

Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures

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KEY WORDS

measles, varicella, seizures, vaccine, fever

ABBREVIATIONS

MMRV—measles-mumps-rubella-varicella

ACIP—Advisory Committee on Immunization Practices

MMR—measles-mumps-rubella

VSD—Vaccine Safety Datalink

RCA—rapid cycle analysis

ICD-9—*International Classification of Diseases, 9th Revision*

RR—relative risk

CI—confidence interval

aOR—adjusted odds ratio

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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WHAT'S KNOWN ON THIS SUBJECT: We previously alerted the ACIP to preliminary evidence of a twofold increased risk of febrile seizures after MMRV when compared with separate MMR and varicella vaccines after monitoring with the VSD RCA surveillance system.



WHAT THIS STUDY ADDS: Using VSD data on twice as many vaccines, we examined the effect of MMRV on risk of seizure and describe here the postvaccination risk interval for increased fever and febrile seizures after vaccination.

abstract

FREE

OBJECTIVE: In February 2008, we alerted the Advisory Committee on Immunization Practices to preliminary evidence of a twofold increased risk of febrile seizures after the combination measles-mumps-rubella-varicella (MMRV) vaccine when compared with separate measles-mumps-rubella (MMR) and varicella vaccines. Now with data on twice as many vaccine recipients, our goal was to reexamine seizure risk after MMRV vaccine.

METHODS: Using 2000–2008 Vaccine Safety Datalink data, we assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines. We compared seizure risk after MMRV vaccine to that after MMR + varicella vaccines by using Poisson regression as well as with supplementary regressions that incorporated chart-review results and self-controlled analyses.

RESULTS: MMRV vaccine recipients (83 107) were compared with recipients of MMR + varicella vaccines (376 354). Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines but not after varicella vaccination alone. Seizure risk during days 7 to 10 was higher after MMRV than after MMR + varicella vaccination (relative risk: 1.98 [95% confidence interval: 1.43–2.73]). Supplementary analyses yielded similar results. The excess risk for febrile seizures 7 to 10 days after MMRV compared with separate MMR + varicella vaccination was 4.3 per 10 000 doses (95% confidence interval: 2.6–5.6).

CONCLUSIONS: Among 12- to 23-month-olds who received their first dose of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2300 doses given instead of separate MMR + varicella vaccines. Providers who recommend MMRV should communicate to parents that it increases the risk of fever and seizure over that already associated with measles-containing vaccines. *Pediatrics* 2010;126:e1–e8

The combination measles-mumps-rubella-varicella (MMRV) vaccine was licensed by the US Food and Drug Administration in 2005. The MMRV vaccine was subsequently recommended by the Advisory Committee on Immunization Practices (ACIP) in 2006, at which time the committee stated a preference for its use over separate measles-mumps-rubella (MMR) and varicella vaccines.

In previous studies, associations between MMR and increased risk for febrile seizures 1 to 2 weeks after vaccination were observed.¹⁻⁴ Although precensure studies of MMRV vaccine among 12- to 23-month-old children revealed higher rates of fever and measles-like rash 1 to 2 weeks later when compared with separate MMR and varicella vaccines,⁵⁻⁷ it was unknown at the time of MMRV licensure whether the higher rate of fevers was similarly associated with increased risk for febrile seizures.

The Centers for Disease Control and Prevention–sponsored vaccine safety surveillance system known as the Vaccine Safety Datalink (VSD) comprises 8 managed care organizations encompassing data on >9 million members annually. The VSD has developed a near-real-time vaccine safety surveillance system known as rapid cycle analysis (RCA),⁸⁻¹⁰ which was designed to monitor for potential associations between specific vaccines and pre-specified adverse events by using weekly data and sequential statistical analysis.¹¹

Beginning in 2007, we used the RCA surveillance system to monitor weekly 6 specific outcomes after MMRV vaccination. On the basis of ~43 000 MMRV doses administered between February 2006 and August 2007, we detected a preliminary signal for an approximately twofold increased risk of febrile seizures occurring 7 to 10 days after MMRV vaccination compared

with separately administered MMR + varicella vaccination. We reported these findings to the ACIP in February 2008, after which the ACIP changed its recommendations from a stated preference for MMRV to no preference for either MMRV or separate MMR + varicella vaccination.¹²

