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Nicola P. Klein, Edwin Lewis, Roger Baxter, Eric Weintraub, Jason Glanz, Allison Naleway, Lisa A. Jackson, James Nordin, Tracy Lieu, Edward A. Belongia and Bruce Fireman

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# 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  
 RCA—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; Mr 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.

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**WHAT'S KNOWN ON THIS SUBJECT:** Febrile seizure risk 7 to 10 days after measles-mumps-rubella-varicella (MMRV) is double that of separate measles-mumps-rubella (MMR) and varicella vaccines among 1-year-olds. Whether MMRV or MMR and varicella affect febrile seizure risk among 4- to 6-year-olds has not been reported.



**WHAT THIS STUDY ADDS:** Using Vaccine Safety Datalink data, we examined risk for febrile seizures after measles-containing vaccines. This study provides reassurance that MMRV and separately administered MMR and varicella were not associated with increased risk of febrile seizures among 4- to 6-year-olds.

## abstract

FREE

**BACKGROUND:** In the United States, children receive 2 doses of measles-mumps-rubella vaccine (MMR) and varicella vaccine (V), the first between ages 1 to 2 years and the second between ages 4 to 6 years. Among 1- to 2-year-olds, the risk of febrile seizures 7 to 10 days after MMRV is double that after separate MMR + V. Whether MMRV or MMR + V affects risk for febrile seizure risk among 4- to 6-year-olds has not been reported.

**METHODS:** Among 4- to 6-year-old Vaccine Safety Datalink members, we identified seizures in the emergency department and hospital from 2000 to 2008 and outpatient visits for fever from 2006 to 2008 during days 7 to 10 and 0 to 42 after MMRV and MMR + V. Incorporating medical record reviews, we assessed seizure risk after MMRV and MMR + V.

**RESULTS:** From 2006 through 2008, 86 750 children received MMRV; from 2000 through 2008, 67 438 received same-day MMR + V. Seizures were rare throughout days 0 to 42 without peaking during days 7 to 10. There was 1 febrile seizure 7 to 10 days after MMRV and 0 after MMR + V. Febrile seizure risk was 1 per 86 750 MMRV doses (95% confidence interval, 1 per 3 426 441, 1 per 15 570) and 0 per 67 438 MMR + V doses (1 per 18 282).

**CONCLUSIONS:** This study provides reassurance that MMRV and MMR + V were not associated with increased risk of febrile seizures among 4- to 6-year-olds. We can rule out with 95% confidence a risk greater than 1 febrile seizure per 15 500 MMRV doses and 1 per 18 000 MMR + V doses. *Pediatrics* 2012;129:809–814

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).<sup>1–3</sup> 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.<sup>4</sup> Subsequent studies confirmed that among toddlers 12 to 23 months old, ages when the risk for febrile seizure peaks,<sup>5</sup> 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.<sup>6,7</sup> One additional febrile seizure occurred for every 2300 doses of MMRV administered instead of separate MMR + V in 1-year-old children.<sup>6</sup> 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.<sup>8</sup>

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.<sup>9</sup> 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.<sup>6</sup> 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.<sup>6,10</sup> 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,<sup>6</sup> 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,<sup>6</sup> 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.<sup>6</sup>

This study had 80% power to detect a relative risk (RR) of 8.5 (2-sided  $\alpha = .05$ ) 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 1100 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

