Measles-Containing Vaccines and Febrile Seizures in Children Age 4 to 6 Years

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KEY WORDS
measles, varicella, seizures, vaccine, fever

ABBREVIATIONS
ACIP—Advisory Committee on Immunization Practices
CDC—Centers for Disease Control and Prevention
CI—confidence interval
ICD-9—The International Classification of Diseases, 9th Revision
KP—Kaiser Permanente
MMR—measles-mumps-rubella vaccine
MMRV—measles-mumps-rubella-varicella vaccine
ROA—rapid cycle analysis
RR—relative risk
V—varicella vaccine
VSD—Vaccine Safety Datalink

Dr Klein led the design of the study, oversaw the data collection, interpreted the data, and was the lead author of the manuscript; Mr Lewis collected the data and together with Mr Fireman conducted the analysis; Mr Fireman also contributed to study design and contributed to critical revision of the manuscript for important intellectual content; Dr Baxter assisted with the study design and contributed to its critical revision for important intellectual content; Dr Weintraub assisted with study design and contributed to the critical revision of the manuscript for important intellectual content; and Drs Glanz, Naleway, Jackson, Lieu, and Belongia contributed to data collection and made critical revisions of the manuscript for important intellectual content.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-3198
doi:10.1542/peds.2011-3198
Accepted for publication Jan 10, 2012
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The combination measles-mumps-rubella-varicella (MMRV) vaccine was licensed by the US Food and Drug Administration in 2005. MMRV was subsequently recommended by the Advisory Committee on Immunization Practices (ACIP) in 2006, with recommended doses at 1 to 2 years and 4 to 6 years of age, at which time the ACIP stated a preference for its use over separate measles-mumps-rubella vaccine (MMR) and varicella vaccine (V) administrations. After the licensure of the MMRV and ACIP recommendation, the US Centers for Disease Control and Prevention (CDC) conducted near real-time surveillance for prespecified safety outcomes after MMRV by using diagnostic code data of the Vaccine Safety Datalink (VSD) in a rapid cycle analysis (RCA). At the time, VSD consisted of managed care organizations sharing data on ~9 million members annually. In 2008, MMRV RCA safety monitoring detected a possible increased risk for seizures after receipt of MMRV. Subsequent studies confirmed that among toddlers 12 to 23 months old, ages when the risk for febrile seizure peaks, measles-containing vaccines were associated with elevated risk of fever and febrile seizure and MMRV was associated with an ∼2-fold increased risk of fever and febrile seizures occurring 7 to 10 days after MMRV compared with separately administered MMR + V. One additional febrile seizure occurred for every 2300 doses of MMRV administered instead of separate MMR + V in 1-year-old children. This finding led to the CDC’s 2010 recommendation that while either MMRV or MMR + V may be administered to 1- to 2-year-olds receiving their first doses, families without a strong preference for MMRV should receive MMR + V. MMR administered as a second dose to 4- to 6-year-old children has not been reported to have an association with an increased risk for febrile seizures. Whether either MMRV or MMR + V is associated with an increased risk for febrile seizures among children aged 4 to 6 years has not been previously investigated. The aim of this study was to assess the risk for febrile seizures after MMRV and MMR + V administration among children aged 4 to 6 years, ages when the risk for febrile seizure is much lower than that for toddlers.

METHODS

Study Population

This was a cohort study in which children aged 48 to 83 months who were members of the 7 participating VSD sites between January 2000 through October 2008 and who received MMRV (Merck & Co), separately administered, same-day MMR (Merck & Co, Inc, West Point, PA) + Va (Merck & Co), or MMR or V administered alone were eligible for study inclusion. We defined a postvaccination seizure event as the first instance during the 42 days after a measles- or varicella-containing vaccine of The International Classification of Diseases, 9th Revision (ICD-9) codes 345* (epilepsy) or 780.3* (convulsion) in the emergency department or hospital. We identified postvaccination medically attended outpatient fever events by using ICD-9 code 780.6 (fever and other physiologic disturbances of temperature regulation) as previously described. We included all years 2000–2008 for seizure events because seizures were rare in this age group. However, we limited investigations of outpatient fever visits to the years 2006–2008 to minimize the potential impact of changes in outpatient coding practices over time and because those were the years during which both MMRV and MMR + V were available. For both seizure and fever outcomes, we included events during the 42 days postvaccination to be consistent with earlier studies. Only postvaccination events that occurred >42 days after a previous seizure or fever event, respectively, were included.

Participating VSD sites were Group Health Cooperative (Washington State), Kaiser Permanente (KP) Colorado, KP Northwest (Oregon), Harvard Vanguard Medical Associates and Harvard Pilgrim Health Care (Massachusetts), HealthPartners (Minnesota), Northern California KP, and Marshfield Clinic (Wisconsin). This study was approved by the institutional review boards of all participating sites.