We continued monitoring children vaccinated with MMRV through October 2008, which resulted in approximately twice as many MMRV doses administered within the VSD than we originally reported. Using this expanded number of vaccinated children and comparing them to recipients of separately administered same-day MMR + varicella vaccines, we report here the risk of febrile seizures after MMRV during both the 7 to 10 days and 42 days after vaccination.

METHODS

Surveillance and Signal Detection

The VSD creates aggregated, dynamic data sets that are updated weekly and contain vaccine information and outcomes as described previously.⁸ MMRV RCA surveillance monitored children 12 to 23 months old during the 42 days after vaccine receipt for 6 outcomes: seizures, thrombocytopenia, encephalitis/meningitis, ataxia, allergic reactions, and arthritis. In this report we focus exclusively on seizures.

Children aged 12 to 23 months who were members of the 7 participating VSD sites and received their first dose of MMRV (Merck & Co, Inc, West Point, PA) were eligible for study inclusion. We defined a seizure event as the first instance during the 42 days after MMRV vaccination with *International Classification of Diseases, 9th Revision* (ICD-9) codes 345* (epilepsy) or 780.3* (convulsion) in the emergency department or hospital. We censored seizures after the first occurrence within the 42 days. To minimize inclusion of follow-up visits as seizures, we ex-

cluded children who had received either ICD-9 code in any inpatient or outpatient setting during the 42 days before the seizure. “Seizure” refers to an event identified electronically, whereas “febrile seizure” refers to a chart-confirmed febrile seizure.

We monitored seizures weekly and compared the cumulative number observed to the number expected on the basis of the historical VSD seizure rates from 2000 to 2006 after MMR vaccine was administered with or without varicella. We defined a “signal” as occurring when the number of seizures 42 days after vaccination significantly exceeded the number expected according to the maximized sequential probability ratio test¹¹; the threshold was set to a level designed to keep the cumulative chance of making a type I error below 5% over several years of weekly analyses. We assessed the statistical significance of temporal seizure clustering by using SaTScan software.^{13,14} Separately for each vaccine exposure, SaTScan evaluated all potential risk-window combinations 1 to 21 days in length, adjusting for multiple testing inherent in the hundreds of time intervals considered.

We examined postvaccination outpatient fever visits by using ICD-9 code 780.6 for fever or febrile illness at all 7 participating VSD sites from January 2000 through October 2008. Similar to seizure cases, fever visits were censored after the first occurrence within the 42 days.

The participating VSD sites were Group Health Cooperative (Washington State), Kaiser Permanente Colorado, Kaiser Permanente Northwest (Oregon), Harvard Pilgrim Health Care (Massachusetts), HealthPartners (Minnesota), Northern California Kaiser Permanente, and Marshfield Clinic (Wisconsin).

Chart Reviews

To assess whether postvaccination seizures were febrile seizures, we conducted the following chart reviews: (1) all seizures during days 0 to 42 after MMRV vaccination; (2) all seizures 7 to 10 days after separately administered, same-day MMR + varicella vaccination; and (3) a random sample of seizures during days 0 to 6 and 11 to 42 after MMR + varicella vaccination. The number of seizures reviewed in group 3 was equivalent to the number of chart-reviewed seizures during days 0 to 6 and 11 to 42 after MMRV vaccination.

We accepted a chart diagnosis of febrile seizure regardless of the presence of a concurrent febrile illness. When available, we captured data regarding previous seizure history, family history of seizures, and whether the seizure resulted in hospitalization. Trained medical record analysts, blinded to the study and the vaccines received, conducted the chart reviews.

Assessment of the Effect of MMRV on Seizure Risk

Seizure risk after MMRV vaccination was compared with seizure risk after 3 comparator vaccines from January 2000 through October 2008: (1) MMR + varicella; (2) MMR alone; and (3) varicella alone. The primary comparison was with MMR + varicella vaccination.

