Original Contribution

Risks of Convulsion and Aseptic Meningitis following Measles-Mumps-Rubella Vaccination in the United Kingdom

E. Miller¹, N. Andrews², J. Stowe³, A. Grant², P. Waight¹, and B. Taylor³

¹ Immunisation Department, Centre for Infections, Health Protection Agency, London, United Kingdom.
² Statistics Unit, Centre for Infections, Health Protection Agency, London, United Kingdom.
³ Centre for Community Child Health, Royal Free and University College Medical School, London, United Kingdom.

Received for publication February 15, 2006; accepted for publication July 28, 2006.

Measles-mumps-rubella (MMR) vaccines containing the Urabe strain of mumps were withdrawn in the United Kingdom in 1992 following demonstration of an increased risk of aseptic meningitis 15–35 days after vaccination. Following introduction of a replacement MMR vaccine (Priorix; GlaxoSmithKline, London, United Kingdom) in 1998, active surveillance of aseptic meningitis and convulsion was established to evaluate the risk associated with the new vaccine. No laboratory-confirmed cases of mumps meningitis were detected among children aged 12–23 months after administration of 1.6 million doses of Priorix (upper 95% confidence limit of risk: 1:437,000) in England and Wales. The upper 95% confidence limit excluded the risk found for mumps meningitis with Urabe vaccines (1:143,000 doses). No cases of aseptic meningitis were detected among children aged 12–23 months, who had received over 99,000 doses of Priorix (upper 95% confidence limit of risk: 1:27,000), in a regional database of hospital-admitted cases. This compares with an observed risk of 1:12,400 for Urabe vaccines. An elevated relative incidence of convulsion was found in the 6- to 11-day period after receipt of Priorix (relative incidence = 6.26, 95% confidence interval: 3.85, 10.18)—consistent with the known effects of the measles component of MMR vaccine—but not in the 15- to 35-day period (relative incidence = 1.48, 95% confidence interval: 0.88, 2.50) as occurred with Urabe-containing vaccines. This study demonstrates the power of active postmarketing surveillance to identify or exclude events too rare to be detected in prelicensure trials.

adverse drug reaction reporting systems; measles-mumps-rubella vaccine; meningitis, aseptic; seizures; vaccines

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases; MCC, meningococcal serogroup C conjugate; MMR, measles-mumps-rubella; RI, relative incidence.

In October 1988, the United Kingdom introduced measles-mumps-rubella (MMR) vaccines for routine immunization of children in their second year of life. At the time these MMR vaccines were introduced, Canadian investigators had reported that the Urabe mumps strain contained in two of the three available vaccines was temporally associated with aseptic meningitis in approximately 1 in 100,000 vaccinees (1). However, it was unclear at the time whether the association was causal and, if so, what the true attributable risk was and whether the adverse effect was exclusively related to vaccines containing the Urabe strain. Enhanced postlicensure surveillance was established in the United Kingdom using the British Paediatric Surveillance Unit scheme, whereby each month pediatricians are sent a card listing a set of defined conditions to be reported, to which meningoccal meningitis after MMR vaccination was added (2). This surveillance found a risk of 1 per 250,000, but within the reports there was a cluster of Urabe-associated cases from
the Nottingham area which gave a substantially greater risk (3). Subsequent epidemiologic studies using laboratory- and hospital-identified cases of aseptic meningitis linked to MMR vaccination records established that the true risk of MMR-associated aseptic meningitis was substantially higher than previously thought (~1 in 10,000–15,000 doses) and was exclusively related to the Urabe mumps strain in the vaccine (4–6). Furthermore, there was an increased risk of hospital admission for febrile convulsion 15–35 days after receipt of a Urabe-containing MMR vaccine (an attributable risk of approximately 1 in 1,500 doses), indicating that the real risk of acute neurologic consequences from the Urabe mumps component of MMR was underestimated when using case ascertainment methods that were reliant on laboratory investigations (5). The time period of increased risk of convolution associated with the Urabe mumps component is later than the 6- to 11-day period in which febrile convolution is attributed to the measles component (7).

Following the withdrawal of Urabe-containing mumps vaccines from use in the United Kingdom in September 1992, the only MMR vaccine used until May 1998 was MMRII, from Sanofi Pasteur (Lyon, France). This vaccine contained the Jeryl Lynn mumps component, which had shown no evidence of an association with either aseptic meningitis or febrile convolution in the 15- to 35-day post-vaccination period (5, 6, 8). Subsequent reports from other countries showed that aseptic meningitis was associated with all mumps vaccine strains except the Jeryl Lynn strain (9, 10). Interestingly, unlike other mumps vaccine viruses strains, the Jeryl Lynn vaccine strain is a mixture of two distinct isolates with heterology in the hydrophobic protein gene (11).