Medical Record Review

Because our previous study among 12- to 23-month-olds found increased risk of febrile seizures 7 to 10 days after MMR or MMRV, the primary analyses in the current study focused on febrile seizures occurring during the 7- to 10-day postvaccination risk period. We therefore reviewed the electronic medical record of seizures occurring 7 to 10 days after vaccination with MMRV or MMR + V to assess whether the seizures were febrile seizures. We accepted as a case a physician diagnosis of febrile seizure.

Statistical Methods

Our primary analysis examined risk of febrile seizures during the 7- to 10-day postvaccination period. To allow comparisons with the previous analysis among 12- to 23-month-olds, we also assessed rates of seizures (electronically identified) and outpatient fever visits during postvaccination days 0 to 42. We estimated the incidence of confirmed febrile seizures per 100 000 doses during 7 to 10 days after MMRV administration and used the 95% Poisson confidence interval for the observed count of confirmed febrile seizures to calculate a confidence interval for febrile seizure incidence. We compared the postvaccination fever rates by using Poisson regressions with adjustment for vaccine exposure, VSD site, age, year, and influenza season as previously defined.
This study had 80% power to detect a relative risk (RR) of 8.5 (2-sided \( \alpha = 0.05 \)) for MMRV versus MMR + V during the 7- to 10-day risk interval. For adequate power to detect an RR of 2, we would need a much larger study population (ie, 1.2 million doses per group) because the background rate of febrile seizures is very low in this age group. However, the low background rate implies that we would have good power to detect a substantial absolute risk of febrile seizures after measles-containing vaccines. For the study population available, post hoc calculations indicated that if the true background rate of febrile seizure in this age group was really as low as 1 per 1,100 person years, then we had 80% power to rule out an absolute risk equal to or higher than 1 per 15,570 doses of MMRV. We used SAS version 9.1 (SAS Institute, Cary, NC) for all analyses.

RESULTS

The study population included 86,750 children aged 4 to 6 years inclusive who were vaccinated with MMRV between January 2006 and October 2008 and 67,438 vaccinated with MMR + V between January 2000 and October 2008. In addition, from January 2000 to October 2008, 479,311 children received MMR alone and 80,985 received V vaccine alone.

Overall, there were very few seizures identified by ICD-9 codes in the electronic data after measles-containing vaccines (Table 1) and no seizure peak during postvaccination days 7 to 10 or 0 to 42 was evident (Fig 1). Based on the codes in the electronic data, incidence of electronically identified seizures 7 to 10 days after MMRV, MMR + V or MMR alone did not differ significantly from each other, although rates were higher after MMRV (Table 1).

Outpatient fever visits are shown graphically in Fig 2. No peak in fever visits during days 7 to 10 after MMRV, MMR, or V alone was apparent. Outpatient fever visits 7 to 10 days were not significantly higher after MMR + V than after MMR alone, although there was a trend in that direction (\( P = 0.09 \); Table 2).

Electronic medical record review of the 4 post-MMRV seizures during days 7 to 10 revealed that 2 individuals were diagnosed with afebrile seizures and 1 record was considered improbable as it was unclear as to whether fever or an

| TABLE 1 | All Seizures After Measles-Containing Vaccines Identified From Electronic Records for 4- to 6-Year-Olds: 2000–2008 |
|-----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Post-Vaccination Days | MMRV, N = 86,750 Doses | MMR + Varicella, N = 67,438 Doses | MMR, N = 479,311 Doses | Varicella, N = 80,985 Doses |
| Rate/10,000 Doses (Number Events) | Rate/10,000 PY (95% CI) | Rate/10,000 Doses (Number Events) | Rate/10,000 PY (95% CI) | Rate/10,000 Doses (Number Events) | Rate/10,000 PY (95% CI) |
| 7–10 | 0.5 (4) | 42.1 (11.5–107.8) | 0 (0) | 0 (0–49.9) | 0.2 (9) | 17.1 (7.8–32.5) | 0 (0) | 0 (0–41.6) |
| 0–42 | 2.2 (19) | 18.8 (11.3–29.4) | 1.5 (10) | 12.7 (6.1–23.4) | 2.1 (99) | 17.8 (14.4–21.6) | 0.7 (6) | 6.4 (2.3–13.9) |

FIGURE 1

Postvaccination seizures among 4- to 6-year-olds by vaccine received, VSD study population 2000–2008.
acute seizure had occurred. Thus, only 1 febrile seizure diagnosis was confirmed, and the absolute risk for febrile seizure 7 to 10 days after MMRV was 1 febrile seizure for 86 750 doses (95% confidence interval [CI], 1 per 3 426 441, 1 per 15 570) or 1.2 febrile seizures per 100 000 doses of MMRV (Table 3). The upper limit of the 95% CI indicates that we can rule out other risk 7 to 10 days after MMRV is no higher than 1 febrile seizure for approximately every 15 500 doses of MMRV (Table 3). The upper limit of the 95% CI indicates that we can rule out that the risk 7 to 10 days after MMRV is no higher than 1 febrile seizure for approximately every 15 500 doses. Similarly, we can rule out that the risk for febrile seizures 7 to 10 days after MMR + V is no higher than 1 febrile seizure per 18 282 doses of same-day, separately administered MMR + V.