We focused the primary analyses on days 7 to 10 after vaccination because early temporal scan statistics indicated that seizures clustered most significantly during days 7 to 10 after MMR + varicella vaccination, a time period consistent with post-MMR fever and seizures.¹⁻⁴ Because we initially defined the 42-day surveillance period, we also examined seizure risk for days 0 to 42, as well as days 0 to 30, to permit comparison with the results of a recent study on MMRV vaccination and febrile seizures.¹⁵

Using the electronic data, we used Poisson regression to compare seizure risk across the 4 different vaccine exposures during days 7 to 10, as well as 5 other risk windows (days 0-4, 5-6, 11-12, 13-30, and 31-42). Additional covariates adjusted for 5 age groups (12, 13-14, 15-16, 17-19, and 20-23 months), 7 VSD sites, respiratory virus seasons (November 1 to April 30 versus May 1 to October 31¹⁶), and 9 calendar years (2000-2008). The dependent variable was the seizure count; the offset (ie, denominator for the seizure count) was person-time. Additional concomitant vaccines were not included, because neither the number nor the receipt of concomitant vaccines was a significant seizure predictor in preliminary analyses.

We also conducted 3 supplementary analyses to (a) account for the result of the chart reviews and the remaining uncertainty regarding unreviewed charts, (b) focus on chart-confirmed febrile seizures during days 7 to 10, and (c) adjust for potential confounders that could differ in the comparison group but should remain stable in each vaccine recipient during the postvaccination period. Because we did not have concurrent controls throughout the entire study period, this self-controlled analysis (c) ("case-centered"¹⁷) was particularly important, because it inherently controlled for unmeasured confounding.

We conducted supplementary analysis (a) by repeating Poisson regressions ($n = 1000$), for which before each analysis we applied to each unreviewed seizure a "confirmation rate" randomly drawn from a normal distribution centered on 83% with a standard error of 5 percentage points (see "Results").

For (b), we used logistic regressions focused entirely on chart-confirmed febrile seizures during days 7 to 10 after MMRV versus MMR + varicella vac-

ination. For (c), we conducted case-centered logistic regressions by using a data set with only 1 record per seizure.¹⁷ The dependent variable was whether the seizure occurred in the risk window; the key predictor was whether exposure was MMRV versus MMR + varicella.

As with the primary analyses, all supplementary analyses were adjusted for age group, site, calendar year, and respiratory virus season. We calculated the excess risk by using the estimated relative risk (RR) and the seizure rate (S) after MMR + varicella vaccination: excess risk = $(RR - 1) \times S$. We used SAS 9.1 (SAS Institute, Cary, NC) for all analyses.

RESULTS

The study population included 83 107 children vaccinated with MMRV between January 2006 and October 2008 and 376 354 vaccinated with MMR + varicella between January 2000 and October 2008. The secondary comparison groups consisted of 145 302 children who received MMR vaccine alone and 107 744 who received varicella vaccine alone from 2000 to 2008 (Table 1).

After vaccination with all measles-containing vaccines, seizure incidence peaked during days 7 to 10; the most prominent peak was recorded after MMRV vaccination (Fig 1). Temporal scan statistics revealed that seizures clustered most significantly during days 8 to 10 for MMRV vaccination (RR: 7.6; $P < .0001$), 7 to 10 days after MMR + varicella vaccination (RR: 4.0; $P < .0001$), and 7 to 11 days after MMR vaccination alone (RR: 3.7; $P < .0001$). No seizure peak was observable after varicella vaccination alone, nor was there any significant temporal clustering. During days 7 to 10, unadjusted rates for seizures were 84.6 seizures per 1000 person-years after MMRV vaccination, 42.2 seizures per 1000

TABLE 1 Age at Vaccination, Number of Seizures, and the Number of Doses Administered in Each of 3 Time Periods According to Vaccine Received: VSD Study Population, 2000–2008