In May 1998, GlaxoSmithKline (London, United Kingdom) developed a replacement MMR vaccine, Priorix, in which the mumps vaccine component (RIT 4385) was derived from one of the two isolates comprising the Jeryl Lynn vaccine. Although it was thought that the origin of the mumps strain in Priorix made it unlikely that it would cause aseptic meningitis, it was possible that the existence of two separate strains in the Jeryl Lynn vaccine was somehow responsible for its lack of pathogenicity (12). The limited size of the pre-licensure trials with Priorix (~7,000 children) meant that a risk of the magnitude of that seen with the Urabe strain could not be excluded. Therefore, enhanced postlicensure surveillance of aseptic meningitis and convolution in the 15- to 35-day period after vaccination with Priorix, using hospital- and laboratory-based methods, was established in the United Kingdom following the launch of the new vaccine in May 1998.

MATERIALS AND METHODS

Aseptic meningitis

Computerized hospital records for children aged 12–23 months with an International Classification of Diseases, Ninth Revision (ICD-9), discharge diagnosis of meningitis categorized as mumps, aseptic or viral (072.1, 047, 321), were identified for the period January 1, 1991–September 30, 1992, prior to the withdrawal of Urabe-containing MMR vaccines, and were linked with MMR vaccination histories as in the earlier study by Farrington et al. (5). These notes were not reviewed, since cases in this analysis had ICD-9 codes that were specific for aseptic meningitis and had been validated in the earlier study (5). Batch numbers were not sought for these cases because Urabe-containing vaccines had comprised approximately 90 percent of the MMR vaccine used at the time. This analysis was used to compare the estimated risk of hospital admission for aseptic meningitis following Urabe mumps vaccine in the study regions with the estimates generated from the earlier studies (4, 5).

Cases of laboratory-confirmed mumps meningitis were also ascertained from reports made to the Centre for Infections from laboratories in England and Wales for the period from October 1992 to the end of June 2004.

Convulsions

Children aged 12–23 months with a discharge diagnosis of febrile convolution (ICD-10 code R560 or R568, febrile convolution or fit, not otherwise specified) who were admitted between January 1, 1998, and June 30, 2002, were identified and linked with computerized immunization records to obtain dates of MMR vaccination. Where available, batch number information was used to identify whether the MMR vaccine was MMRII or Priorix. Only those children linked with one MMR dose when aged 12–23 months were retained for the analysis; information on concomitant meningococcal serogroup C conjugate (MCC) vaccination was also extracted. Case note review was not conducted for these children because of their large numbers and because the earlier study using the ICD-9 codes had indicated a high degree of specificity (5).
MMR vaccine exposure by manufacturer

The numbers of doses of Priorix and MMRII given to children aged 1–2 years in England and Wales and in the two regions during the entire study period (1998–2004) were estimated from MMR vaccine coverage rates and the proportions of the total MMR doses distributed nationally and in the two regions by manufacturer (United Kingdom Department of Health, unpublished data, 2006).

Statistical methods

For aseptic meningitis, the absolute risk in the 15–35 days after MMR vaccination during the period May 1998–June 2001 was estimated, along with a 95 percent confidence interval. By means of Fisher’s exact test, this risk was compared with that estimated for the period from January 1991 to the end of September 1992, when Urabe-containing MMR vaccines were predominantly given.

For convulsions, relative incidence was estimated using the self-controlled case-series method (5) and cases identified using ICD-10 code R560 or R568. The risk periods investigated were 6–11 days postvaccination and 15–35 days postvaccination. A prevaccination period of 2 weeks was removed from the background risk by treating it as a separate risk period to allow for delayed vaccination due to convulsion. Age was controlled for in the analysis using 12 1-month age groups. Repeat convulsion episodes within individuals were regarded as new episodes if they occurred at least 10 days apart. This interval was chosen on the basis of the distribution of gaps between episodes, which showed a sharp decline within the first 5 days and maintained a constant level thereafter. Where an increased relative incidence was identified, the vaccine-attributable risk was calculated on the basis of the background risk of convulsion in the second year of life and the vaccine-attributable fraction. The relative incidence of convulsion was estimated overall as well as by vaccine manufacturer and by whether or not MCC vaccine was given concurrently. The relative incidence was also estimated using the more specific case definition of febrile convulsion (ICD-10 code R560) in the first diagnostic field.

