding factors due to age, sex, vaccination age, vaccination place, and other fixed characteristics are thereby eliminated (20).

**Definition of time periods**

The time period observed was 1 year before the onset of aseptic meningitis; however, of this observed duration, we excluded the 6 months after birth because of the maternal immunoglobulin effect. A predefined 42-day hazard period before the onset of meningitis was compared with the previous days of the observed past-year period. This approach is analogous to that of a highly stratified retrospective cohort study. In this paradigm, within each stratum there is exactly one case event, and all person-time is contributed by a single person (23). The case events may have been either exposed or unexposed by an MMR vaccination during the 42-day period. Within each stratum, the amount of person-time considered a hazard period is 42 days, the maximum incubation period for the mumps virus. The control period can then be calculated by subtracting the hazard period in days from the number of observed days in a year.

**Statistical analysis**

Relative risks were estimated by using a method for sparse person-time data, the Mantel-Haenszel estimator of the rate ratio (20). Note that the Mantel-Haenszel estimator represents the association between the response and exposures after controlling for confounding variables. In our analysis, we formulated a $2 \times 2$ table for each study subject. By forming a table for each subject, we controlled for subject variability. Thus, our analysis was based on a matched fashion. All $p$ values were two tailed, and all relative risks were computed with 95 percent confidence intervals. All analyses were conducted by using the SAS (version 8.1) software program (SAS Institute, Inc., Cary, North Carolina).

**RESULTS**

In 1998, 677 children aged 8–36 months were admitted to general hospitals in Korea with a diagnosis of aseptic meningitis. Of these cases, 123 matched the study criteria for aseptic meningitis and the confirmed MMR vaccination date was available. We analyzed 67 children who received the
Aseptic Meningitis following MMR Vaccine

MMR vaccination during a 1-year period before onset of aseptic meningitis. Among these children, 38 received MMR vaccines with the Jeryl Lynn or Rubini strain and 29 received the Urabe or Hoshino strain. Between these two groups, no significant differences were found regarding gender, area, time of meningitis onset, or age at MMR vaccination. However, the mean age of the Jeryl Lynn or Rubini group was higher than that of the Urabe or Hoshino group (\(p < 0.01\)). There was a significant difference in the meningitis onset week after MMR vaccination between the two groups. Of the 29 children in the Urabe or Hoshino group, 13 contracted aseptic meningitis within 6 weeks, and six cases of the disease occurred the third week after MMR vaccination. In the 38 members of the Jeryl Lynn or Rubini group, only three contracted the disease within 6 weeks after vaccination (\(p < 0.01\)) (table 1).

Table 2 shows the relative risk of aseptic meningitis by the mumps strains and by other characteristics. The relative risk for aseptic meningitis associated with use of the Urabe or Hoshino strain was 5.5 (95 percent confidence interval (CI): 2.6, 11.8). Gender, area, time of meningitis onset, and MMR vaccination age were not significantly related to onset of aseptic meningitis. However, children less than age 18 months had an increased risk of aseptic meningitis (relative risk (RR) = 11.0, 95 percent CI: 4.0, 30.8) compared with children aged 18 months or older (table 2). The group that received the Jeryl Lynn or Rubini strain had no risk of aseptic meningitis (RR = 0.6, 95 percent CI: 0.18, 1.97). Gender, area, and time of meningitis onset were not significantly related to aseptic meningitis in this group either. The weekly relative risk for aseptic meningitis after MMR vaccination with the Urabe or Hoshino strain was higher at the third week (RR = 15.6, 95 percent CI: 5.9, 41.2) and was elevated until the end of the hazard period (figure 2).

**DISCUSSION**

The risk of aseptic meningitis associated with MMR vaccination with the Jeryl Lynn or Rubini strain was not significant (RR = 0.6) and had no relation to other character-
istics such as age, gender, and season of the year. However, with the Urabe or Hoshino strain, we found that the relative risk of aseptic meningitis within 6 weeks of vaccination was 5.5; at the third week after vaccination, the risk rose to 15.6. These results are similar to those from a study showing an increased risk in the 3-week period after a mass Brazilian vaccination (RR = 14.3, 95 percent CI: 7.9, 25.7) (12). However, the risk was lower than Farrington et al.’s reported risk of 38.1 (95 percent CI: 4.3, 336) 15–35 days after vaccination (11).

The attributable fraction among the exposed children within 6 weeks after vaccination containing the Urabe or Hoshino strain was 84.6 percent (95 percent CI: 54.6, 98.1), similar to the 86.5 percent found with the Brazilian mass vaccination (12). However, the attributable fraction was different according to the level of control. In the Brazilian mass vaccination, the attributable fraction by using the case-series method was 95 percent and was similar to the 97 percent found in the United Kingdom study that also used a case-series method (11).