	MMRV (<i>n</i> = 83 107)	MMR + Varicella (<i>n</i> = 376 354)	MMR Alone (<i>n</i> = 145 302)	Varicella Alone (<i>n</i> = 107 744)	All (<i>N</i> = 712 507)
Age at vaccination, <i>n</i> (%)					
12 mo	44 182 (53.2)	192 912 (51.3)	57 217 (39.4)	27 452 (25.5)	321 763 (45.2)
13–14 mo	19 534 (23.5)	92 117 (24.5)	27 737 (19.1)	14 381 (13.3)	153 769 (21.6)
15–16 mo	11 319 (13.6)	59 254 (15.7)	37 718 (26)	31 702 (29.4)	139 993 (19.6)
17–19 mo	5292 (6.4)	21 723 (5.8)	15 571 (10.7)	23 923 (22.2)	66 509 (9.3)
20–23 mo	2780 (3.3)	10 348 (2.7)	7059 (4.9)	10 286 (9.5)	30 473 (4.3)
Seizures 0–42 d, <i>n</i>	189	598	151	129	1067
Seizures 7–10 d, <i>n</i>	77	174	42	15	308
Doses administered between 2000 and November 2003, <i>n</i> (%)	1134 (1.4)	205 572 (54.6)	95 470 (65.7)	64 520 (59.9)	366 696 (51.5)
Doses administered between December 2003 and January 2006, <i>n</i> (%)	149 (0.2)	105 629 (28.1)	32 039 (22.0)	26 475 (24.6)	164 292 (23.1)
Doses administered between February 2006 and October 2008, <i>n</i> (%)	81 824 (98.5)	65 153 (17.3)	17 793 (12.2)	16 749 (15.5)	181 519 (25.5)

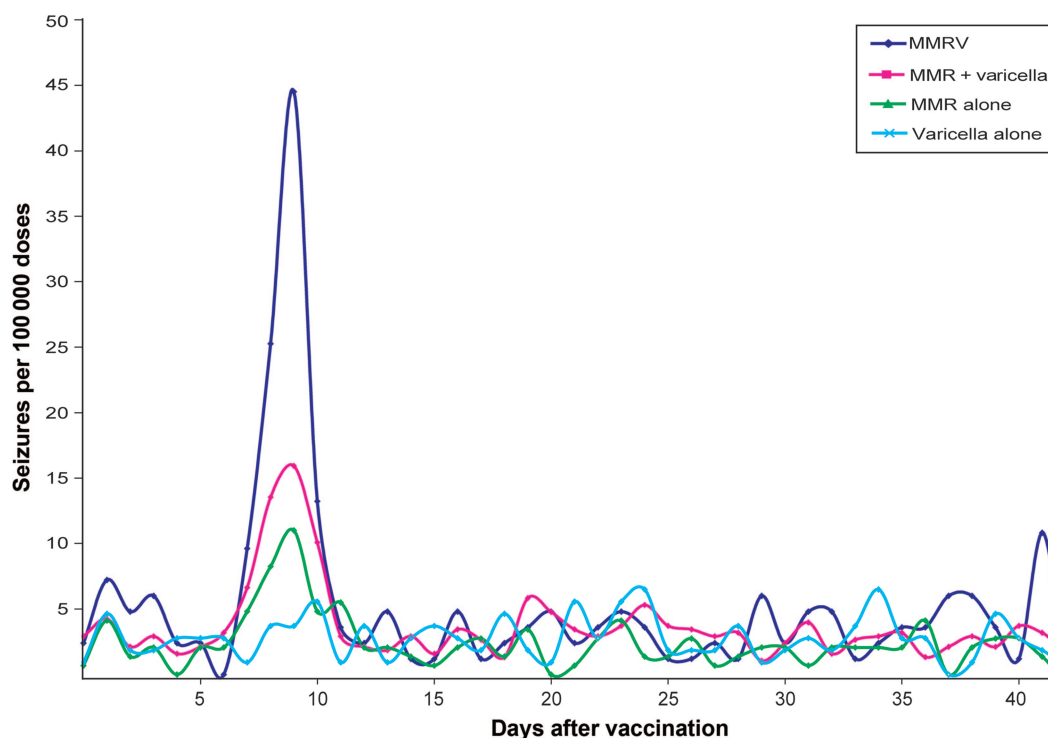


FIGURE 1

Postvaccination seizures among 12- to 23-month-olds according to vaccine received: VSD study population, 2000–2008.