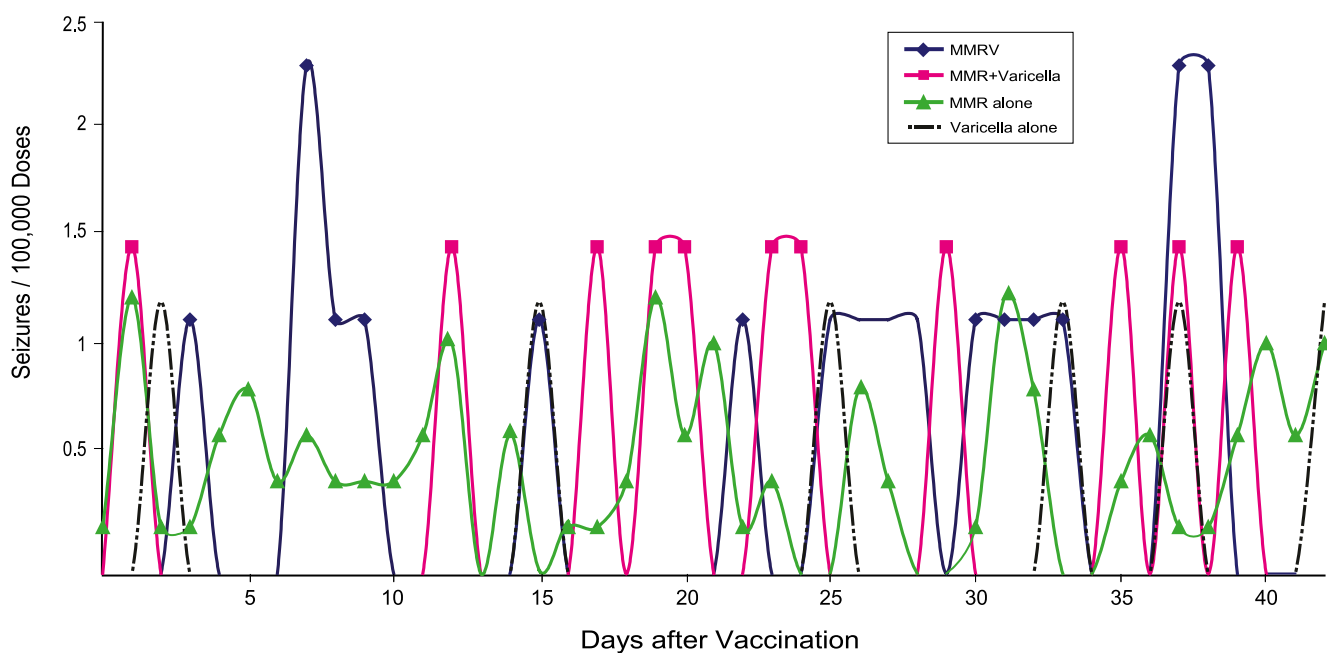
on the codes in the electronic data, incidence of electronically identified seizures 7 to 10 days after MMRV, MMR + V or MMR alone did not differ significantly from each other, although rates were higher after MMRV (Table 1).

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 ( $P = .09$ ; 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

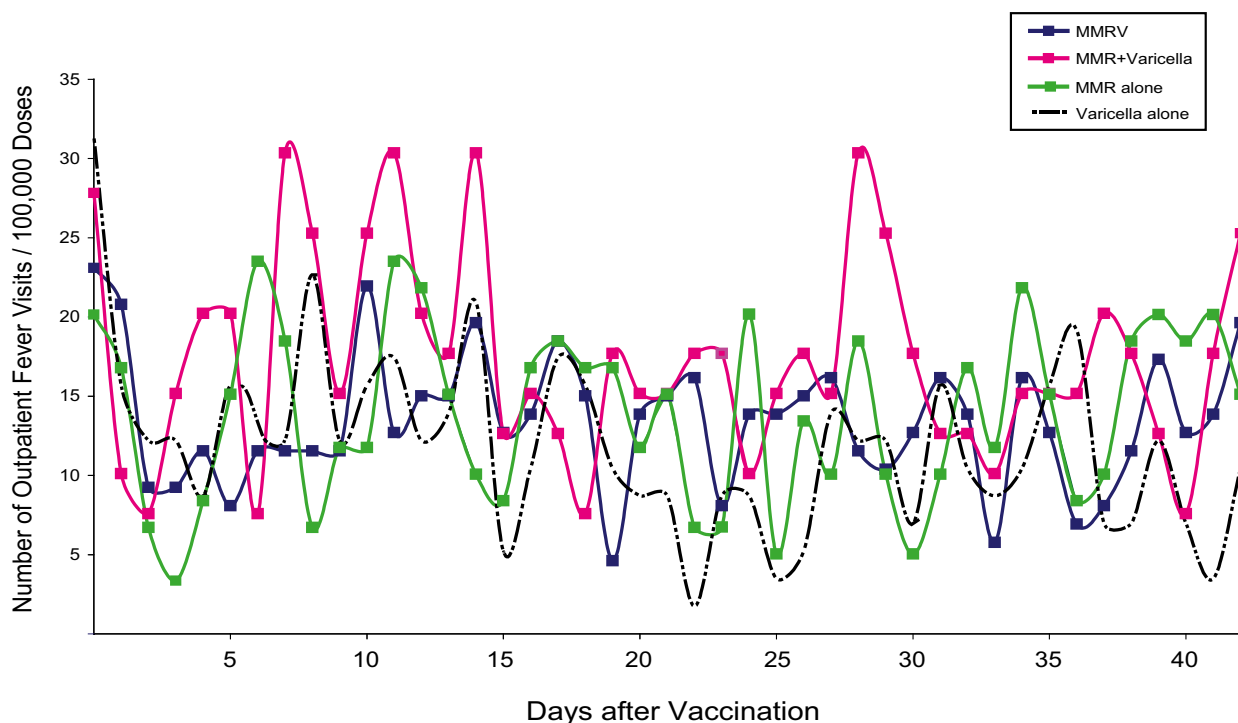
**TABLE 1** All Seizures After Measles-Containing Vaccines Identified From Electronic Records for 4- to 6-Year-Olds: 2000–2008

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)	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.