RESULTS

Aseptic meningitis

Case notes were available for review for 41 of the 45 hospital admissions occurring during the period May 1998–June 2001 with ICD-10 discharge diagnoses of viral meningitis, mumps, meningitis in other infections classified elsewhere, and meningitis due to other and unspecified causes. After review, seven cases were confirmed as aseptic meningitis, 22 as bacterial meningitis, one as chemical meningitis, and one as meningitis, unspecified; the remaining 10 admissions were found not to be for meningitis. Of the seven case children with aseptic meningitis, four had not received any MMR vaccine before admission and three were admitted with aseptic meningitis 47, 140, and 153 days after MMR vaccination. Thus, no cases of aseptic meningitis

<table>
<thead>
<tr>
<th>Case definition</th>
<th>Urabe population</th>
<th>Priorix population</th>
<th>Absolute risk</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic meningitis</td>
<td>January 1991–September 1992, North and South Thames regions, England</td>
<td>Priorix cases</td>
<td>0</td>
<td>99,177</td>
<td>1:27,000</td>
</tr>
<tr>
<td>Laboratory-confirmed mumps-positive cerebrospinal fluid</td>
<td>October 1988–September 1992, England and Wales</td>
<td>Urabe cases</td>
<td>16</td>
<td>2,280,000</td>
<td>1:143,000</td>
</tr>
</tbody>
</table>

* Data were obtained from the paper by Farrington et al. (5).
were found within 15–35 days of MMR vaccination during the study period. The number of doses of Priorix MMR vaccine given to children aged 12–23 months was estimated as 99,177 on the basis of the size of the birth cohort, vaccine coverage, and the percentage of nationally distributed doses of MMR vaccine that contained the Urabe strain (table 1).

During the period January 1991–September 1992, prior to the withdrawal of Urabe-containing MMR vaccines, six cases of aseptic meningitis were identified from the computerized hospital records; four of these children had received MMR vaccine within 15–35 days before onset. The relative incidence for this risk period was 25.9 (95 percent confidence interval (CI): 2.8, 233), and the absolute risk for Urabe-containing vaccines (based, as before, on birth cohort, vaccine coverage, and percentage of Urabe vaccine doses distributed) was estimated as 1 in 12,400 doses (table 1).

Six cases of laboratory-confirmed mumps meningitis were reported to the Centre for Infections from laboratories in England and Wales between October 1992 and June 2004 (age range, 5–26 years). The 5-year-old patient (the only case in an age group targeted for routine MMR vaccination) had not received any MMR vaccine because of parental refusal. The estimated number of doses of Priorix given to children aged 12–23 months during the period was 1,612,360. The percentage of nationally distributed doses of MMR vaccine that contained the Urabe strain (table 1).

Of the 66 convulsions occurring in the 6- to 11-day period (table 2), the number attributable to vaccination based on the relative incidence was estimated as 50 (66 × 3.09/4.09 = 50). Therefore, the vaccine-attributable fraction of all convulsions occurring in the second year of life was 5.1 percent (50/988). In the national Hospital Episode Statistics data set, 1.7 percent of children in England had an admission for convulsion in the second year of life; therefore, the attributable risk per dose was estimated as 0.00087 (0.017 × 0.051 = 0.00087) or 1 in 1,150 doses.

The relative incidence in the 2-week prevaccine period was below 1, as expected. The 3- to 6-week prevaccination period was also examined but did not show a reduced relative incidence (relative incidence (RI) = 1.01), so this period was included in the background.

Stratification by manufacturer suggested a higher relative incidence in the 6- to 11-day period for Priorix (RI = 6.26) than for MMRII (RI = 3.64), though this difference was not significant (p = 0.11). There was no difference in relative incidence between manufacturers in the 15- to 35-day period (table 2). Among children who had received MCC vaccine at the same time as MMR vaccine, the relative incidence of having an admission for convulsion in the 6- to 11-day period after vaccination was higher (RI = 7.74, 95 percent CI: 3.82, 15.71) than that for children not receiving the vaccines at the same time (RI = 3.81, 95 percent CI: 2.87, 5.05). This difference was not statistically significant (p = 0.08).

### TABLE 2. Relative incidence of hospital admission for convulsion within defined risk periods before and after measles-mumps-rubella (MMR) vaccine in children aged 12–23 months, according to type of MMR vaccine received, England and Wales, 1998–2002

<table>
<thead>
<tr>
<th>Type of MMR vaccine</th>
<th>No. of days before or after MMR vaccination</th>
<th>No. of admissions</th>
<th>RI*</th>
<th>95% CI*</th>
<th>No. of admissions</th>
<th>RI</th>
<th>95% CI</th>
<th>No. of admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td>0.38</td>
<td>0.22, 0.64</td>
<td>13</td>
<td>4.09</td>
<td>3.14, 5.33</td>
<td>66</td>
</tr>
<tr>
<td>Priorix</td>
<td></td>
<td></td>
<td>0.47</td>
<td>0.15, 1.40</td>
<td>3</td>
<td>6.26</td>
<td>3.85, 10.18</td>
<td>19</td>
</tr>
<tr>
<td>MMRII</td>
<td></td>
<td></td>
<td>0.39</td>
<td>0.18, 0.84</td>
<td>6</td>
<td>3.64</td>
<td>2.44, 5.44</td>
<td>27</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td>0.32</td>
<td>0.13, 0.81</td>
<td>4</td>
<td>3.53</td>
<td>2.23, 5.61</td>
<td>20</td>
</tr>
</tbody>
</table>

* RI, relative incidence; CI, confidence interval.
† Number of admissions in that risk period.
Analysis using a more specific diagnosis definition was carried out using ICD-10 code R560 (febrile convulsion) only in the first diagnosis field. There were 52 cases in the 6- to 11-day period, with the relative incidence increasing slightly to 4.27 (95 percent CI: 3.17, 5.76). In the 15- to 35-day period, there were 57 cases, and the relative incidence increased to 1.33 (95 percent CI: 1.00, 1.77), a borderline-significantly raised relative incidence.