person-years after MMR + varicella vaccination, and 26.4 seizures per 1000 person-years after MMR vaccination alone. Unadjusted rates during days 7 to 10 were nearly 8 times higher for MMRV and 4 and 3.5 times higher for MMR + varicella and MMR vaccination alone, respectively. At the largest VSD site (113 MMRV lots used), increased seizure risk was not limited to particular lots.

We next explored receipt of MMRV vaccine and outpatient visits for fever. Similar to the timing of postvaccine seizures, outpatient fever visits sharply increased during days 7 to 10; the most activity occurred after MMRV vaccination (Fig 2). Temporal scan statistics revealed significant clustering during days 7 to 10 for all measles-containing vaccines (RR after MMRV: 6.1; RR after MMR + varicella: 4.4; RR

after MMR alone: 4.3; $P < .0001$ for all). There was no temporal clustering of fever visits after varicella vaccination alone.

We subsequently reviewed the charts of seizure cases during the 42 days after MMRV or MMR + varicella vaccination. Of the 491 cases identified, 40 charts were missing or had missing data. Review of the remaining charts

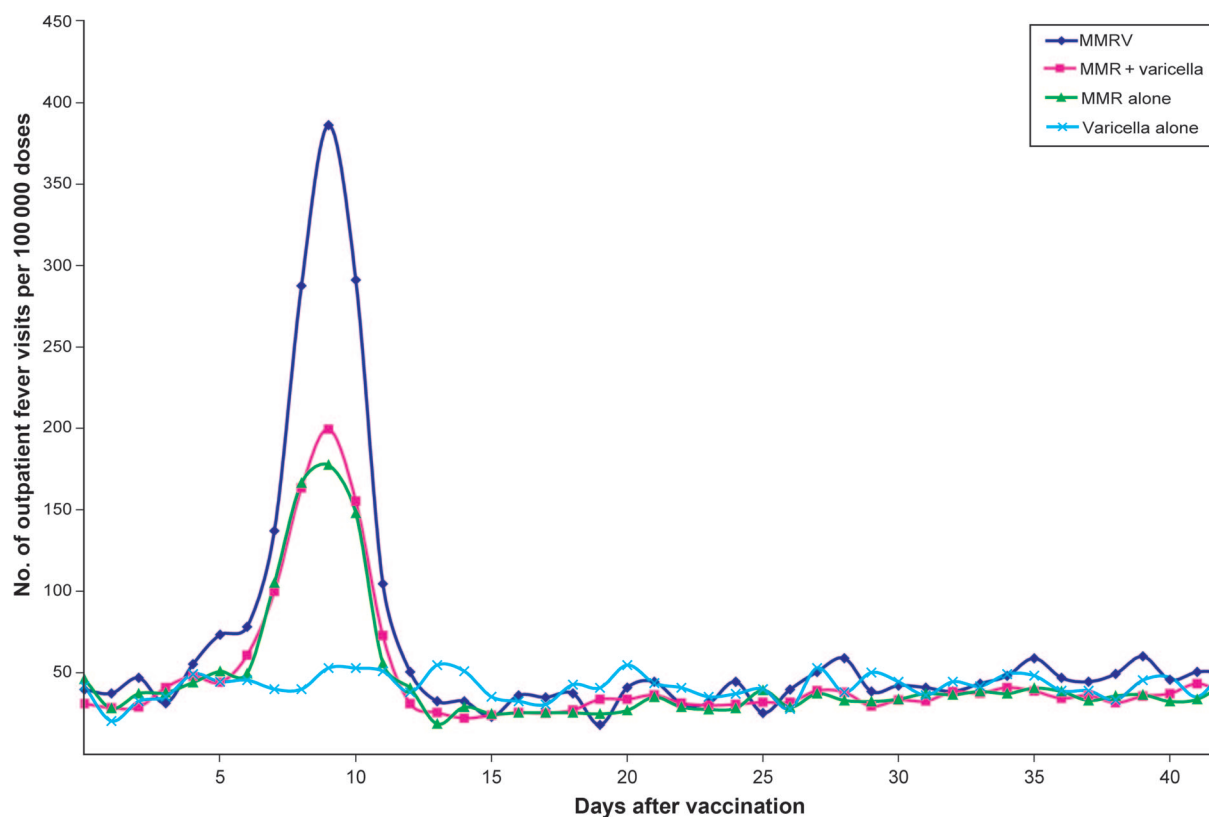


FIGURE 2

Postvaccination outpatient fever visits among 12- to 23-month-olds according to vaccine received: VSD study population, 2000–2008.

($n = 451$) revealed that 424 (94%) of the cases were acute seizures and 392 (87%) were febrile seizures. The overall confirmation rate of febrile seizures after vaccination was consistent between the MMRV and MMR + varicella vaccines (Table 2). Regardless of vaccine, the overall febrile-seizure confirmation rate was significantly higher within days 7 to 10 (90% [95% confidence interval (CI): 87–94]) when compared with outside days 7 to 10 (83% [95% CI: 78–88]; $P = .024$); there were no differences in febrile-seizure confirmation rates between recipients of the MMRV and MMR + varicella vaccines (Table 3).