To obtain a rough estimate of the incidence rate of aseptic meningitis among vaccinees, we applied our findings to 288 children—those whose addresses were unknown or those whose parents were unable to contact by telephone. As a result, we estimated an additional 23 cases of aseptic meningitis patients after receiving the Urabe or Hoshino strain. Among 441 aseptic meningitis cases, 34 could have contracted the disease as a result of vaccination with the Urabe or Hoshino strain (7.7 percent, 95 percent CI: 5.4, 10.6). In Korea, the birth cohort of 1997 was 720,000, the MMR vaccination rate was 90 percent, and the Urabe or Hoshino strain was used in about 50 percent of cases (3, 24). We conservatively estimate the risk of aseptic meningitis with the Urabe or Hoshino strain to be 1 in 10,500 doses (34 cases out of 0.324 million doses). This result was slightly higher than other results: 1/14,000 in Brazil (12) and 1/16,000 in the United Kingdom (11).

In this study, even though there was no biologic evidence such as vaccine strains in cerebrospinal fluid, we were able to identify the causal link between aseptic meningitis and the MMR vaccine by using the following criteria: 1) The Urabe or Hoshino strain was associated with a higher risk than the Jeryl Lynn or Rubini strain, as found in other studies; 2) the third week after vaccination was associated with the highest risk; and 3) the attributable fraction by using the case-series method was 95 percent and was similar to the 97 percent found in the United Kingdom study that also used a case-series method (11).

TABLE 2. Relative risk of aseptic meningitis onset following measles-mumps-rubella vaccination, by vaccine strains and other characteristics, Korea, 1998

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. receiving MMR vaccination during the 6 weeks before meningitis onset</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>p value†</th>
<th>No. receiving MMR vaccination during the 6 weeks before meningitis onset</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>17</td>
<td>11</td>
<td>11.0</td>
<td>4.0, 30.8</td>
<td>0.04</td>
<td>11</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>≥18</td>
<td>12</td>
<td>2</td>
<td>1.5</td>
<td>0.3, 7.0</td>
<td>27</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>10</td>
<td>6.7</td>
<td>2.7, 16.5</td>
<td>0.46</td>
<td>24</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>3</td>
<td>3.5</td>
<td>0.8, 14.9</td>
<td>14</td>
<td>2</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>12</td>
<td>5</td>
<td>5.5</td>
<td>1.7, 17.4</td>
<td>0.62</td>
<td>22</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Rural</td>
<td>17</td>
<td>8</td>
<td>6.8</td>
<td>2.6, 17.8</td>
<td>16</td>
<td>2</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Time of meningitis onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring (March–May)</td>
<td></td>
<td>3</td>
<td>1</td>
<td>3.7</td>
<td>0.3, 44.2</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Summer (June–August)</td>
<td></td>
<td>20</td>
<td>7</td>
<td>3.7</td>
<td>1.5, 9.5</td>
<td>28</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Autumn (September–November)</td>
<td></td>
<td>3</td>
<td>3</td>
<td>3.7</td>
<td>1.5, 9.5</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Winter (December–February)</td>
<td></td>
<td>3</td>
<td>2</td>
<td>11.0</td>
<td>0.96, 127.1</td>
<td>5</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>MMR vaccination age (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>2</td>
<td>1</td>
<td>4.0</td>
<td>0.3, 63.3</td>
<td>0.81</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥12</td>
<td>27</td>
<td>12</td>
<td>5.7</td>
<td>2.6, 12.5</td>
<td>33</td>
<td>3</td>
<td>0.7</td>
<td>0.22, 2.42</td>
</tr>
</tbody>
</table>

* MMR, measles-mumps-rubella.
† Test for homogeneity was used for two categories, test for trend when three or more categories were compared.
Aseptic Meningitis following MMR Vaccine

163


risk as biologic characteristics of the mumps virus; and 3) there were no differences in risk by gender, area, and age of vaccination within 3 years of age. One retrospective study suggested that the majority of cases of aseptic meningitis occurring within 1 month of measles-mumps vaccinations were caused by insufficiently attenuated mumps virus vaccines (25).