**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

Post-Vaccination, d	MMRV, N=86 570 Doses		MMR + Varicella, N=39 536 Doses		MMR, N= 59 538 Doses		Varicella, N= 57 366 Doses	
	Rate/10 000 Doses (Number Events)	Adjusted Rate/100 PY (95% CI)	Rate/10 000 Doses (Number Events)	Adjusted Rate/100 PY (95% CI)	Rate/10 000 Doses (Number Events)	Adjusted Rate/100 PY (95% CI)	Rate/10 000 Doses (Number Events)	Adjusted Rate/100 PY (95% CI)
7–10 <sup>a</sup>	5.7 (49)	5.2 (3.9–6.8)	9.6 (38)	8.8 (6.2–12)	4.9 (29)	4.4 (3–6.4)	6.3 (36)	5.7 (4–7.9)
0–42 <sup>b</sup>	57.9 (501)	5 (4.5–5.4)	74.9 (296)	6.4 (5.7–7.2)	60 (357)	5.2 (4.6–5.7)	51.2 (294)	4.4 (3.9–4.9)

<sup>a</sup> 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.

<sup>b</sup> None of the comparisons between day 0–42 fever visits were statistically significant.

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 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.

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

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

## 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. 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<sup>9</sup> observed that postvaccination seizures rates during the 30 days after MMR were lower for 4- to 6-year-olds receiving it as a second dose than they were for 10- to 12-year-olds receiving their second MMR. More recently, Esteghamati and colleagues evaluated febrile seizures after a second dose of MMR administered to 4- to 6-year-olds in Iran, reporting an incidence of 17 febrile seizures per 100 000 children (95% CI, 5.5–39.8) during the 4 weeks post vaccination.<sup>11</sup> While it is difficult to compare our results directly due to differences in postvaccination risk intervals, during the 42 days after MMR

alone, we identified 99 seizures in the electronic data per 479 311 MMR doses (Table 1), which translates into 20.7 seizures per 100 000 MMR doses. The incidence of seizures after MMR alone as identified by our electronic records is similar to that of previous reports.

Febrile seizures typically occur in children between the ages of 6 months and 5 years, with the incidence peaking at ~18 months of age.<sup>12</sup> As febrile seizures are generally much less likely to occur among 4- to 6-year-old children, it is probably not too surprising that we did not detect increased febrile seizures after MMRV or MMR + V among 4- to 6-year-old children given the low background rate of febrile seizures in this age group.

In general, fever visits after all measles-containing vaccines for 4- to 6-year-olds were quite low during postvaccination days 7 to 10 and 0 to 42; rates of outpatient fever visits in this age group were ~1/10th as high as what we observed after MMRV and MMR + V among 12- to 23-month-olds.<sup>6,7</sup> It is likely that our study also included some children who did not respond to their first dose of MMR and subsequently had a febrile response after MMRV or MMR + V at 4 to 6 years; however, we were unable to specifically identify those potentially vulnerable individuals. Prelicensure studies have not reported differences in postvaccination fever rates between 4- and 6-year-olds receiving MMRV or MMR + V as a second dose.<sup>10,13–15</sup> Similarly, previous postlicensure safety studies also

did not detect associations between second-dose MMR given at age 4 to 6 years and increased fever.<sup>5,9</sup> In our study, MMR + V trended toward higher rates for outpatient fever during day 7 to 10 visits, although this observation could be due to chance alone, as well as variations in coding and diagnostic practices at the varying VSD sites, differences between children who received MMR + V versus those who received MMR alone, selective use of 1 vaccine or another at VSD sites, and other unmeasured confounding variables.

## CONCLUSIONS

We found no evidence that MMRV or MMR + V is associated with an elevated risk of febrile seizures among 4- to 6-year-olds during the 6 weeks after vaccination. At most, even if these vaccines were responsible for all febrile seizures that occur 7 to 10 days after immunization, there would only be 1 febrile seizure for every 15 500 doses of MMRV or 1 febrile seizure for every 18 000 doses MMR + V administered.

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