Primary analysis revealed significantly higher seizure risk after MMRV than after MMR + varicella vaccination during days 7 to 10 (RR: 1.98 [95% CI: 1.43–2.73]), as well as during 2 longer intervals (Table 4). MMRV vaccination was

not associated with significantly elevated seizure risks during any of the 5 intervals outside days 7 to 10 (data not

shown). In all risk windows, seizure risk after MMR vaccination alone was similar to that after MMR + varicella

TABLE 2 Chart Verification of Electronically Identified Postvaccination Seizures in the Emergency Department and Hospital

	All Reviewed Charts ($N = 451$), n (%) ^a	MMRV ($N = 183$), n (%)	MMR + Varicella ($N = 268$), n (%)
Acute seizure diagnosed	424 (94)	172 (94)	252 (94)
Not an acute seizure	8 (3)	3 (2)	5 (2)
No evidence of seizure event/ insufficient information	19 (4)	8 (4)	11 (4)
Febrile seizure diagnosed	392 (87)	160 (87)	232 (87)

^a Does not include 40 cases in which either the charts or the visit of interest were missing.

TABLE 3 Febrile-Seizure Rate: Percent That Were Chart-Confirmed

Risk Window After Vaccination	Vaccine		P^a	Overall Percent Confirmed (95% CI)
	MMRV, % (N Confirmed/ N Reviewed)	MMR + Varicella, % (N Confirmed/ N Reviewed)		
Days 7–10	92 (70/76)	90 (138/154)	.55	90 (87–94)
Days 0–6 and 11–42	84 (90/107)	82 (94/114)	.74	83 (78–88)

The total number of MMRV-recipient charts reviewed was 183; the total number of MMR + varicella-recipient charts reviewed was 268.

^a Comparison between percentage confirmed between MMRV and MMR + varicella vaccines for the stated postvaccination period.

TABLE 4 Risk for Febrile Seizures After MMRV Compared to Separately Administered Same-Day MMR and Varicella Vaccines (2000–2008) During Different Postvaccination Risk Periods

Days After Vaccination	Analysis Incorporates Chart-Confirmation Rate?	RR (95% CI) ^a	P	Excess Risk per 10 000 Doses (95% CI)
7–10	No	1.98 (1.43–2.73)	<.0001	4.6 (2.8–5.9)
	Yes	2.04 (1.44–2.90)	<.0001	4.3 (2.6–5.6)
0–42	No	1.42 (1.11–1.81)	.005	6.7 (1.7–12.9)
	Yes	1.46 (1.11–1.92)	.008	6.2 (2.0–9.5)
0–30	No	1.40 (1.06–1.85)	.017	5.1 (0.8–10.8)
	Yes	1.44 (1.05–1.97)	.023	4.7 (0.7–7.6)