In our study, the mean age of children in the Jeryl Lynn or Rubini group (20.0 months; standard deviation, 4.7) was significantly higher than the 17.6 months (standard deviation, 6.3) of those in the Urabe or Hoshino group. However, between the two groups, no differences were found according to gender, area, time of meningitis onset, or age at vaccination. Older children are more susceptible to aseptic meningitis, and the usual age for MMR vaccination is 12–15 months. Therefore, the lower mean age of the Urabe or Hoshino group meant that the aseptic meningitis cases according to mumps vaccination were included more often in the Urabe or Hoshino group than in the Jeryl Lynn or Rubini group. Children aged 18 months or older had a lower risk than those in the younger age group, meaning that older children have an increased risk of aseptic meningitis from other viruses such as enteroviruses. Older children have a higher basic risk of aseptic meningitis, but the risk associated with the vaccine was not much higher than the basic risk. Similarly, during the epidemic period of the summer, the risk of contracting aseptic meningitis by vaccine was not much higher than the basic risk of meningitis from enteroviruses. During nonepidemic periods, when the risk of aseptic meningitis by enteroviruses is lower, the risk of meningitis by vaccine was much higher: 28 (95 percent CI: 3.2, 243.8). On the basis of our entire data analysis, as age increased, the incidence of aseptic meningitis increased until a child reached the age of 5 years. Therefore, underestimation of relative risk could have occurred in our analysis and could have falsely exonerated the Jeryl Lynn or Rubini strains.

However, in this study, the differences in incidence based on symptom criteria were not significant (less than age 12 months, 21.6; age 12–23 months, 26.0; and age 24–35 months, 27.0 per 100,000, respectively; \( p > 0.05 \)). In the laboratory-confirmed cases, the incidence in children less than age 12 months (11.2 per 100,000) was lower than that for children aged 2–3 years (20.1 and 23.1 per 100,000, respectively) because the physicians and the parents of patients preferred not to use the cerebrospinal fluid test in infants, but this test was performed more often in older children.

Grouping subjects by the Jeryl Lynn and the Rubini and by the Urabe and the Hoshino strains can be considered the weak point of this study. However, the incidence of meningitis was not significantly different between the Urabe and Hoshino strains in the Japanese data (14). Moreover, a World Health Organization position paper also mentioned that the Hoshino strain has immunogenic properties similar to those of the Urabe strain (8).

The case-crossover study design does not produce the bias caused by control selection, but bias by case selection can still remain (26, 27). In our study, the loss to follow-up and the exclusion of children not vaccinated may have introduced a bias. Since vaccination history was investigated in 2000–2001 although hospitalization occurred in 1998, many patients had moved to another place, and we could not find their new addresses or phone numbers. However, the probability that a subject was lost to follow-up was not related to aseptic meningitis or MMR vaccination. Thus, it did not cause any bias, although we may have lost some efficiency. In this study, the MMR vaccine coverage rate was high—about 98.8 percent (251/254)—so very few children were excluded because they had not been vaccinated. We excluded the cases from clinics and small-scale hospitals because we thought that the mild cases that did not require hospitalization would not be a barrier to vaccination. In Korea, the medical insurance coverage rate is very high; it is rare that severe cases are not hospitalized.

FIGURE 2. Relative risk (RR) of aseptic meningitis onset following measles-mumps-rubella (MMR) vaccination including the Urabe or Hoshino strain, Korea, 1998. Error bars, 95 percent confidence intervals.
Since the incidence of aseptic meningitis increases with age, older patients could be selected as cases in this study, but this influence may have decreased the relative risk. We included patients for whom vaccination records were available, but the incidence of records being kept decreased with increasing age of the child, which in turn increased the relative risk. However, in the t test for age in months between the group with available vaccination records and the group without the records, the differences were not statistically significant (p > 0.05). Therefore, the relative risk we found could have been underestimated. We used Cochran-Mantel-Haenszel statistics to test an association between MMR vaccination and aseptic meningitis, and we obtained the Mantel-Haenszel odds ratio estimator as a measure of association. In another study, we used Monte Carlo simulation studies to show the appropriateness of the case-crossover design in studying a vaccine’s adverse events (unpublished data).

In epidemiologic studies, the exposure measurement can be a potential source of bias. Since we used vaccination records that contained a definite history, and MMR vaccination occurs just once during infancy in children less than 3 years of age, this study did not have any potential bias related to exposure measurement. This factor is an advantage of our study in comparison with other retrospective studies.

In conclusion, by using the case-crossover design, we estimated the relative risk by vaccine strains, demographic factors, and other related factors, and results were comparable to those from other cohort or surveillance studies. Even though this study was retrospective and used only case data, it proved to be a very efficient method of study. An alternative study design in which only data on cases are used has been proposed for investigating acute adverse events (28) and assessing drug reactions (29). This method is similar in spirit to the case-crossover design and has been used in vaccine adverse event studies (11, 30, 31). When vaccination coverage is high or cohort study is difficult for rare events, this design can be a good solution for researching vaccine adverse events.

ACKNOWLEDGMENTS

The work for the first author was supported by the Korea Food and Drug Administration (KFDA-01-1-4). The work for the second author was supported (in part) by the Korea Science and Engineering Foundation (KOSEF) through the Statistical Research Center for Complex Systems at Seoul National University.

REFERENCES