## DISCUSSION

Based on >86 000 doses of MMRV administered to 4- to 6-year-olds, we found no evidence of an elevated febrile seizure risk during the 6 weeks post vaccination. We examined absolute risk for febrile seizures 7 to 10 days after MMRV and MMR + V and our results demonstrate that among 4- to 6-year-olds, we can rule out an absolute risk of >1 febrile seizure per 15 500 doses of MMRV, even if we assume that all the risk for febrile seizures during days 7 to 10 after MMRV was due entirely to the vaccine. For the 7 to 10 days after vaccination, we can similarly rule out an absolute risk greater than 1 febrile seizure per 18 000 doses of MMR + V.

### TABLE 3  Confirmed Febrile Seizures 7–10 Days after Vaccination Among 4- to 6-Year-Olds: 2000–2008

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Confirmed Febrile Seizures Post-Vaccination Days 7–10</th>
<th>Per Total Doses (95% CI)</th>
<th>Per 100 000 Doses (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRV</td>
<td>1 per 86 750 (1 per 3 426 441, 1 per 15 570)</td>
<td>1.2 (0.03, 6.4)</td>
<td></td>
</tr>
<tr>
<td>MMR + Varicella</td>
<td>0 per 67 438 (0, 1 per 18 282)</td>
<td>0 (0, 5.5)</td>
<td></td>
</tr>
</tbody>
</table>

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**FIGURE 2**

Postvaccination outpatient fever visits among 4- to 6-year-olds by vaccine received, VSD study population 2006–2008.

**TABLE 2**  Outpatient Fever Visits Following Measles-Containing Vaccines Identified from Electronic Records Among 4- to 6-Year-Olds: 2006–2008

<table>
<thead>
<tr>
<th>Post-</th>
<th>MMRV, N=86 570 Doses</th>
<th>MMR + Varicella, N=39 536 Doses</th>
<th>MMR, N= 59 538 Doses</th>
<th>Varicella, N= 57 366 Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination, d</td>
<td>Rate/10 000 Doses (Number Events)</td>
<td>Adjusted Rate/100 PY (95% CI)</td>
<td>Rate/10 000 Doses (Number Events)</td>
<td>Adjusted Rate/100 PY (95% CI)</td>
</tr>
<tr>
<td>7–10</td>
<td>5.7 (49) 5.2 (3.9–6.8)</td>
<td>9.6 (38) 8.8 (6.2–12)</td>
<td>4.9 (29) 4.4 (3–6.4)</td>
<td>6.3 (36) 5.7 (4–7.9)</td>
</tr>
<tr>
<td>0–42</td>
<td>57.9 (501) 5 (4.5–5.4)</td>
<td>74.9 (296) 6.4 (5.7–7.2)</td>
<td>80 (357) 5.2 (4.6–5.7)</td>
<td>51.2 (294) 4.4 (3.9–4.8)</td>
</tr>
</tbody>
</table>

* None of the 7–10 d pairwise rate/PY comparisons were statistically significant. \( P = .09 \) for rates/PY of fever visits 7–10 d MMR + V compared with MMR alone, adjusted for vaccine exposure, age, site, year, influenza season.

b None of the comparisons between day 0–42 fever visits were statistically significant.
of MMR + V. Due to the small number of seizure events during days 0 to 42 and 7 to 10 (~1/10th as high than that seen in 12- to 23-month-olds), our analyses had limited power to assess the relative risk of seizures after MMRV when compared with seizures after MMR + V. This study did have adequate power, however, to rule out a substantial absolute risk for febrile seizures after MMRV and MMR + V. To our knowledge, this is the first study to evaluate the risk of febrile seizures after MMRV or MMR + V among 4- to 6-year-old children. These results provide reassuring evidence that neither MMRV nor MMR + V appears to be associated with an increased risk of postvaccination febrile seizures in this age group.

A limited number of studies have evaluated the risk of febrile seizures after MMR alone in 4- to 6-year-olds. None have specifically evaluated for the risk of febrile seizures during the 7- to 10-day postvaccination risk interval. Davis et al. observed that postvaccination day postvaccination risk interval. Davis et al.9 observed that postvaccination day postvaccination risk interval. Davis et al.9 observed that postvaccination day postvaccination risk interval. Davis et al.9 observed that postvaccination day postvaccination risk interval. Davis et al.9 observed that postvaccination day postvaccination risk interval. Davis et al.9 observed that postvaccination day postvaccination risk interval. Davis et al.9 observed that postvaccination day postvaccination risk interval. Davis et al.9 observed that postvaccination day postvaccination risk interval. Davis et al.9 observed that postvaccination day postvaccination risk interval. 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