^a All analyses were adjusted for age, VSD site, and each year and respiratory season by using Poisson regression analysis.

vaccination, whereas seizure risk after varicella vaccination alone was relatively low (<0.17 per child-year follow-up). Restricting the analyses from November 2003 through October 2008 yielded similar results for MMRV vaccine (RR for postvaccine days 7–10: 2.46 [95% CI: 1.46–4.08]; $P = .0008$; RR for postvaccine days 0–42: 1.44 [95% CI: 1.12–1.86]; $P = .0049$).

Supplementary Poisson regression analyses that accounted for chart reviews (a) yielded a comparable seizure RR for MMRV vaccine during days 7 to 10 (RR: 2.04 [95% CI: 1.44–2.90]) (Table 4). Supplementary logistic regression restricted to chart-verified febrile seizures during days 7 to 10 (b) produced a slightly higher estimate (adjusted odds ratio [aOR]: 2.17 [95% CI: 1.61–2.93]). Finally, case-centered analyses (c) for MMRV versus MMR + varicella vaccines also indicated increased risk of seizures during both days 7 to 10 (aOR: 1.92 [95% CI: 1.39–2.66]) and days 0 to 42 (aOR: 1.3 [95% CI: 1.03–1.65]) when compared with postvaccination days 43 to 180.

Estimates of the excess number of febrile seizures per 10 000 children given MMRV instead of MMR + varicella vaccines are listed in Table 4. MMRV vaccination was associated with 4.3 additional seizures per 10 000 doses (95% CI: 2.6–5.6) during the 7 to 10 days after vaccination.

The proportion of children with postvaccination febrile seizures with a history of seizures was similar between

MMRV vaccine (23 of 141 [16%]) and MMR + varicella vaccines (42 of 193 [22%]; $P = .21$; data were available for 334 of 392 cases). Of those with a febrile seizure, there was a positive seizure family history among 30% of MMRV vaccine recipients compared with 29% of those who received the MMR + varicella vaccines ($P = .90$); data regarding family history were missing from 47% of the charts (206 of 392). During days 7 to 10, 6% of the subjects with febrile seizures after MMRV vaccination were hospitalized versus 17% after MMR + varicella vaccination ($P = .023$).

DISCUSSION

We analyzed >459 000 12- to 23-month-old children vaccinated with either MMRV or separate MMR and varicella vaccines and found the MMRV vaccine to be associated with increased fever and seizures 7 to 10 days after vaccination. Our different analytic approaches (Poisson, logistic, and case-centered regressions) yielded similar results, indicating that the MMRV vaccine, when compared with MMR + varicella vaccines, was associated with a twofold increased risk of having a febrile seizure 7 to 10 days after vaccination. In particular, the case-centered analyses strengthened our results, because they addressed confounding caused by coding or diagnostic practices, data errors, patient demographics, or care-seeking behavior; such confounding would not selec-

tively affect seizures during postvaccination days 7 to 10 more than other postvaccination days. Our findings are consistent both with results of prelicensure studies during which higher fever after MMRV vaccination was noted^{5–7} and a recent postlicensure study from which MMRV vaccination was reported to be associated with increased febrile seizures during days 5 to 12.¹⁵ We estimate that there will be an additional 4.3 febrile seizures 7 to 10 days after vaccination for every 10 000 doses of MMRV vaccine given instead of MMR + varicella vaccines, or that there will be 1 additional febrile seizure 7 to 10 days after vaccination for every 2300 MMRV doses administered to 12- to 23-month-olds instead of separately administered same-day MMR + varicella doses.

To our knowledge, this report represents the first instance of confirming the association of an adverse event with a particular vaccine after a signal detected by a real-time active vaccine safety surveillance system. The large size of the VSD population, along with our validation of electronically identified seizures with chart review, demonstrates the versatility and validity of the VSD RCA surveillance system, which we believe can serve as a framework for future vaccine- and drug-safety endeavors.