**DISCUSSION**

This study confirms that the risk of aseptic meningitis with Priorix vaccine, if it exists at all, is significantly lower than that with Urabe-containing mumps vaccine. The study allowed the exclusion of risks as rare as 1 in 437,000 for laboratory-confirmed mumps meningitis with non-Urabe-containing MMR vaccines. This demonstrates the power of postlicensure surveillance methods based on active ascertainment of cases linked with independently collected vaccination records. Postlicensure surveillance that relies on passively reported cases that are temporally associated with vaccination is necessarily incomplete and is unsuitable for epidemiologic analysis.

Estimates obtained using record linkage methods are robust, as demonstrated by the similarity between the relative incidence estimate for aseptic meningitis admission 15–35 days postvaccination in our two study regions prior to withdrawal of Urabe-containing MMR vaccines (RI = 25.9, 95 percent CI: 2.8, 233) and the estimate obtained using similar case ascertainment and record linkage methods in five districts in England (RI = 38.1, 95 percent CI: 4.3, 336) in the earlier study (5).

The attributable risk of hospital admission for convulsion following receipt of any MMR vaccine was estimated as 1 in 1,150 doses for the 6- to 11-day postvaccination period, based on an estimated relative incidence of 4.09. The excess risk of convulsion in this period was attributable to the measles component of MMR vaccine (7) and was similar to that reported in other record linkage studies of MMR vaccines in the United Kingdom (5) and the United States (8) and in a large prospective cohort study in the United Kingdom (14). The last absolute risk estimate was close to that found for single-antigen measles vaccine using similar follow-up methods in United Kingdom children (7).

The relative incidence of convulsion in the 6- to 11-day period was higher for Priorix than for MMRII, although the difference was not significant. Furthermore, the “unknown manufacturer” group, which contained a mixture of Priorix and MMRII vaccines, had a relative incidence estimate similar to that for MMRII vaccine, suggesting that a large difference between manufacturers is unlikely. The measles vaccine virus is the Schwarz strain in Priorix and the Edmonston-Enders strain in MMRII, both of which are derived from the Edmonston strain, so major differences in pathogenicity seem unlikely. Furthermore, no differences between these strains were found in the propensity to cause convulsion when given as single-antigen measles vaccine (7).

There was some evidence that children given MCC vaccine at the same time as MMR vaccine may have a somewhat higher risk of convulsion in the 6- to 11-day postvaccination period (RI = 7.74, 95 percent CI: 3.82, 15.71) than children who receive MMR but not MCC vaccine at the same time (RI = 3.81, 95 percent CI: 2.87, 5.05), though this finding was not statistically significant. Given the expected time course of reactions to MCC vaccine (maximal within the first 3 days) (15), any causal association seems unlikely. However, further studies of the risk of convulsion after MCC vaccine are in progress using record linkage methods.

The analysis of convulsion in the 15- to 35-day period based on children discharged with a diagnosis of febrile or unspecified convulsion in any diagnosis field showed no evidence of an increased risk after receipt of non-Urabe MMR vaccine. The relative incidence estimate for this period in our study (RI = 1.13, 95 percent CI: 0.87, 1.48) was comparable to that reported in earlier studies using a similar case definition and analytical method in children who were eligible only to receive MMRII vaccine (RI = 1.08, 95 percent CI: 0.85, 1.38) (16) and in earlier cohorts of children who received MMRII vaccine when Urabe-containing MMR vaccines were also available (RI = 1.04, 95 percent CI: 0.56, 1.93) (5). Again the similarity of the relative incidence estimates from these three studies provides evidence of the robustness of the record linkage and statistical methods we employed.

In conclusion, our active surveillance study using record linkage and the self-controlled case-series analysis method has shown no evidence to suggest that the new MMR vaccine used in the United Kingdom since mid-1998 and derived from the Jeryl Lynn-containing MMR vaccine causes aseptic meningitis attributable to its mumps component.

**ACKNOWLEDGMENTS**

The authors thank GlaxoSmithKline (London, United Kingdom) for financial assistance in purchasing some of the data downloads for this study.

Conflict of interest: none declared.

**REFERENCES**