In this study, chart review verified 94% of electronically identified seizures as acute seizures, with 87% of all being febrile seizures. Our findings contrast with those of other studies for which lower confirmation rates were reported when they identified seizures in emergency departments and outpatient settings.^{3,18} We attribute our high confirmation rate to limiting case identification to the emergency department or inpatient setting. A recent VSD study similarly reported a high positive predictive value for seizures identified in emer-

gency department and inpatient settings.¹⁹ The reason for fewer hospitalizations after MMRV vaccination is not clear; however, possible explanations include changes in clinical practice during the time period of the study, growing awareness by physicians of associations between measles-containing vaccines and febrile seizures (and a tendency not to hospitalize such patients), or other unmeasured differences in the clinical features of the febrile seizures.

We found no evidence of an increased risk for postvaccination seizures outside the defined 7- to 10-day risk period, yet the overall RR remained elevated for the entire postvaccination time period (both 30 days and 42 days) because of the risk during the 7- to 10-day period. Our results contrast with those of a Jacobsen et al¹⁵ study, in which the authors, despite finding a significantly increased febrile-seizure risk during days 5 to 12 days, were unable to determine if there was an overall increase in seizures during the 30 days after vaccination; we attribute the disparities to their smaller sample size and differences in seizure case definitions. Our results provide evidence that MMRV vaccine is associated with an overall increased risk in postvaccination febrile seizures regardless of whether the risk period evaluated was 7 to 10, 0 to 30, or 0 to 42 days. An important consideration is that the increased risk for febrile seizures during longer postvaccine time periods does not indicate that MMRV causes a sustained increased risk for febrile seizures; rather, the increased overall risk for febrile seizures after MMRV vaccination is caused by the excess of febrile sei-

zures that occur 7 to 10 days after immunization.

Previous studies have revealed that MMR vaccine is associated with increased fever and seizures after vaccination.^{3,4} Consistent with these reports, our study results show that both MMRV and MMR vaccines, but not varicella vaccine alone, are associated with increased outpatient fever visits and seizures 7 to 10 days after vaccination, with MMRV vaccine increasing fever and seizure twice as much as the MMR + varicella vaccines. This is an important consideration for providers evaluating the excess risk of febrile seizures associated with MMRV compared with MMR + varicella vaccines; MMRV vaccine doubles an already elevated risk for febrile seizures. The Centers for Disease Control and Prevention recently recommended that although either vaccine may be used as the first dose for 1- to 2-year-olds (and the costs of purchasing either vaccine are similar²⁰), families without a strong preference for MMRV vaccine should receive the MMR + varicella vaccines. Providers who consider using MMRV vaccine should discuss with families and caregivers the risks and benefits.²¹

Our study had several limitations. The first was that we used a largely historical comparison group. We do not believe, however, that this method affected our findings, because we obtained similar results when we restricted the analyses to more recent years and with the case-centered approach, which inherently controls for the possible confounders of most concern with historical comparisons. Another potential limitation was that our febrile-seizure case definition was a clinical diagnosis in the chart. Because

the febrile-seizure confirmation rate was the same regardless of vaccine, we do not believe that this created meaningful bias in our results. In addition, in the context of large safety studies designed to evaluate potential safety signals, we believe that it is appropriate to include probable cases so that we do not overlook a true vaccine safety signal.

CONCLUSIONS

Among 12- to 23-month-olds receiving their first dose of measles-containing vaccine, the risk of fever and seizure are elevated 7 to 10 days after vaccination. The use of MMRV vaccine instead of separate MMR + varicella vaccines approximately doubles the risk for fever and febrile seizures, resulting in 1 additional febrile seizure for every 2300 doses of MMRV vaccine administered instead of separate MMR and varicella vaccines. Providers who choose to use the combination vaccine should be aware of and clearly communicate this increased risk to the families and caregivers of their patients.

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